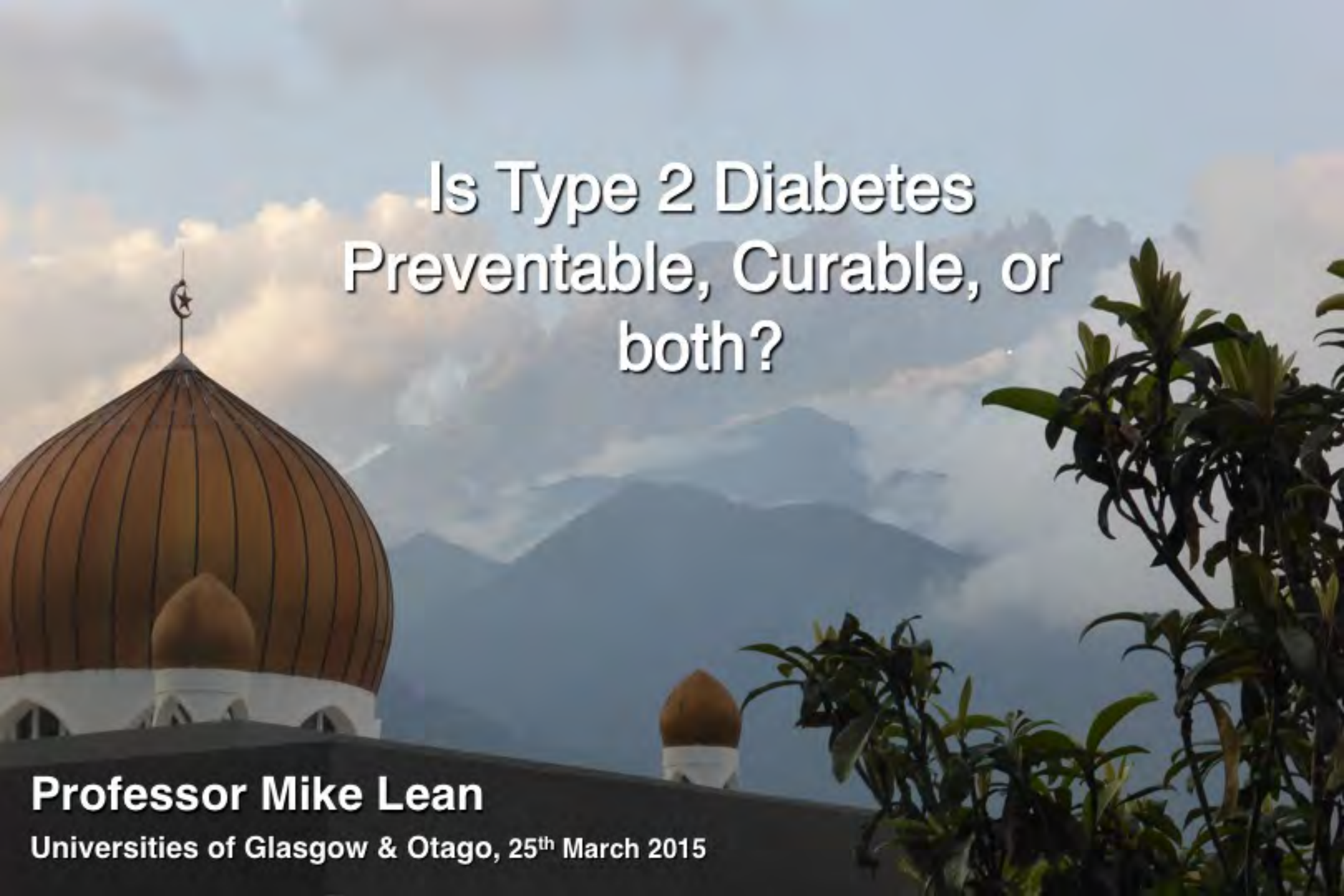
Is Type 2 Diabetes Preventable, Curable, or both?
Professor Mike Lean
Universities of Glasgow & Otago, 25th March 2015


ID KAHANDAMAN DI
GUNTING B.LAGADAN
HUGUAN MANANGNUD
ID NULUHON KINABALU
1888 – 1966
TAMAN
KINABALU
LOW'S PEAK
(4095.2M)
SERVICE TO ALL HUMANITY
ROTARY INTERNATIONAL DISTRICT 3310

KINABALU

MEMPUNYAI

YANG BOLEH
AAN YANG SEJUK,
GI.

NOTICE

SABAH PARKS REGULATIONS REQUIRED THAT ALL PERSON INTENDING TO CLIMB TO THE SUMMIT MUST BE ACCOMPANIED BY A REGISTERED MOUNTAIN GUIDE.

WARNING

DO NOT CLIMB IF YOU ARE SUFFERING FORM OR HAVE A HISTORY OF THE FOLLOWING AILMENTS :-

(1) HEART DISEASE
(2) HYPERTENSION
(3) CRONIC ASTHMA
(4) PEPTIC ULSER
(5) SEVERE ANEMIA
(6) DIABETES
(7) EPILEPTIC FITS
(8) ARTHRITIS
(9) PALPITATION
(10) HEPATITIS (JAUNDICE)
(11) MUSCULAR CRAMPS
(12) OBESITY (OVER WEIGHT)
(13) ANY OTHER SICKNESS THAT MAY BE TRIGGERED BY SEVERE COLD, EXERTION, AND HIGH ALTITUDE.


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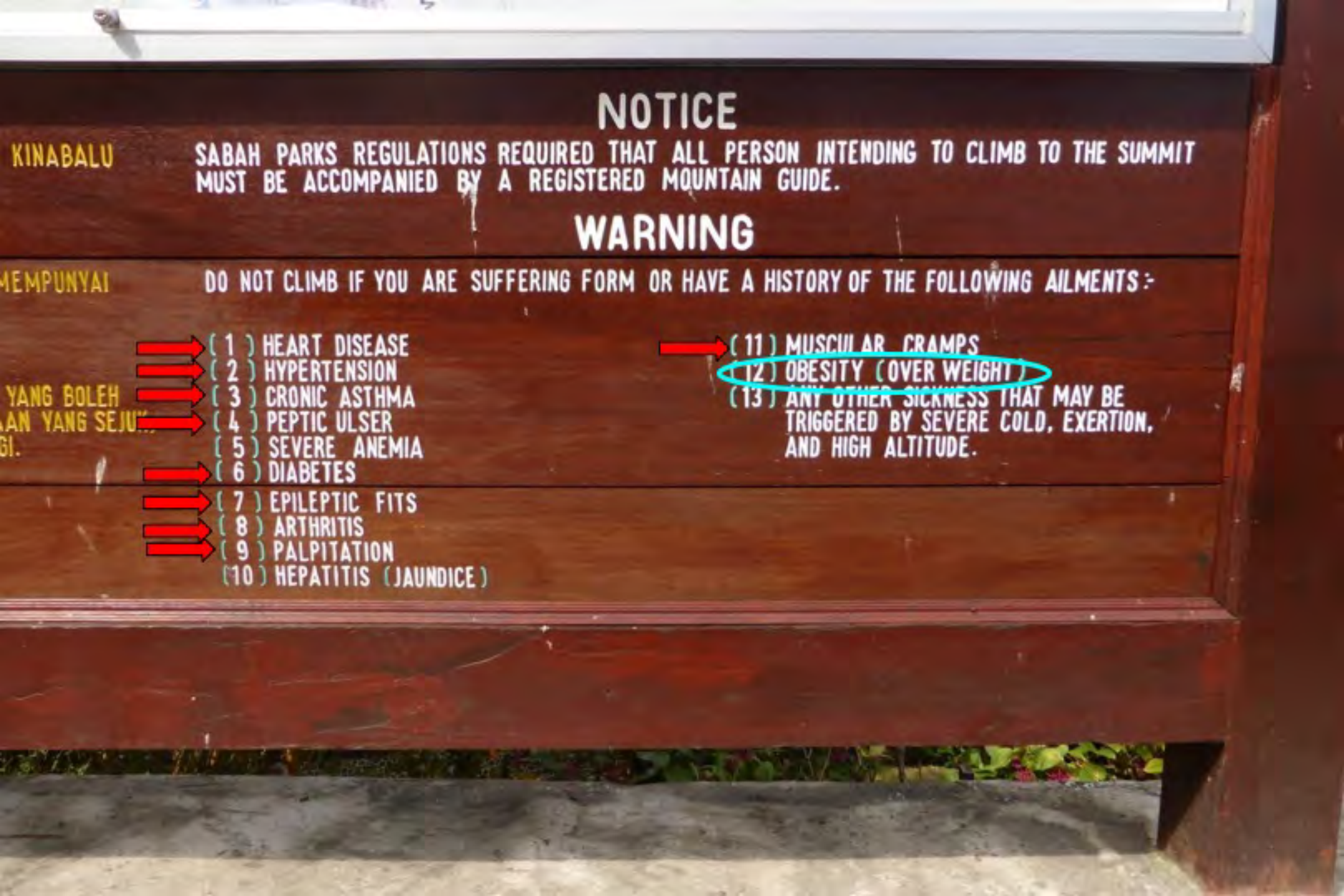
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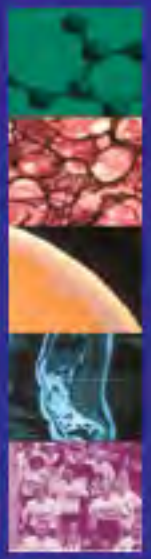

What do people with diabetes actually want?

• **To forget about it…… ….to not be diabetic?**	**???**
• Less complications?	Drugs? **Diet**
• Feel better?	Less drugs **(Diet)**
• Less anxiety?	Less drugs & hypos **(Diet)**
• Weight loss?	**Diet**
• Less problematic issues?	**Diet** **(Grant et al, Adelaide)**

Life-expectancy is still reduced 6-10 years by T2DM, despite all our drug treatments

Age (years)	England life expectancy (2005–2007) males (yrs)	T2DM life expectancy (2000–2007) males (yrs)	England life expectancy (2005–2007) females (yrs)	T2DM life expectancy (2000–2007) females (yrs)
0	77.65	69.58	81.82	71.91
30	48.59	39.86	52.44	41.16
40	39.08	30.82	42.71	32.04
50	29.85	23.14	33.26	24.68
60	21.24	16.92	24.28	17.69
70	13.70	12.60	16.05	12.06
80	7.74	5.98	9.17	7.64
90	3.96	3.68	4.49	6.44

Risk-reduction with current guideline treatment of T2DM (polypharmacy) *Maximum possible =15%*

Echouffo-Tcheugui, Sargeant, Prevost, Williams, Barling, Butler*,Fanshawe, Kinmonth, Wareham & Griffin (Diabetic Medicine 2008)

Model of the effect of treatment combinations	Absolute risk reduction (or risk difference) Estimate (%)	Range
Absolute risk calculated with UKPDS engine		
No additive effect: single most effective treatment (lipid-lowering therapy)	7.2	4.9–9.5
Additive effect of glucose, lipid- and blood pressure-lowering therapies	15.2	13.2–16.9
Additive effect of glucose-, lipid-, blood pressure-lowering therapies and aspirin	18.0	16.7–19.5
Absolute risk calculated with Framingham equation		
No additive effect: single most effective treatment (lipid-lowering therapy)	8.0	5.4–10.5
Additive effect of glucose-, lipid- and blood pressure-lowering therapies	16.9	14.6–18.8
Additive effect of glucose-, lipid-, blood pressure-lowering therapies and aspirin	20.0	18.4–21.6

NB: Aspirin does not prevent new CHD in T2DM. Belch et al, BMJ 2008

Mortality by BMI (general population)

Influence of weight loss on mortality is complicated, especially over long times:

Intentional
vs
Unintentional

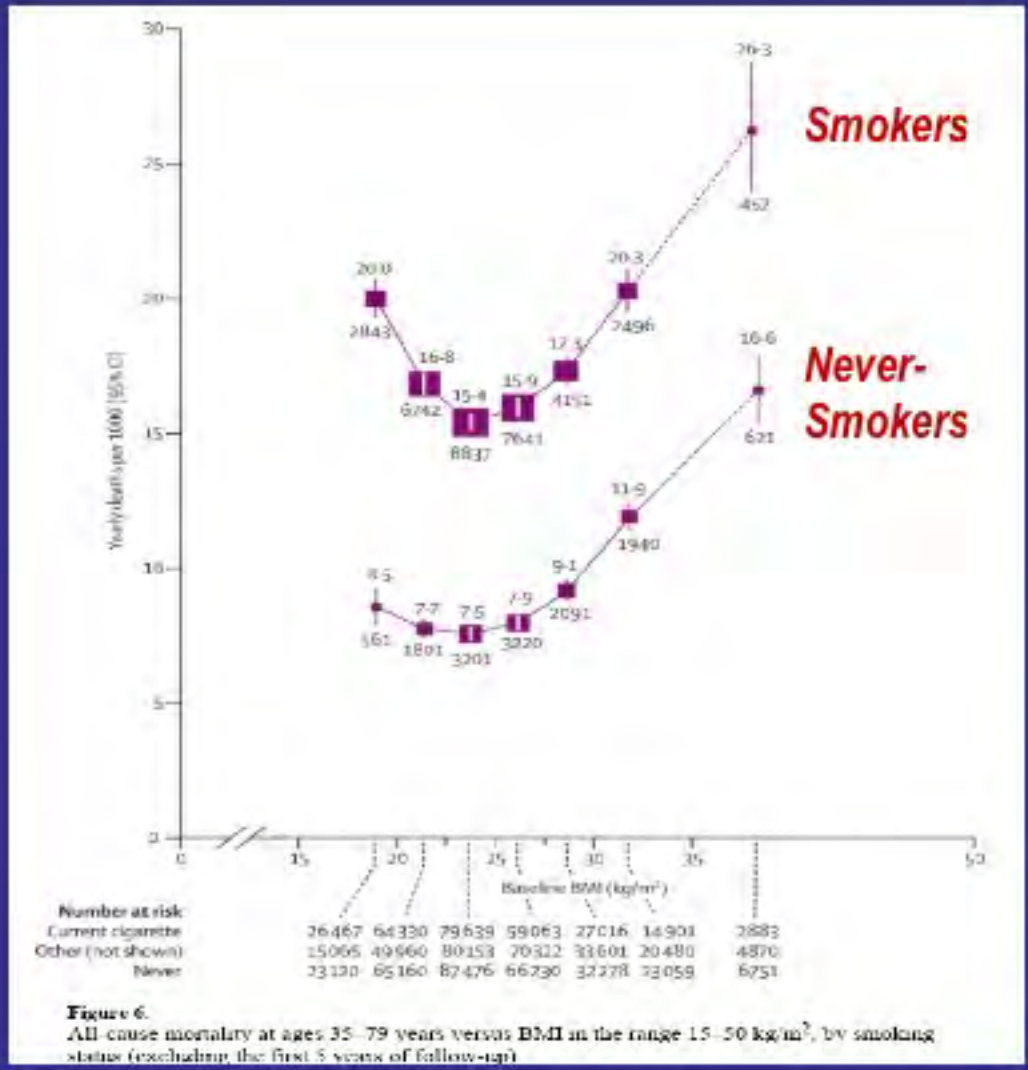

Figure 6.
All-cause mortality at ages 35–79 years versus BMI in the range 15–50 kg/m², by smoking status (excluding the first 5 years of follow-up)

Prospective Studies Collaboration (Whitlock et al)
Lancet 2009

Life expectancy is reduced by obesity:

BMI 30-35: reduced 2-4 years

BMI 40-50: reduced 8-10 years

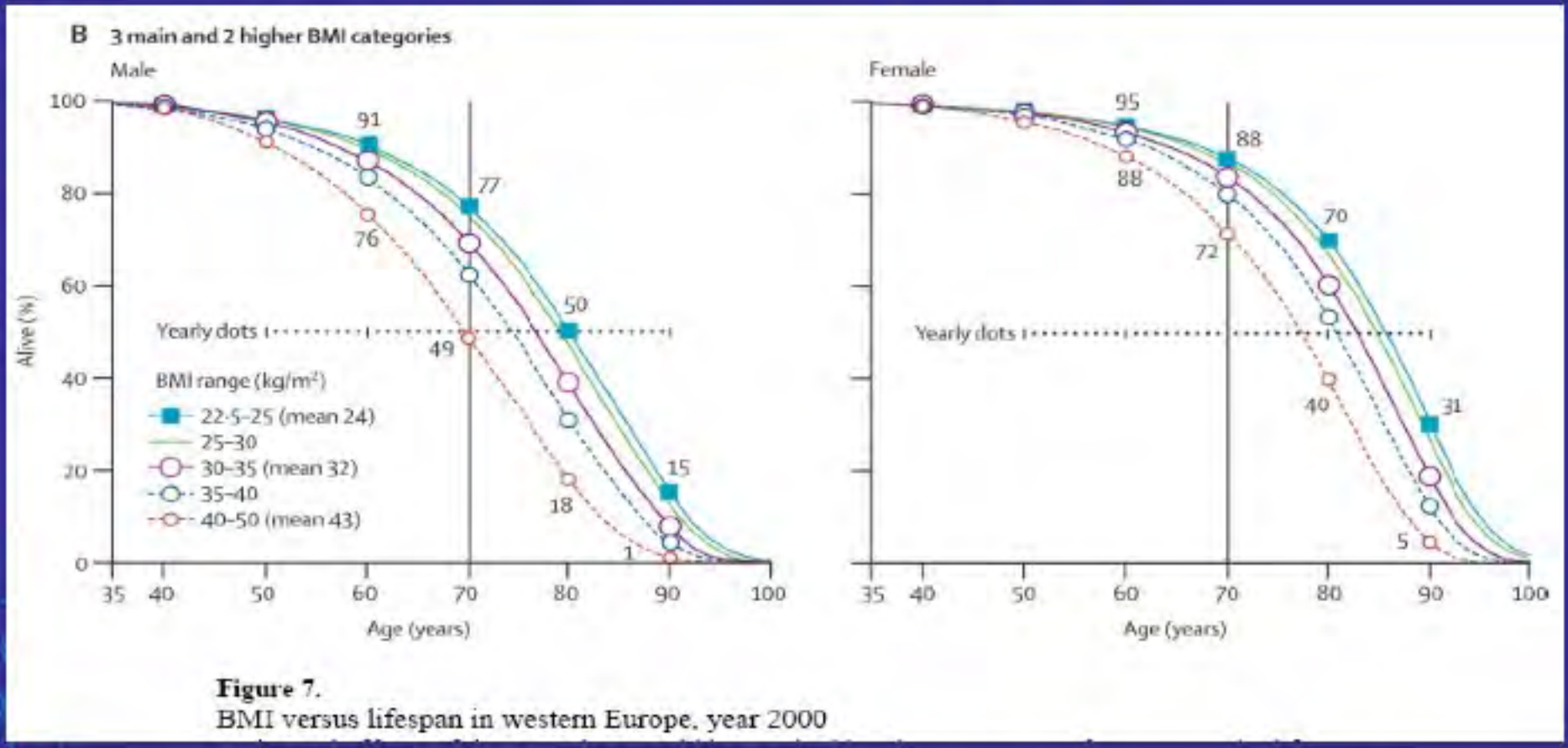

Figure 7.
BMI versus lifespan in western Europe, year 2000

Prospective Studies Collaboration (Whitlock et al)
Lancet 2009 (cf, Fontaine et al 2003)

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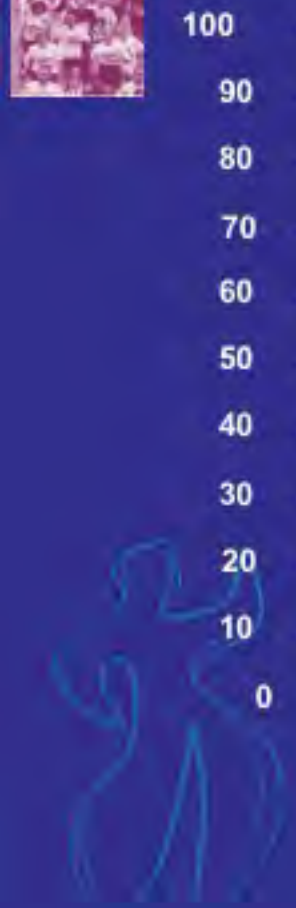
Weight gain/ obesity is the main cause of T2DM - and necessary, whatever the genes: High BMI

Colditz GA et al. Ann Int Med, 1995

Adjusted RR

(BMI <22 = referent)



Most T2DM requires adult weight gain >15kg

Median BMI 30 at diagnosis

100
90
80
70
60
50
40
30
20
10
0

<22 | 22-22.9 | 23-23.9 | 24-24.9 | 25-26.9 | 27-28.9 | 29-30.9 | 31-32.9 | 33-34.9 | >35

BMI (kg/m²)

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Excess fat in key organs – precursor to diabetes

Diet energy > exercise
Sat Fat, Low Fruit & Veg

↑Glucose Output

↑TG → ↑SD. LDL, ↑apoB

ALT
GGT
CRP,
PAI-1

Large insulin-res fat cells

FFAS/
Adiponectin
PAI-1,
IL-6, TNF-α AMGII

↓ Glucose Uptake

↓ Insulin

ALT - Salmeron et al, Diabetes 2001
PAI-1 - Festa et al, Diabetes 2002
Adiponectin - Lindsay et al, Lancet 2002
Leptin, Salmeron et al, AJE
Salmeron Clin Endocr

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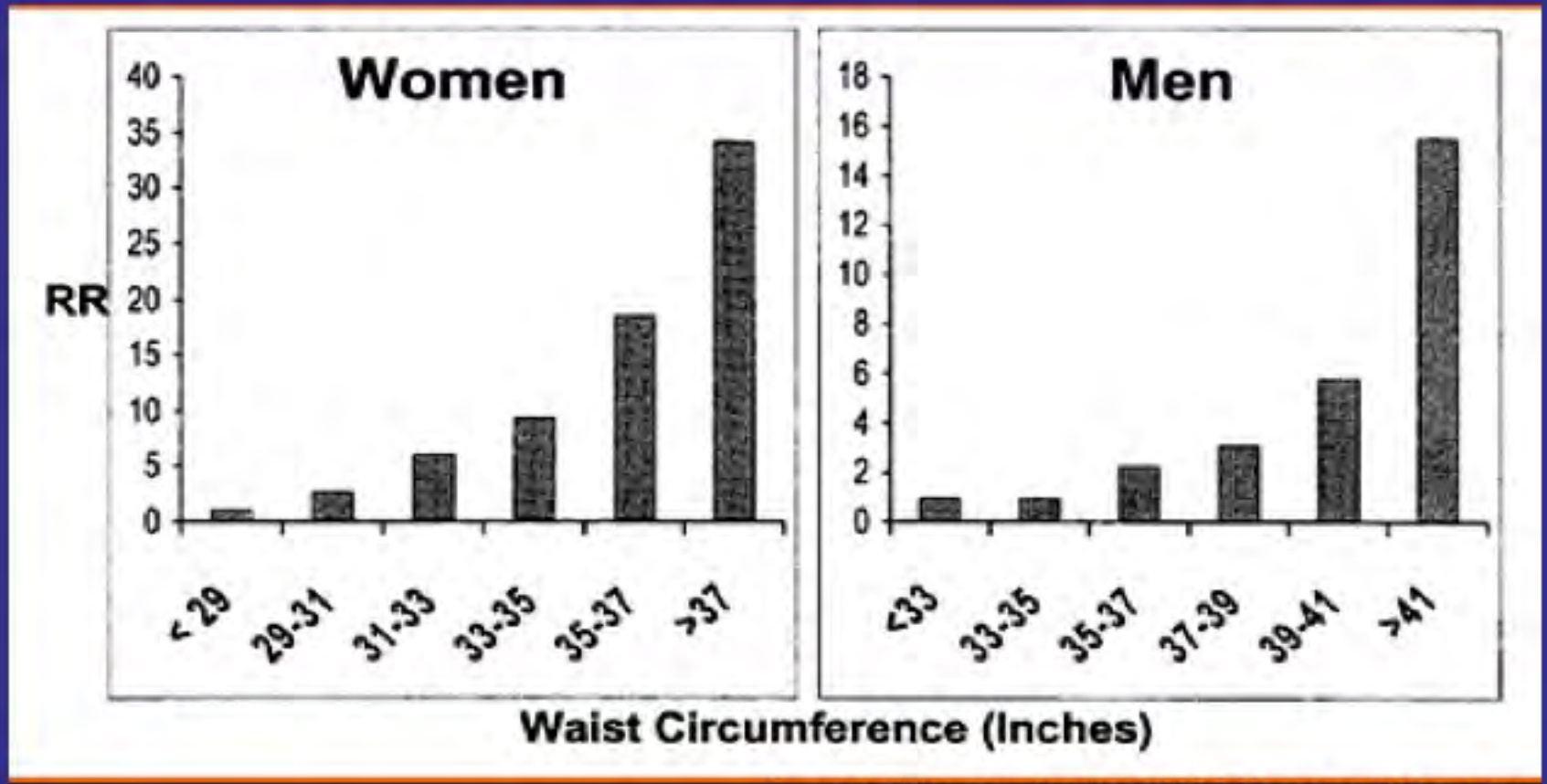
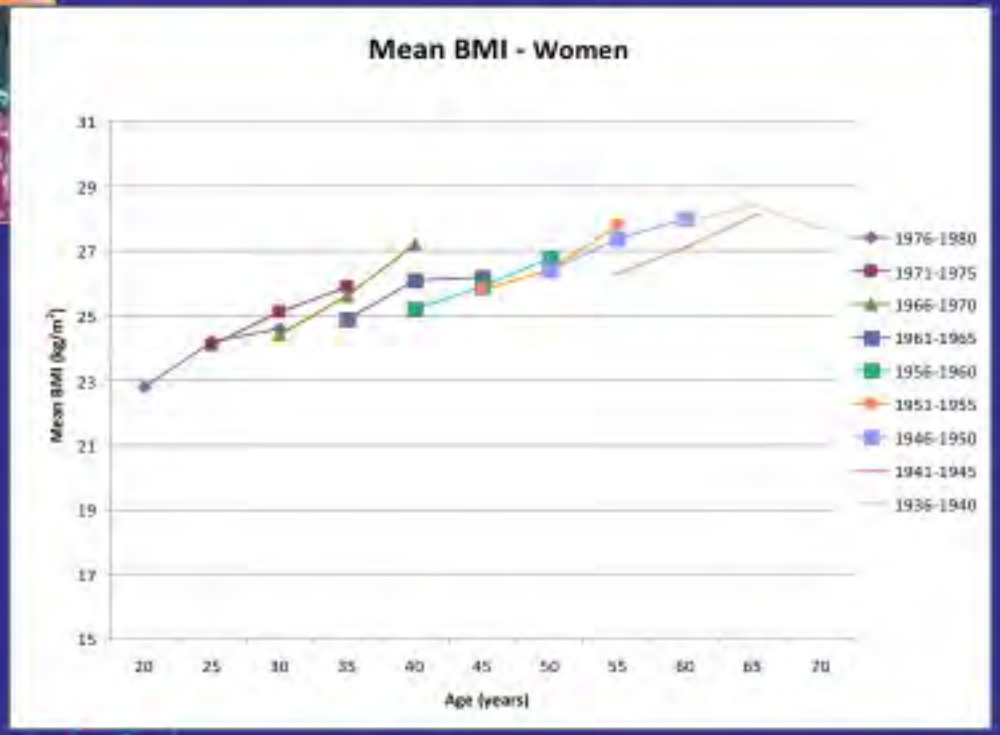
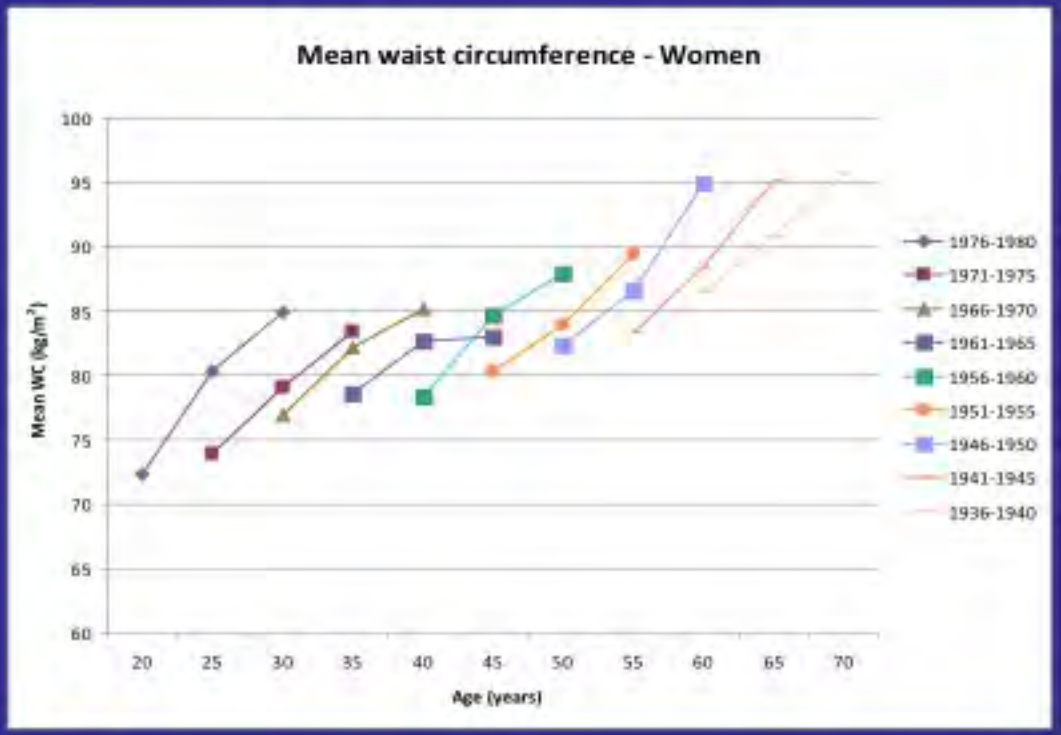
Large waist circumference promotes Type 2 Diabetes (even with normal BMI)



Source: J Womens Health © 2003 Mary Ann Liebert, Inc.

Changing shapes as people age
Scottish Health Surveys 1998-2008





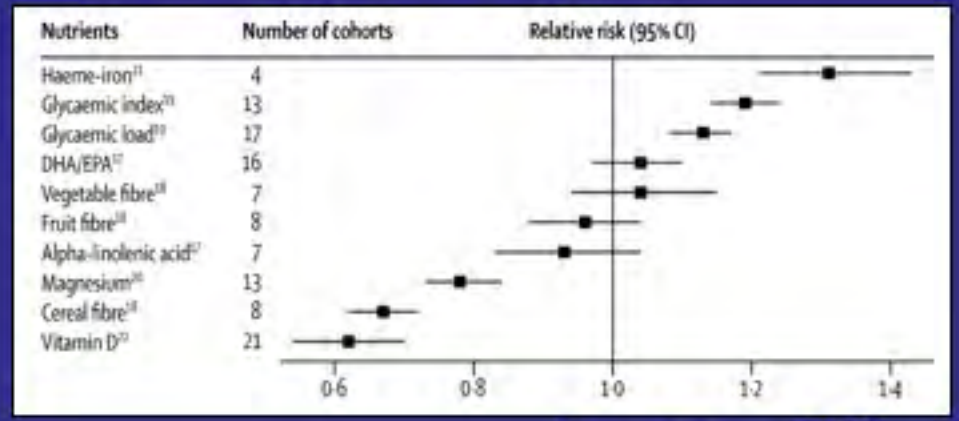
Women are continuing to get fatter even when Weight/BMI is not increasing much - 'Sarcopenic Obesity'

Lean et al, Int J Obesity 2012

Diabetes Prevention: weight control is vital

- DPP and DPS: mean 4kg weight loss and exercise prevented most progression from IGT to T2DM (57% prevented)
  - Weight loss is the dominant element (Torgerson, XENDOS trial)
  - No need for LELD/VLED

- Additional diabetes prevention
  - Regular physical activity (increase type-1 muscle fibres)
  - Low saturated fat diet
  - Fruit and vegetables
  - Magnesium
  - Cereal fibre
  - Low GI



The Counterweight Project

Audit/Needs Assessment
setting priorities

Practice
Training
setting
guidelines

Intervention Programme
measuring performance

Evaluation
improving
performance

Evaluate

Feedback

Improve

(Kai-zen)

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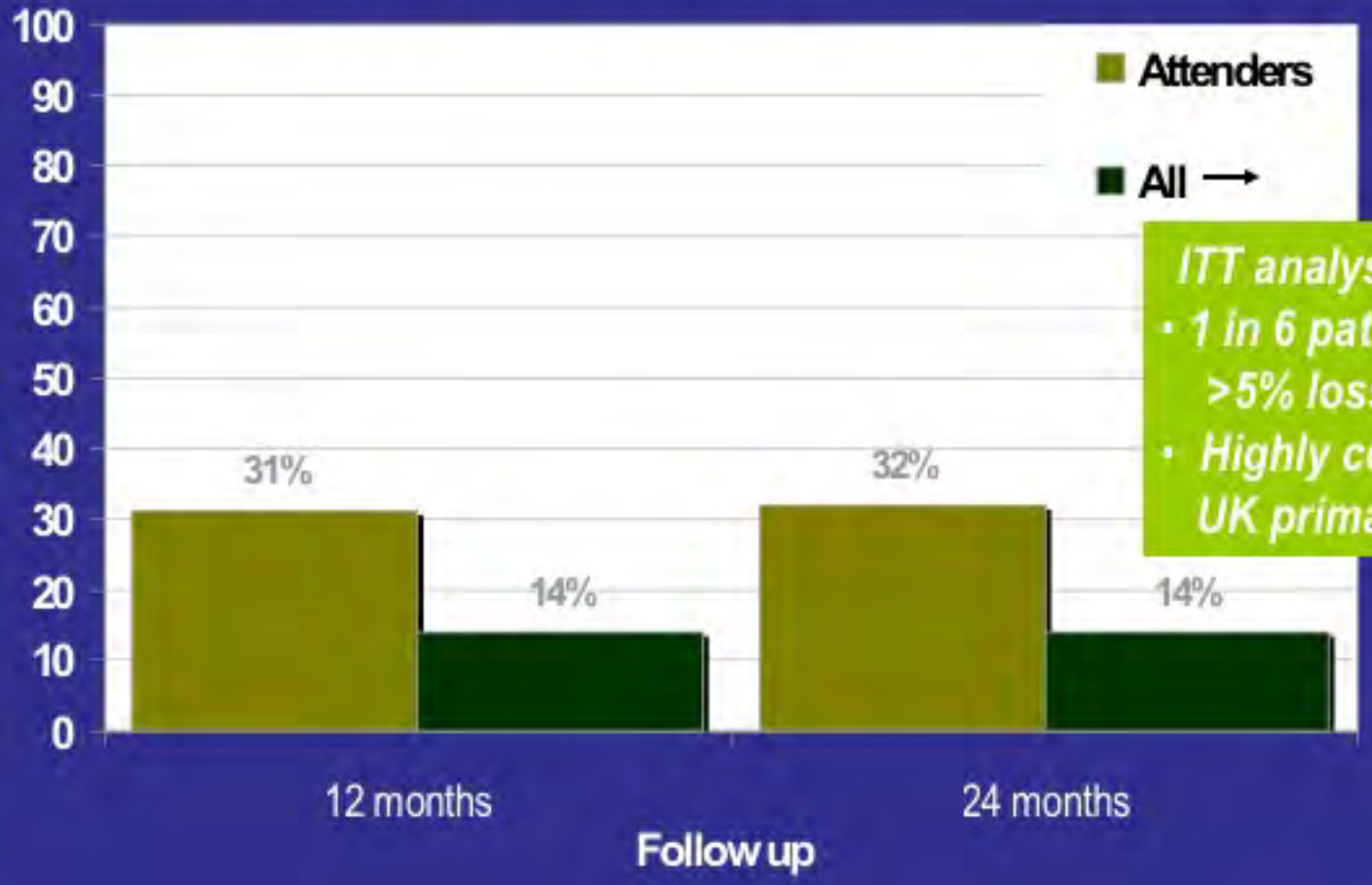
Counterweight: evidence-based multi-facetted programme achieving targets in real life

Ross et al, Br J Gen Practice. 2008; Lean et al, Int J Clin Practice 2010



% achieving ≥5% wt loss target

ITT analysis
- *1 in 6 patients achieved >5% loss at 12m & 24m*
- *Highly cost-efficient in UK primary care*

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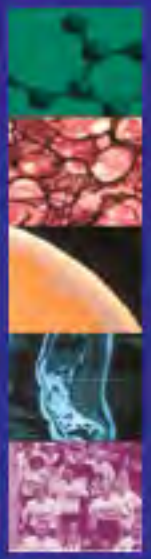

How good are the Counterweight results?

• Original Evaluation: (n = 1906)	1 in 6 maintain >5% weight loss at 12 or 24 months (1 in 3 attenders)
• Scottish Govt. Evaluation: (n = 6715)	1 in 10 maintain >5% weight loss at 12 months (1 in 3 attenders)
c.f. Smoking Cessation	1 in 14 quit at 12 months

What do patients actually want to lose? (And doctors)

'2 or 3 stones' (15-21kg)

Family Practice 2012

Br. J. General Practice 2008

ISD Scotland 2011 May

Int J Obes 1999

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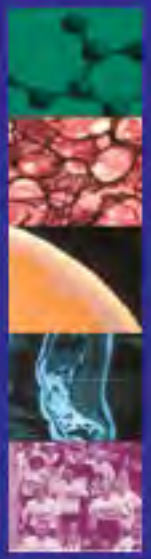
Counterweight: evidence-based multi-facetted programme achieving targets in real life

Ross et al, Br J Gen Practice. 2008; Lean et al, Int J Clin Practice 2010



Only 2% maintain >15kg loss at 12-24 months

% achieving ≥5% wt loss target

ITT analysis

- *1 in 6 patients achieved >5% loss at 12m & 24m*
- *Highly cost-efficient in UK primary care*

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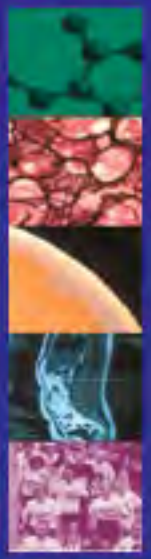
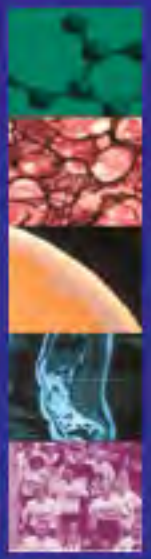


Severe obesity and T2DM prevalence:
estimates from a systematic review

BMI (kg/m^2)	Diabetes Prevalence
30-40	10%
40-50	15%
50-60	15-30%
60-70	20-30%
> 70	30-50%

Grieve, Fenwick & Lean. Obesity Reviews, 2013

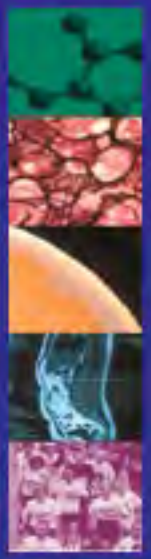


The new epidemic: Severe and complicated obesity

SIGN 115: Management of Obesity 2010

"In patients with BMI>35 kg/m^2 obesity-related comorbidities are likely to be present therefore weight loss interventions should be targeted to improving these comorbidities; in many individuals **a greater than 15-20% weight loss (will always be over 10 kg) will be required to obtain a sustained improvement in comorbidity"**.

Current prevalence of BMI >35 = 9%



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SIGN 115: Management of Obesity 2010

Corrected!

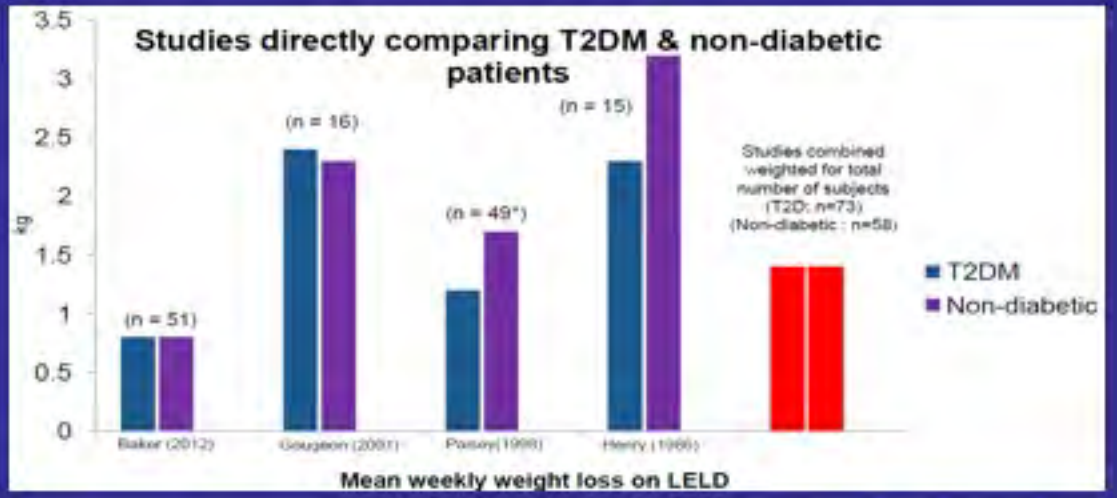
"In patients with BMI>35 kg/m^2 obesity-related comorbidities are likely to be present therefore weight loss interventions should be targeted to improving these comorbidities; in many individuals **a greater than 15-20kg weight loss (will always be over 10%) will be required to obtain a sustained improvement in comorbidity"**.

Current prevalence of BMI >35 = 9%

Weight loss for people with T2DM

- With conventional diets, they lose less than non-diabetic people
  - Already doing their best with diet
  - Distracted by having to take 6-8 different drugs every day
  - Insulin and sulphonylureas increase weight
  - Metabolic rate falls when diabetes is better controlled

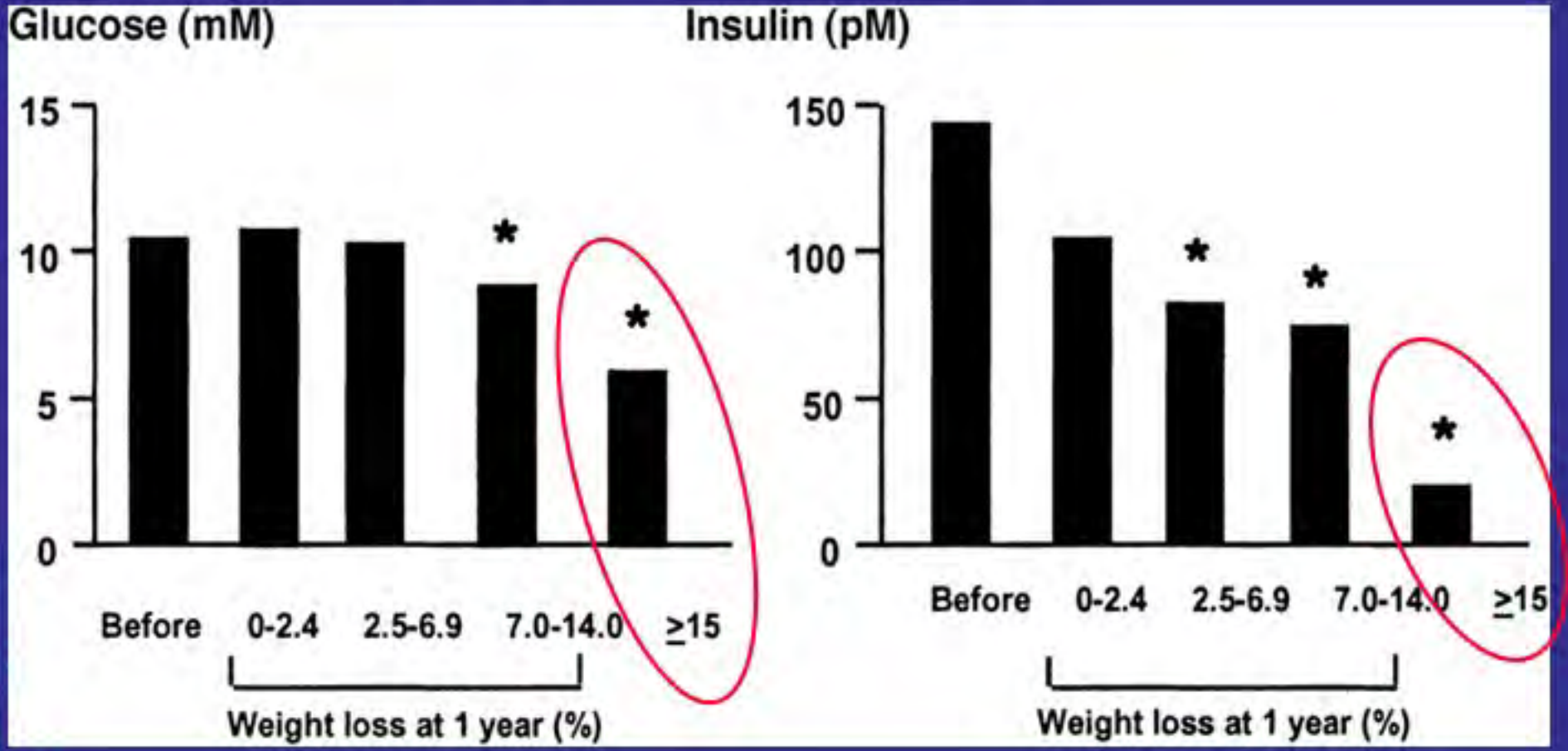
- **With VLCD/ formula diets, they lose the same amount**



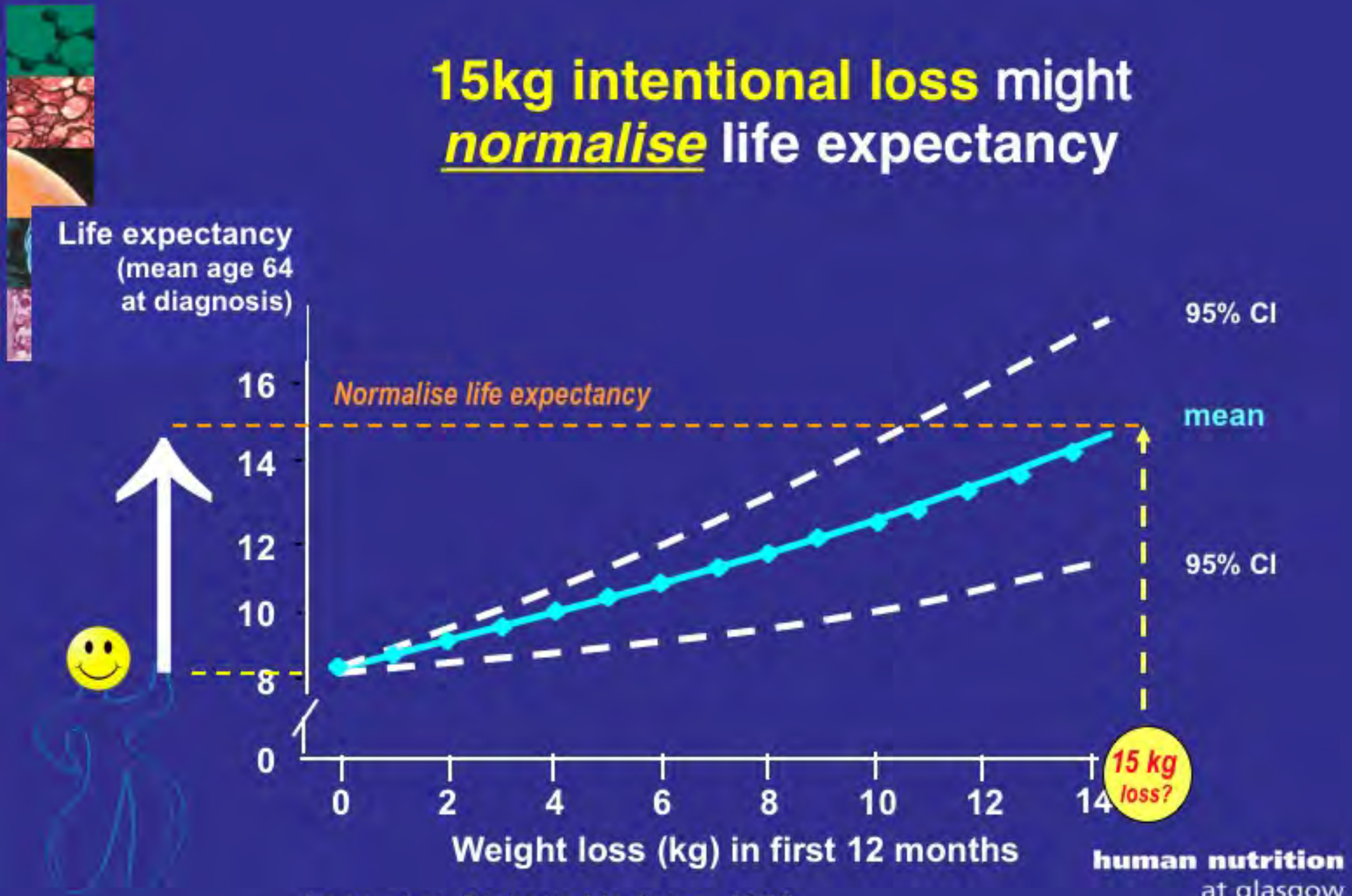
Leslie, Taylor & Lean, 2014 Diabetologia under review

Weight-loss >15% normalises insulin and glucose at 12 months in T2DM patients

Wing et al. Klein, S. Obesity Research (2001)



15kg intentional loss might *normalise* life expectancy



Lean et al. Diabetic Medicine, 1990

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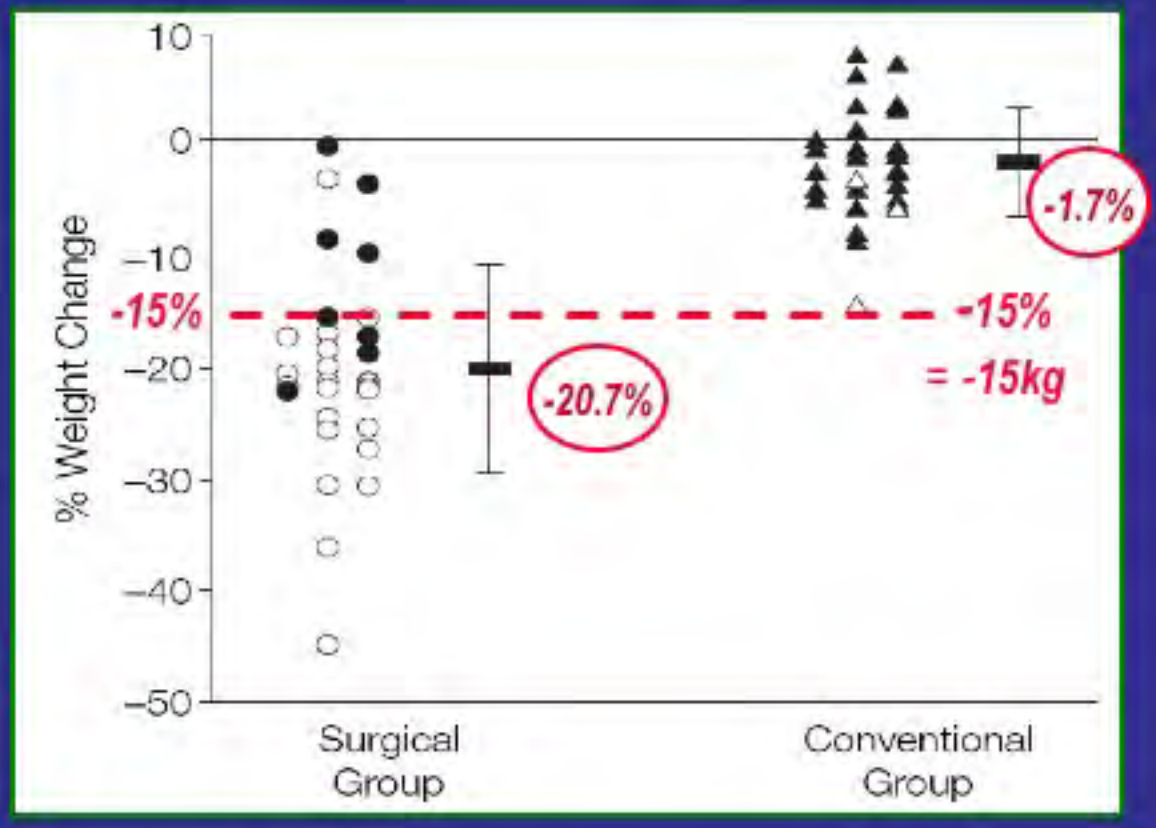
15 kg weight loss normalises glucose tolerance: 2-year RCT, gastric band vs diet advice



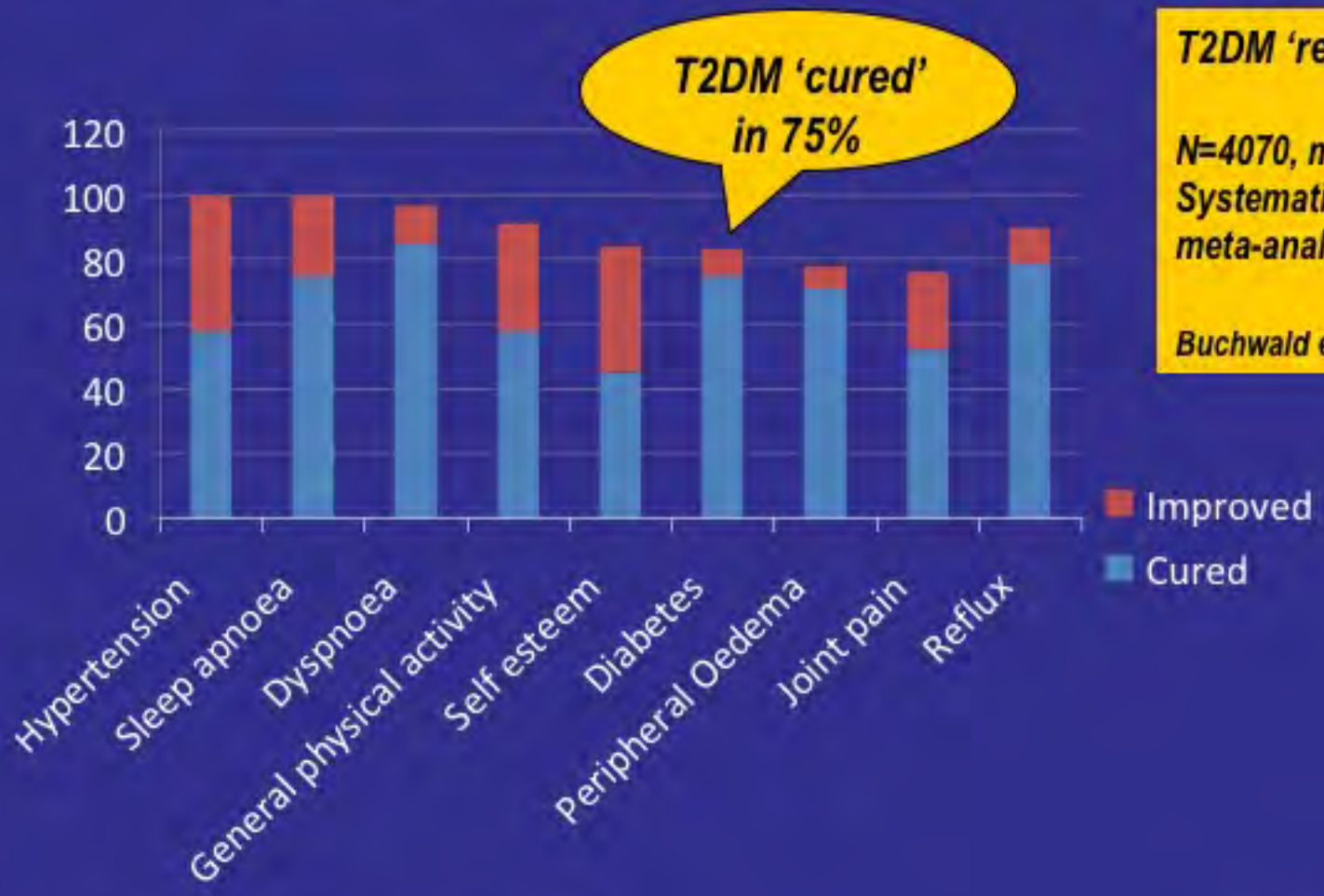
Conventional group
△ Achieved remission of type 2 diabetes — 13%
▲ Did not achieve remission of type 2 diabetes

Surgical group
○ Achieved remission of type 2 diabetes — 73%
● Did not achieve remission of type 2 diabetes

Dixon et al (2008) JAMA

Multiple clinical benefits from major weight loss

4 y after laparoscopic adjustable gastric banding



T2DM 'resolved' in 78%

N=4070, mean age 40, BMI 48, Systematic review and meta-analysis

Buchwald et al Am J Med, 2009

Frigg et al. Obes Surg, 2004

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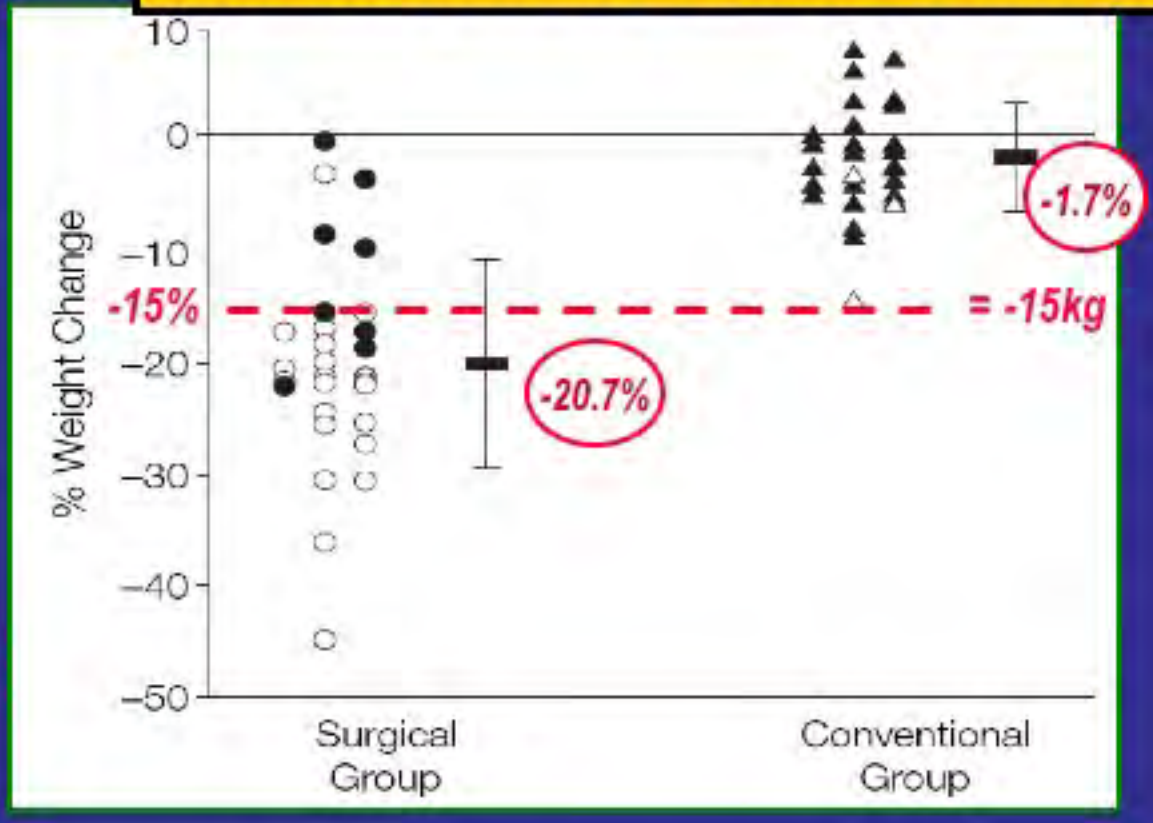
15 kg weight loss normalises glucose tolerance:
2-year RCT, gastric band vs diet advice

Can we achieve similar results without surgery?



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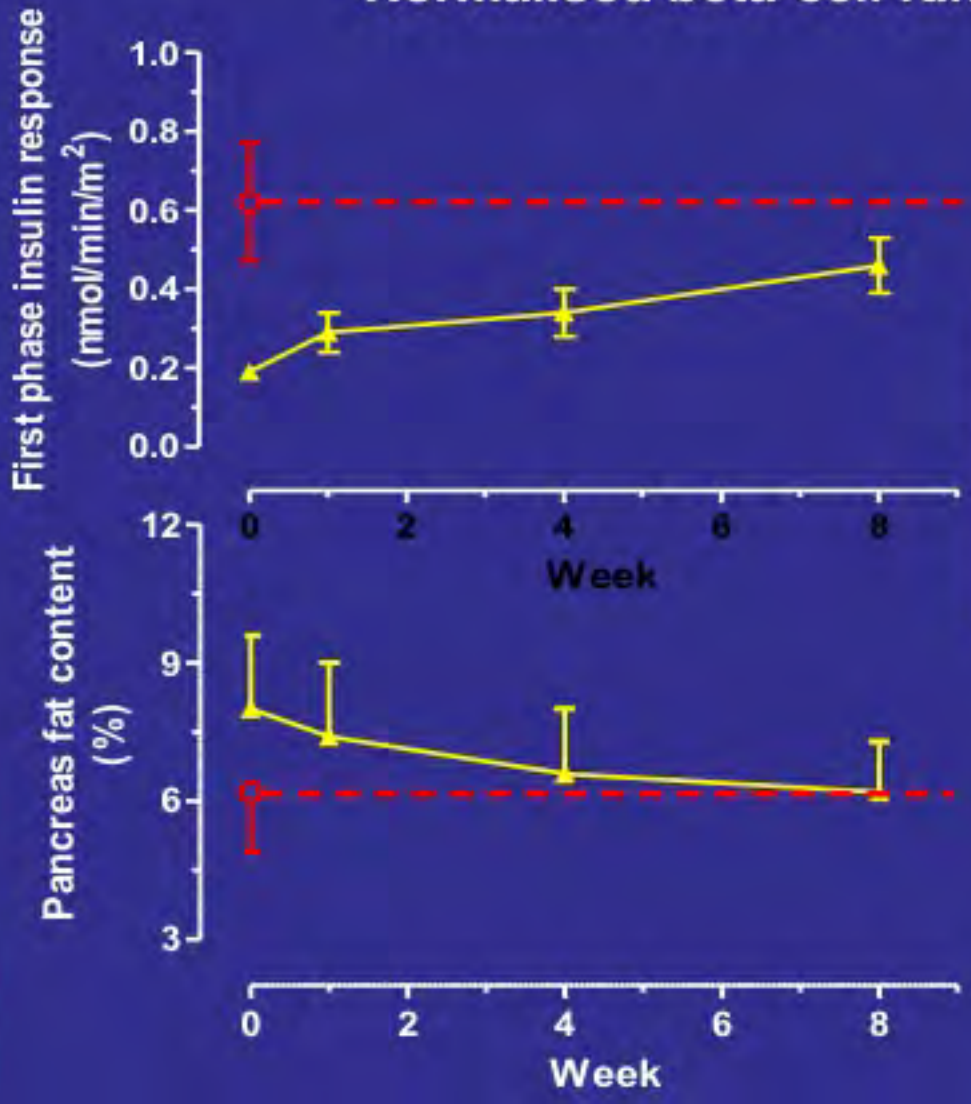
- △ Achieved remission of type 2 diabetes — 13%
- ▲ Did not achieve remission of type 2 diabetes

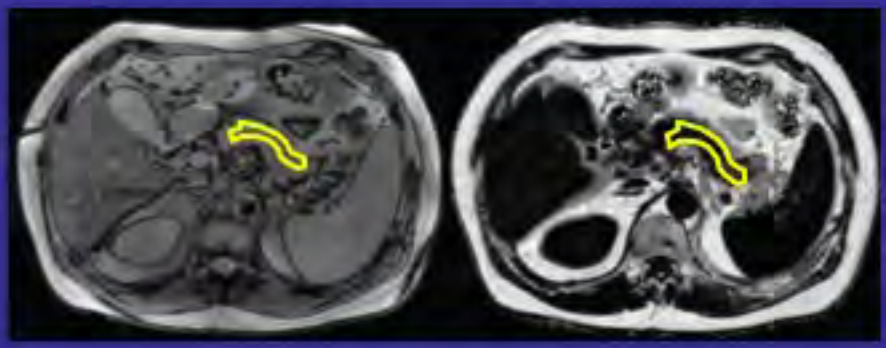
Surgical group
- ○ Achieved remission of type 2 diabetes — 73%
- ● Did not achieve remission of type 2 diabetes

Dixon et al (2008) JAMA

15kg weight loss on 450kcal/d diet

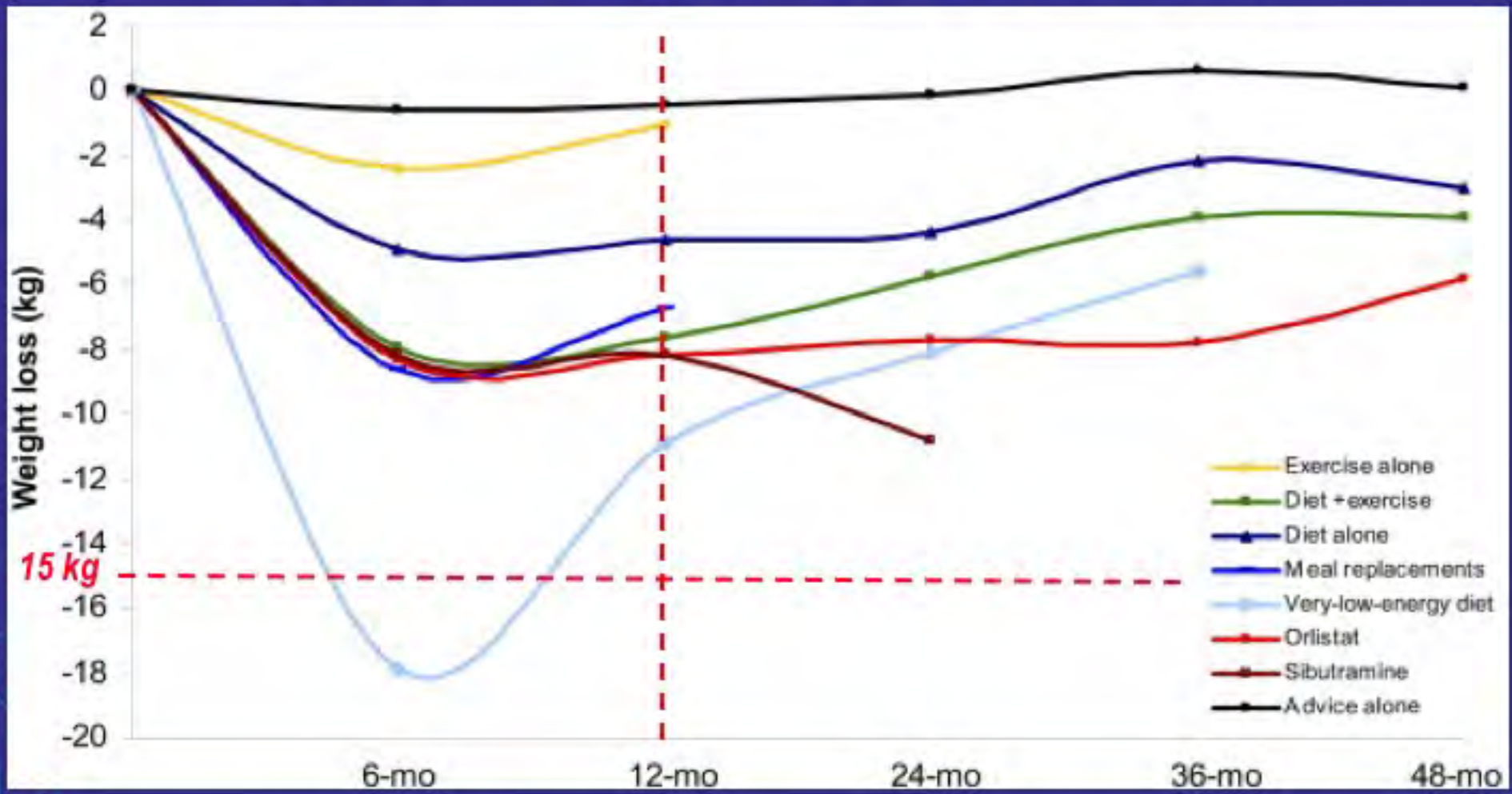
Normalised beta-cell function and pancreas fat





Lim et al, Diabetologia 2011

Meta-analysis of non-surgical trials with 1-year follow-up. (*Franz MJ et al JADA 2007)*



Average weight loss in subjects completing 1-year
80 studies, n = 26,455, completers =18,199 (69%)

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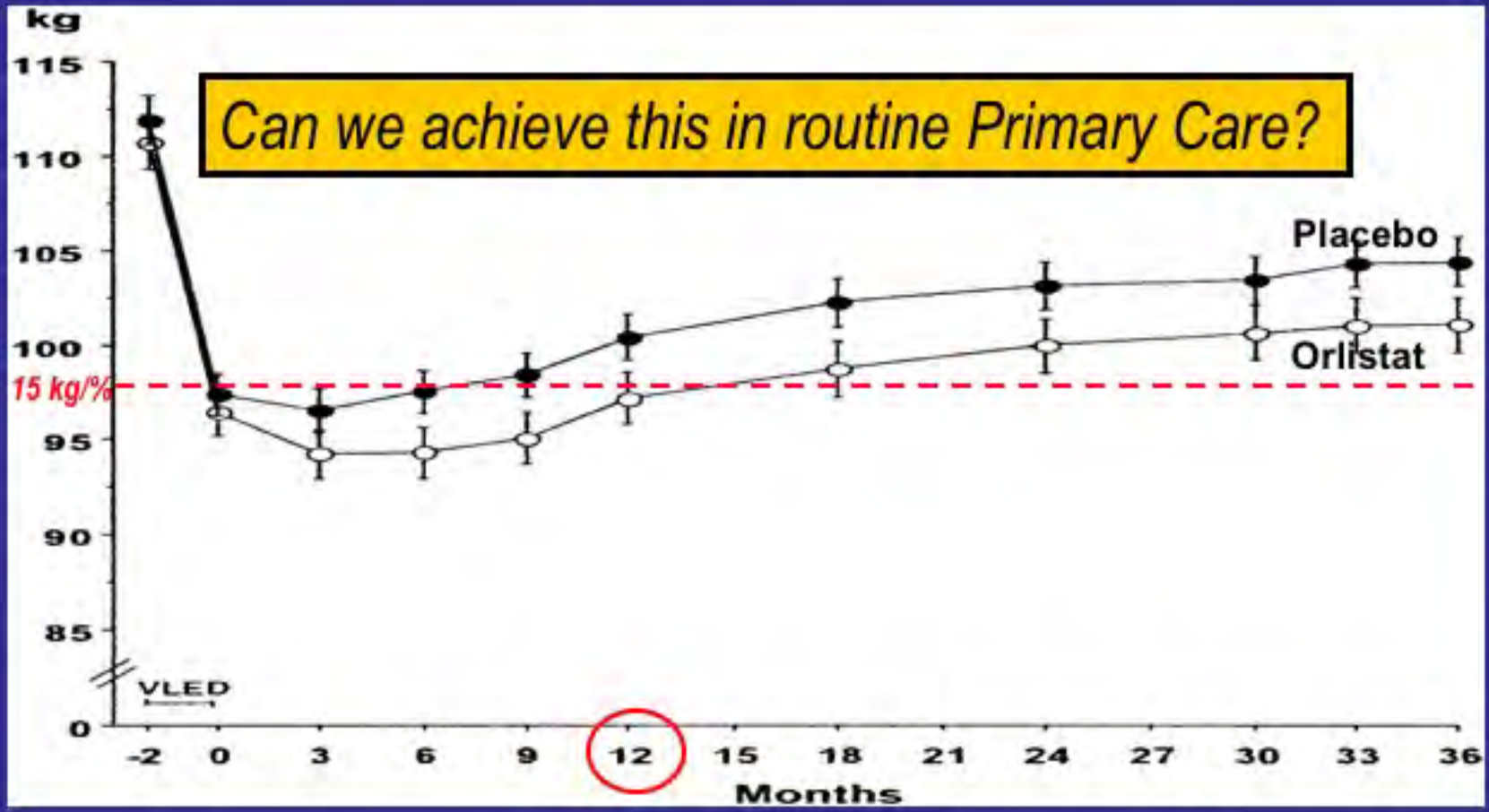
Weight maintenance with orlistat after VLED

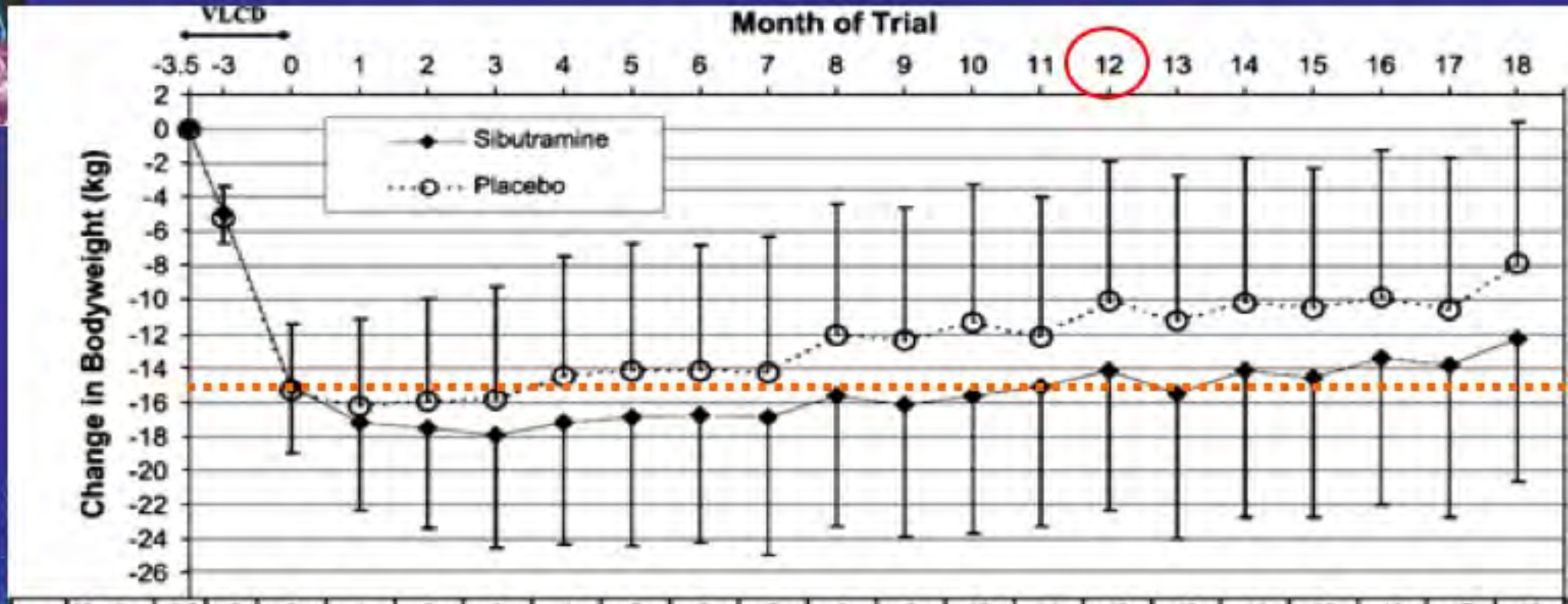
50% of attenders maintained >15kg loss at 12m

Richelsen et al Diabetes Care; 2007



Combining VLED with sibutramine for long-term maintenance, in a GP setting

Mathus-Vliegen EMH for Balance Study Group Eur J Clin Nutr 2005

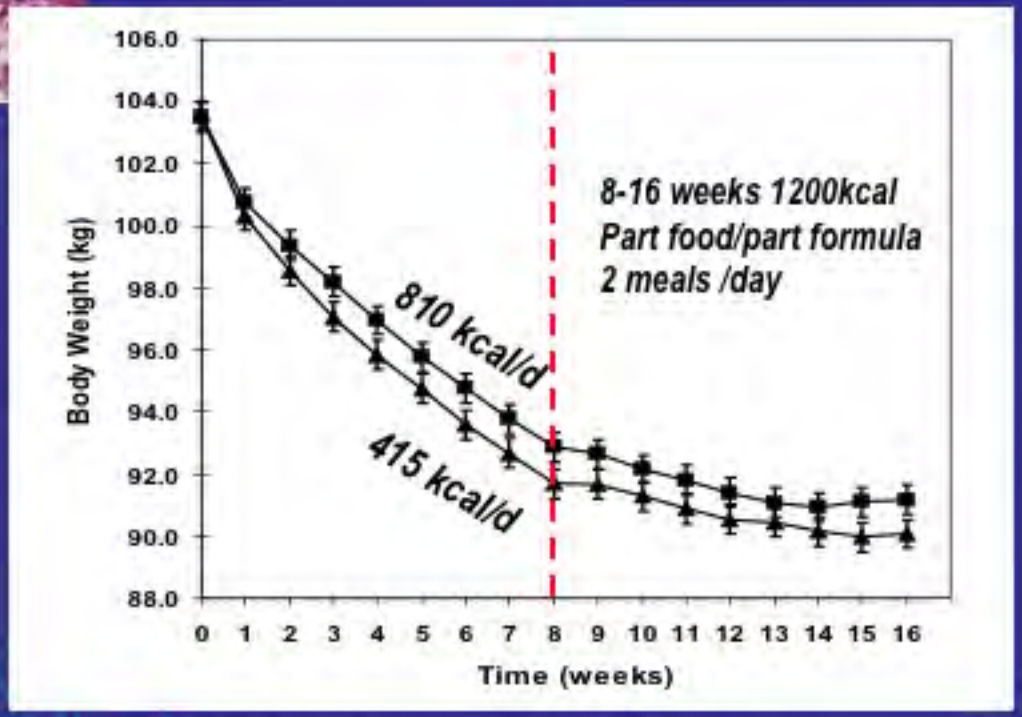


	Month	-3.5	-3	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Sbt	N=	94	94	94	90	90	88	86	81	83	80	74	74	68	67	76	63	61	57	56	49	62
Pcb	N=	95	95	95	93	91	90	88	86	85	78	72	71	68	61	78	56	50	46	47	34	58

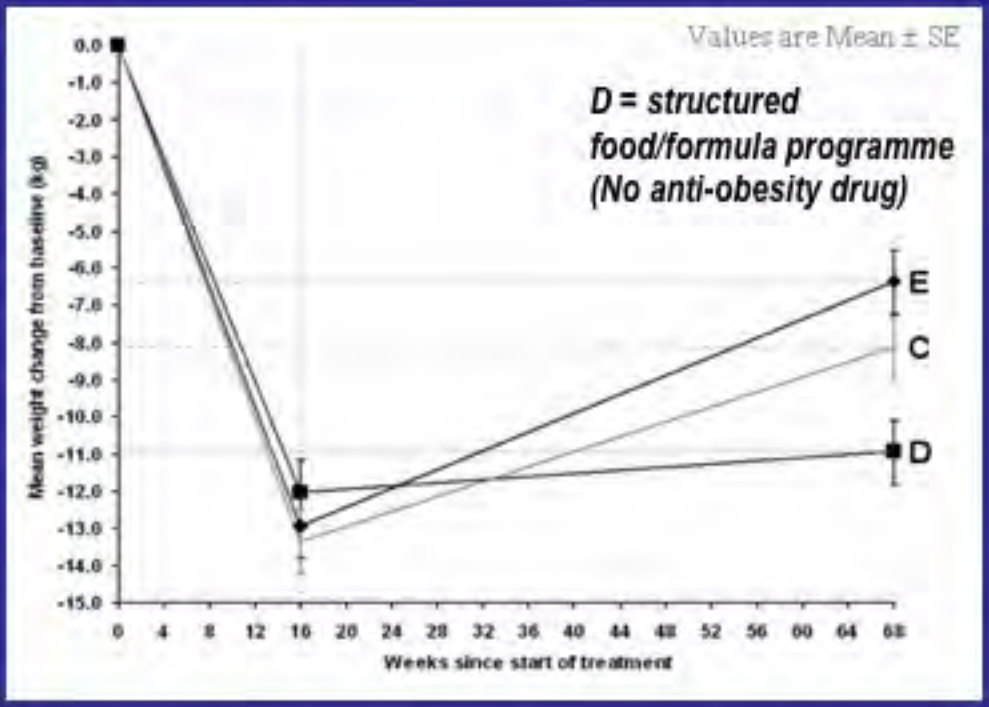
Little difference between 415kcal VLED or 810kcal LED

Copenhagen Weight Loss in Knee Osteoarthritis trial

(Bliddal et al, secondary care, dietitian managed)



No difference in weight loss
n=96 per group



Better maintenance with a structured programme
n=64 per group

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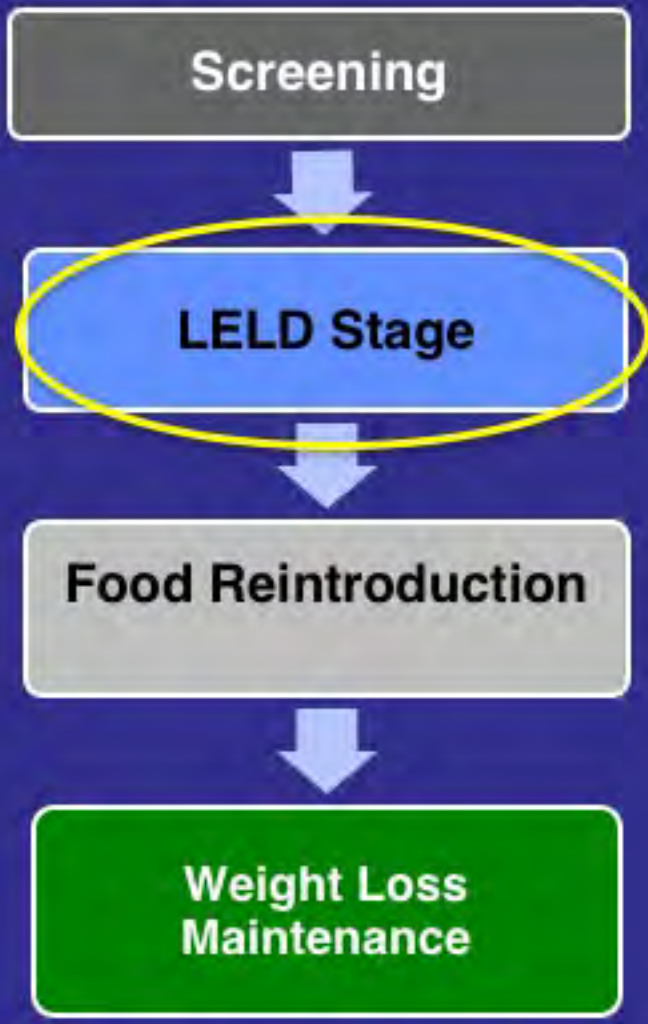
Counterweight-Plus - Protocol

Nutritionally complete LELD either:

1) Homemade (811calories/day)
2) Commercial (832calories/day)
   - Cambridge Weight Plan
3) Mix and match

Plus:

- Structured patient education
  - Step down approach optional
- >2.25l fluid per day (4 pints)
- Fibre supplement



Lean et al , Br J GP (2013)

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Weight Loss Maintenance- Protocol

Stepped Food Reintroduction

- Introduce one 360-400 kcal meal
- Add a meal every two weeks
- Meals based on eatwell plate
- Offer Orlistat

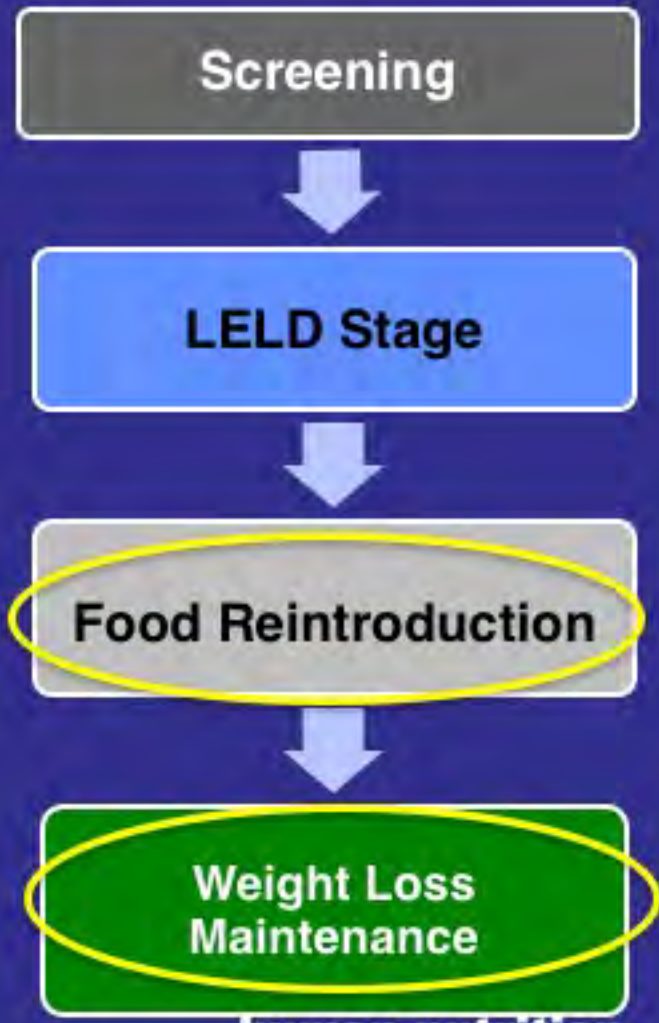
Maintenance

- Low fat diet (30% fat)
- Estimate 500 kcal/d deficit
- 2500 kcal/d upper limit
- Behavioural strategies

Relapse Management

- Offer orlistat
- Second attempt LELD stage

Lean et al , Br J GP (2013)



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Counterweight LELD Feasibility Study

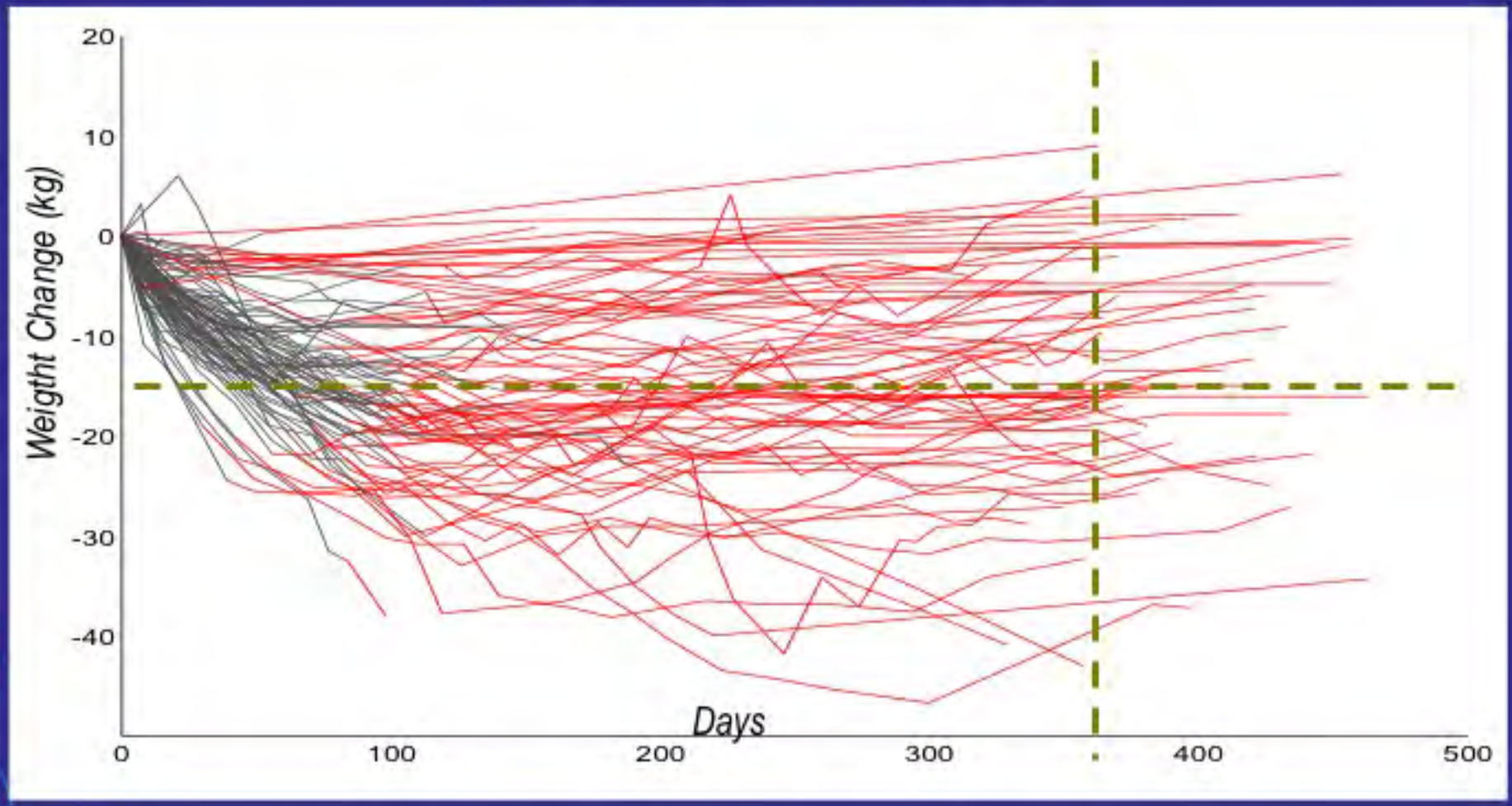
- 22 general practices in 7 Scottish Health Boards took part
- 6 practice nurses and 8 dietitians trained to deliver it
- No extra funding

- 91 patients entered over 6 months
- 78% women, mean BMI 48 (131kg)
- Average 14 visits, mean 5 hours contact, over 12 months

- Feasible to deliver in routine primary care
- Highly acceptable to both patients and practitioners
- Demands high personal responsibility, but well supported

Lean et al , Br J General Practice (2013)

Initial weight loss is the main determinant of long-term results



Lean et al , Br J General Practice (2013)

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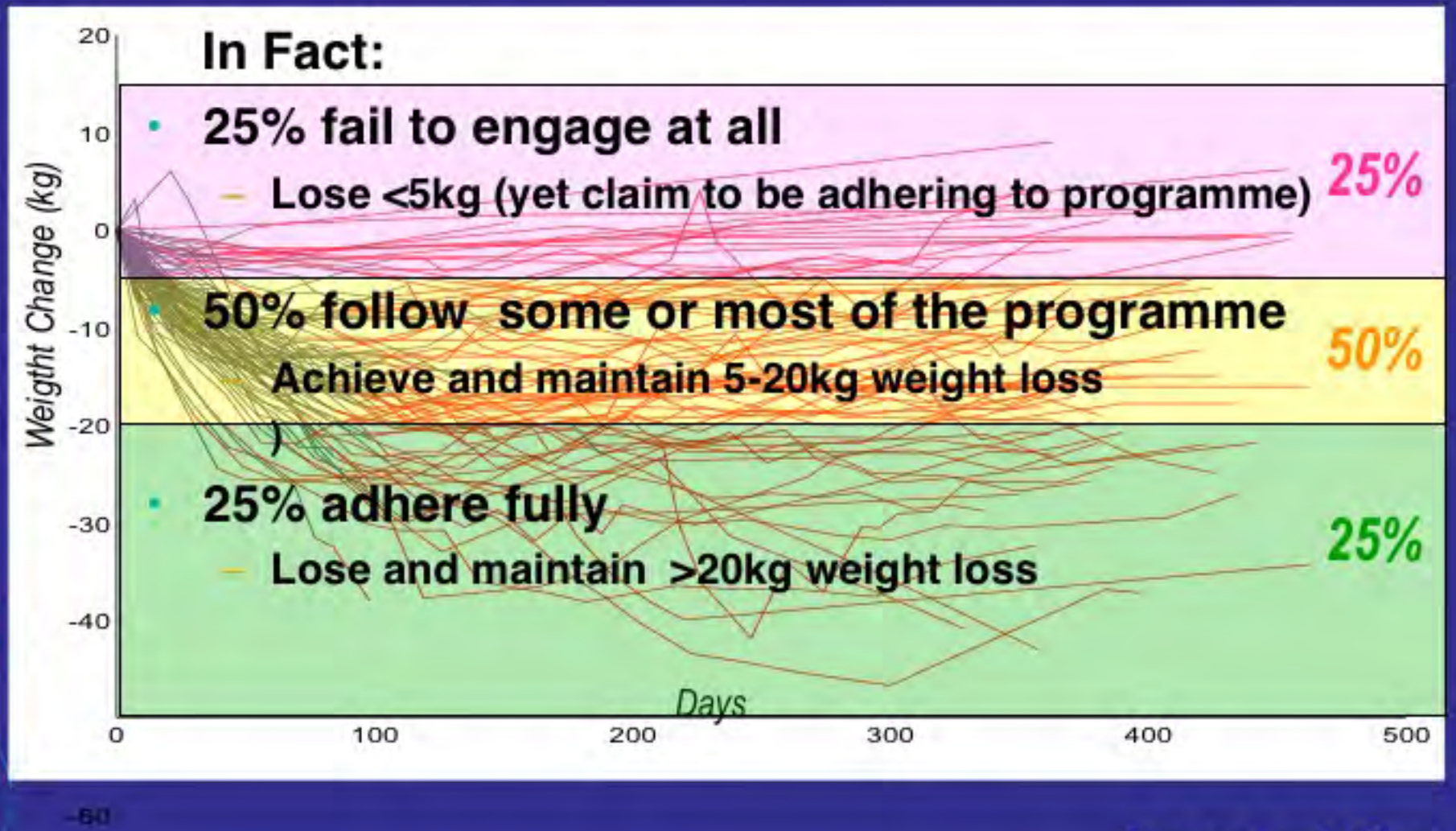
Popular Belief: Patients regain all the weight, or more



Lean et al , Br J General Practice (2013)

'Total Diet Replacement' and structured long-term weight maintenance: Counterweight-Plus

Maintaining weight loss ≥15kg at **12 months:**

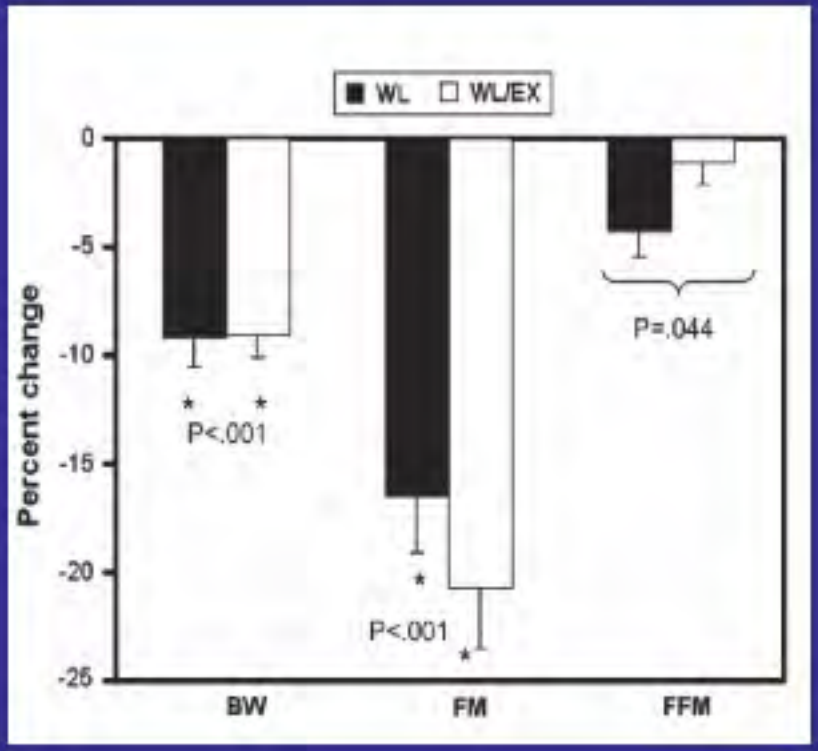
- 33% of all 91 patients
- 44% of patients with a known 12-month weight
- 57% of those who lost >15kg on LELD

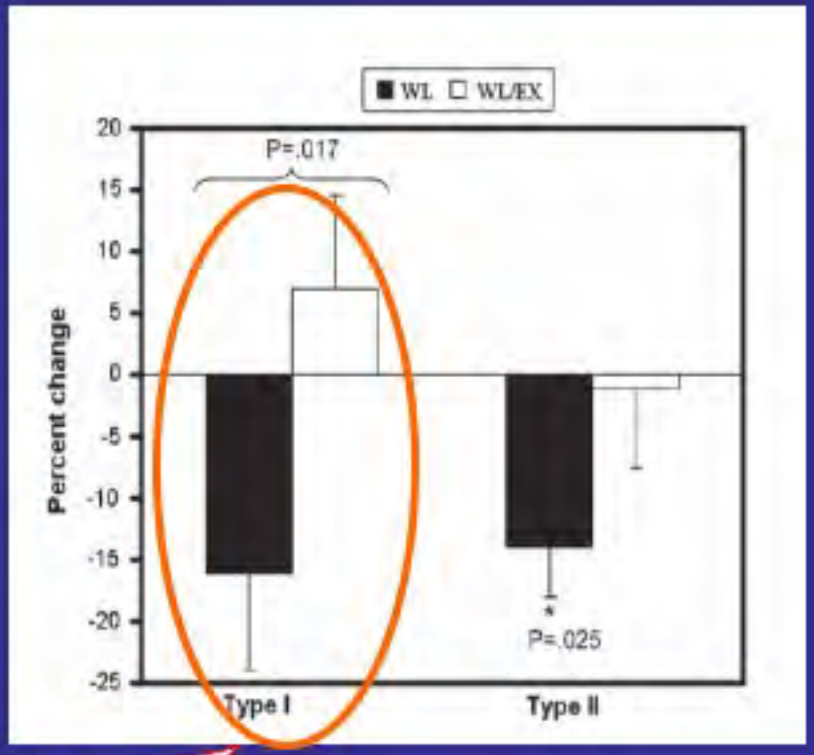
- **Highly cost-effective:**
  - 3-5 times as many can lose >15kg as with bariatric surgery

Lean et al, Br J General Practice (2013)

Weight loss depletes muscle mass and function if exercise is not included

(Chomenowski et al, LOOKAHEAD)





Oxidative, slow-twitch type-1 muscle fibres

Population response to information on reversibility of Type 2 diabetes

- T2DM people want to be non-diabetic
- Many can lose 15kg
- Most become non-diabetic

S. Steven, E. L. Lim and R. Taylor

Magnetic Resonance Centre, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK

Accepted 10 January 2013

Abstract

Aims Following publication of the Counterpoint Study (on the reversibility of Type 2 diabetes using a very low energy diet), the extent of public interest prompted the authors to make available, on a website, general information about reversing diabetes. Shortly thereafter, individuals began to feed back their personal experiences of attempting to reverse their diabetes. We have collated this information on the effects of energy restriction in motivated individuals with Type 2 diabetes that has been achieved outside a research setting.

Methods Emails, letters and telephone communications received between July 2011 and September 2012 were evaluated (n = 77: 66 men, 11 women). Median diabetes duration was 5.5 years (3 months–28 years). Reversal of diabetes was defined as achieving fasting capillary blood glucose < 6.1 mmol/l and/or, if available, HbA_{1c} less than 43 mmol/mol (6.1%) off treatment.

Results Self-reported weight fell from 96.7 ± 17.5 kg at baseline to 81.9 ± 14.8 kg after weight loss ($P < 0.001$). Self-reported fasting blood glucose levels fell from 8.3 mmol/l (5.9–33.0) to 5.5 mmol/l (4.0–10.0) after the weight loss period ($P < 0.001$). Diabetes reversal was considered to have occurred in 61% of the population. Reversal of diabetes was observed in 80, 63 and 53% of those with > 20, 10–20 and < 10 kg weight loss, respectively. There was a significant correlation between degree of weight loss and reported fasting glucose levels (Rs −0.38, $P = 0.006$). Reversal rates according to diabetes duration were: short (< 4 years) = 73%, medium (4–8 years) = 56% and long (> 8 years) = 43%.

Conclusion These data demonstrate that intentional weight loss achieved at home by health-motivated individuals can reverse Type 2 diabetes. Diabetes reversal should be a goal in the management of Type 2 diabetes.

DiRECT

Diabetes Remission Clinical Trial

2013-2018
funded by DiABETES UK
to Mike Lean and Roy Taylor

- Cluster-Randomised Trial: Counterweight-Plus* 810kcal/d LELD and weight maintenance programme vs usual care
  - Both arms follow current clinical guidelines
  - 280 patients, BMI >27, diagnosed T2DM <6 years, not on insulin
- Co-primary endpoints: weight loss >15kg and non-diabetic HbA1c
  - at 12 & 24 months off all drugs (plus life-long clinical monitoring)

- Mechanistic and Magnetic Resonance studies
- Qualitative and process evaluation

- Planned economic analyses

* Supported by Cambridge Weight Plan

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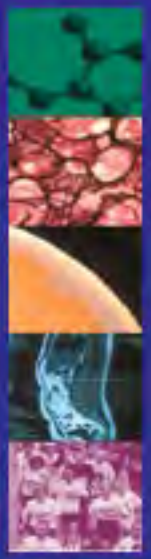

DiRECT
Diabetes Remission Clinical Trial

Mechanistic Studies – Newcastle

(n = 88, at baseline, 3 &12m)

Day 1

Pancreas and liver fat	Abdominal Magnetic Resonance scanning
Beta-cell function	Stepped hyperglycaemic clamp & arginine stimulation, to measure maximal insulin

Day 2

Whole body glucose & lipid oxidation	Indirect calorimetry (fasting & rested)
$VLDL_1$ and VLDL-apoB100 secretion	Intralipid (fat) infusion
PNPLA3 genotyping	

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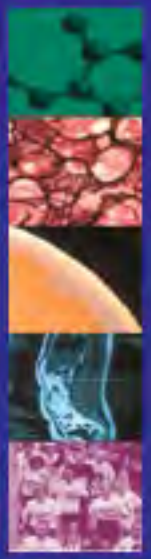

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Qualitative Evaluations

During WL, FR and Maintenance phases

Participants:

Cognitive, affective and social predictors of adherence	Mobile phone based Ecologic Momentary Assessment (EMA)
Barriers, facilitators & strategies for self-control	Semi-structured theory domain interviews
Quality of Life	EQ-5D questionnaire

Health Professionals:

Barriers to implementation & ease of engagement with the intervention	Semi-structured theory domain interviews

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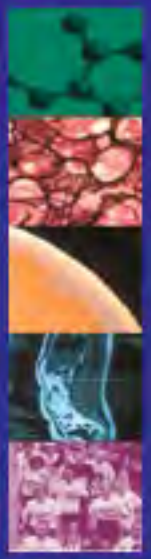

DiRECT
Diabetes Remission Clinical Trial

Team

Principal Investigators

Professor Mike Lean
Professor Roy Taylor

Co-investigators

Professor Ashley Adamson
Professor Ian Ford
Professor John Mathers
Louise McCombie
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Professor Naveed Sattar
Dr Kieran Hollingsworth
Hazel Ross

Study Coordinator

Dr Wilma Leslie

Research Associates

Alison Barnes
Naomi Brosnahan
George Thom

Partners:
Glasgow University, Newcastle University,
Diabetes UK, Counterweight Ltd, Cambridge Weight Plan

NHS
Greater Glasgow and Clyde

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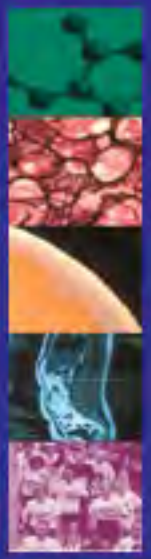


Conclusions

1. 'Well-treated' type 2 diabetes is not a well-treated patient
   - Still a devastating disease, despite drugs and guidelines

2. Being non-diabetic is now a reasonable goal
   - Maintain waist <80 cms (women), <94cms (men)
   - If pre-diabetic: lose 5kg and maintain weight loss
   - If diabetic: lose >15kg and maintain weight loss

3. Personal commitment to weight control is essential
4. Matched professional commitment and training is essential

5. Public Health responsibility is essential to oppose obesogenic commercial and political activities

Routine management of T2DM

1st priority - reduce dietary fats (esp. saturated fat)
and lose >15kg weight, maintaining physical activity

- Not just sugar avoidance
- Not primarily drugs
- Formula diets are more effective than conventional lifestyle advice, and more cost-effective than bariatric surgery

2nd priority - prevent weight gain/ treat obesity in pre-diabetic family members

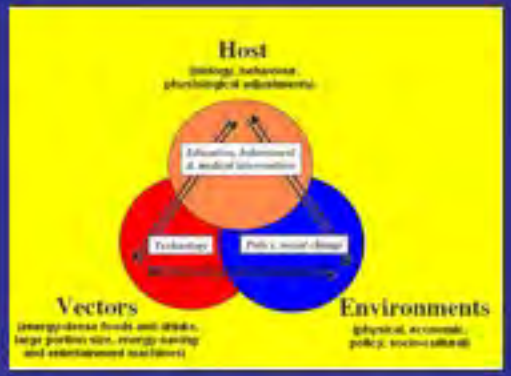
So - Doctors and nurses must be trained, and resourced, to offer:

- Optimal evidence-based diets, for weight loss
- Lifestyle advice & support for long-term weight maintenance

Ethics of treatments for diabetes

- No drug should be prescribed without urging personal responsibility, with professional support, for diet and lifestyle change
- No clinical trial in T2DM patients should be permitted unless optimal diet and lifestyle advice is given to both intervention and placebo arms
- Prescribing physicians should have training and resources to provide optimal evidence-based diet and lifestyle advice
    - AND ACCEPT THAT NOT ALL WILL SUCCEED

Epidemic!*



Medical Responsibility

Optimal medical treatment within available resources

- Diet & lifestyle
- Drugs
- Surgery

Political Responsibility

Government interventions to remove primary causes

- Catering outlets — increasing
- Meals/snacks outside home — increasing
- Portion sizes — increasing

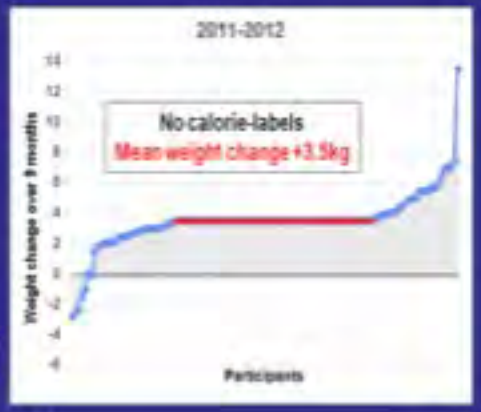
- Physical inactivity……

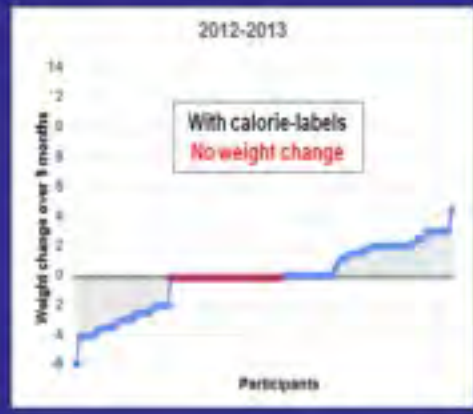
*** WHO: 'Critical Threshold for Intervention'**

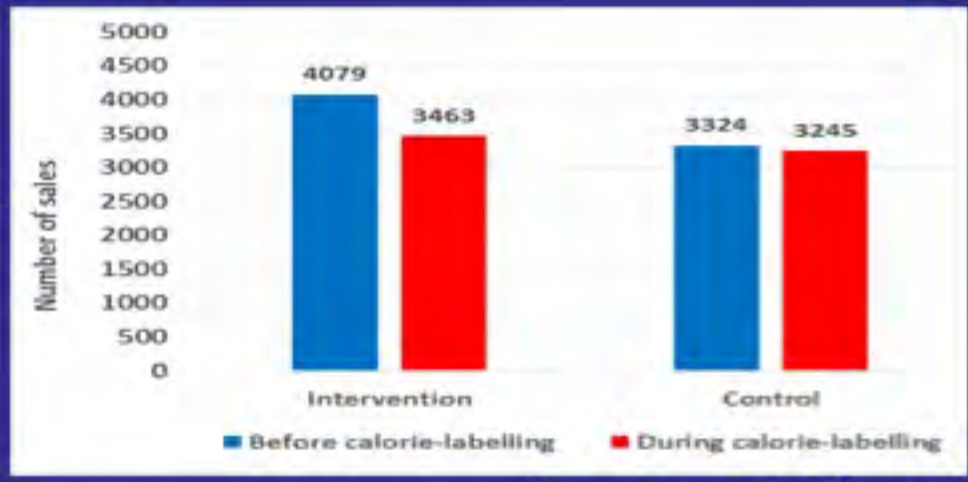
New evidence for primary prevention of obesity:
---------- prominent Calorie-Labelling

- Systematic Review: Overall no effect of calorie labelling, but -124kcal for those who noticed the labels (Nikolaou et al, IJO, 2014)
- Meals currently supplied to young adults are excessively calorie-rich (Nikolaou et al Int J Obesity, 2014)
- Prominent main-meal calorie-labelling prevents weight gain over 9 months in young adults (Nikolaou et al, Obesity 2014)
- Prominent calorie-labelling at self-serve food outlets leads to lower-calorie choices (Nikolaou et al Preventive Medicine, 2014)

(all: Nikolaou, Hankey & Lean, 2014)







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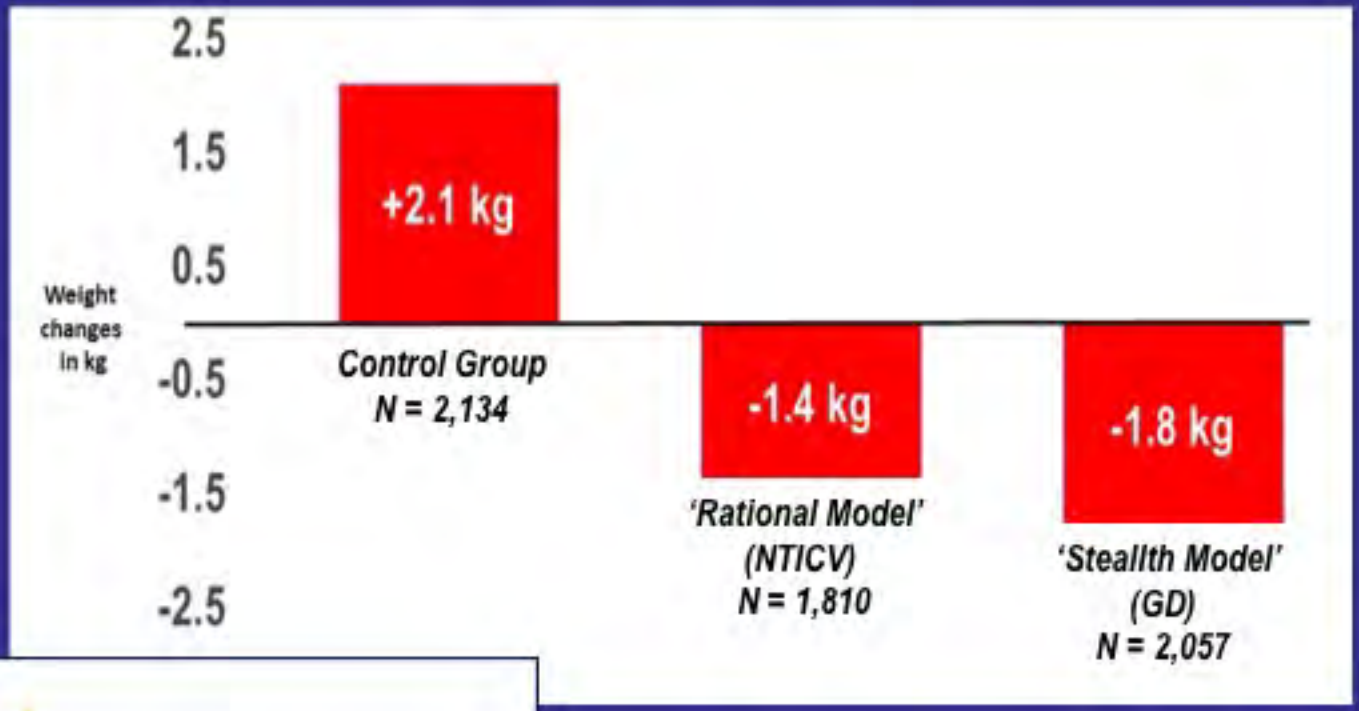
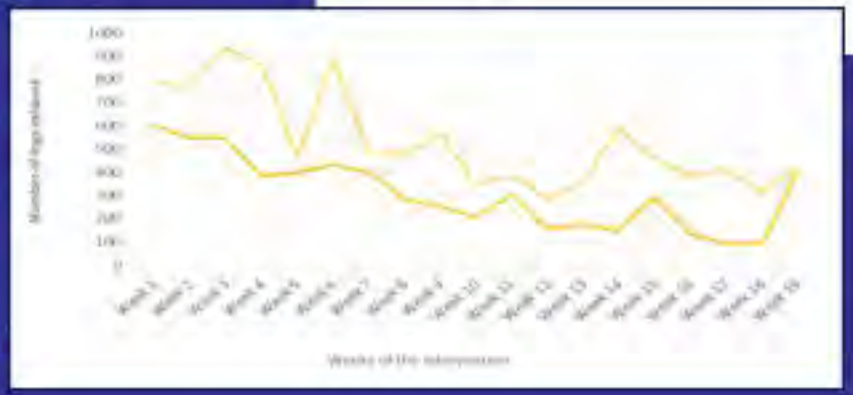
9-month weight changes in 20,975 young adults randomised to an on-line public health intervention





(Nikolaou, Hankey & Lean, under review, 2015)

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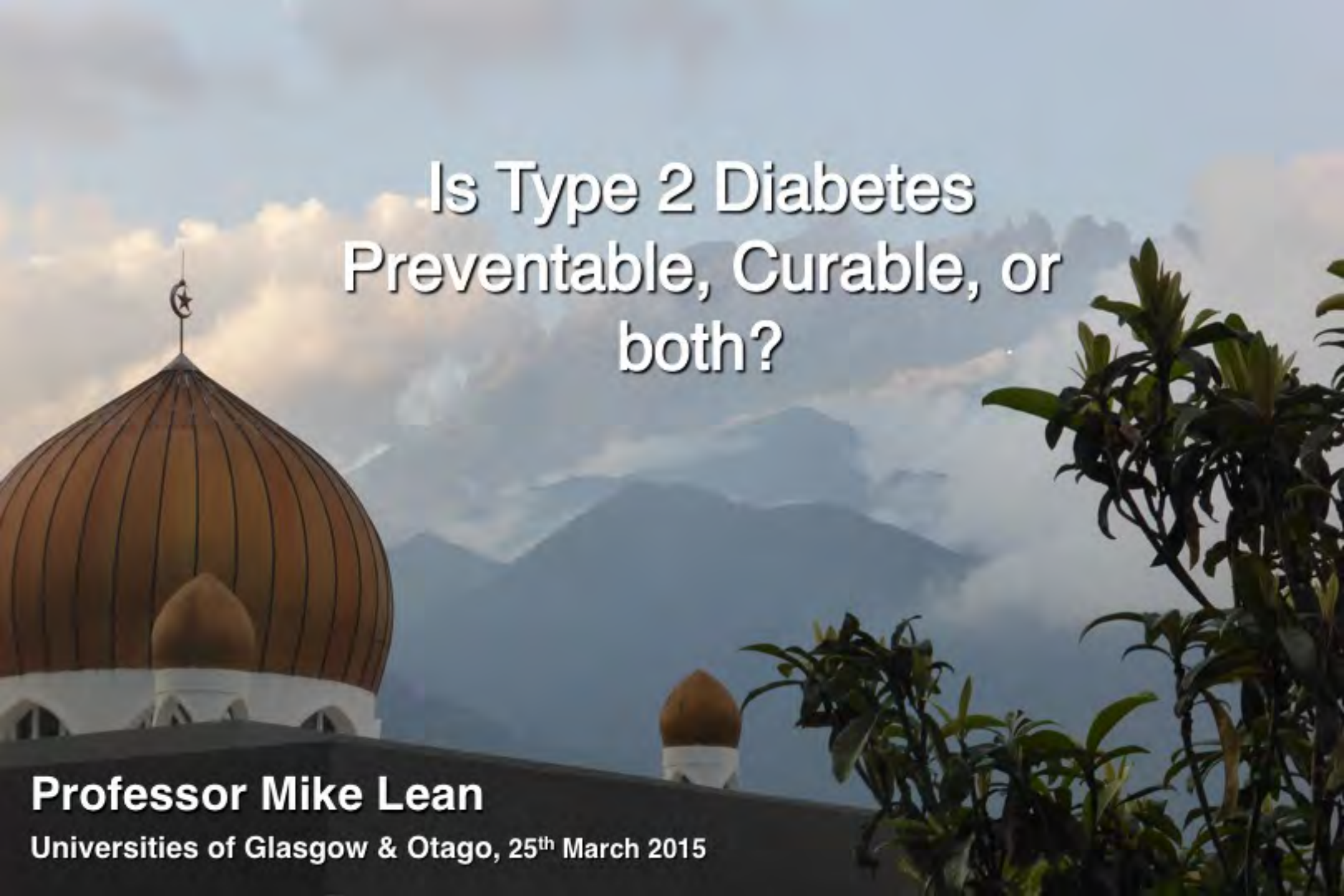
You can all help prevent obesity/diabetes

You can all help prevent obesity/diabetes

(Completely out of Order)

(Completely off the map)


Is Type 2 Diabetes Preventable, Curable, or both?
Professor Mike Lean
Universities of Glasgow & Otago, 25th March 2015


ID KAHANDAMAN DI
GUNTING B.LAGADAN
HUGUAN MANANGNUD
ID NULUHON KINABALU
1888 – 1966
TAMAN
KINABALU
LOW'S PEAK
(4095.2M)
SERVICE TO ALL HUMANITY
ROTARY INTERNATIONAL DISTRICT 3310

KINABALU

MEMPUNYAI

YANG BOLEH
AAN YANG SEJUK,
GI.

NOTICE

SABAH PARKS REGULATIONS REQUIRED THAT ALL PERSON INTENDING TO CLIMB TO THE SUMMIT MUST BE ACCOMPANIED BY A REGISTERED MOUNTAIN GUIDE.

WARNING

DO NOT CLIMB IF YOU ARE SUFFERING FORM OR HAVE A HISTORY OF THE FOLLOWING AILMENTS :-

(1) HEART DISEASE
(2) HYPERTENSION
(3) CRONIC ASTHMA
(4) PEPTIC ULSER
(5) SEVERE ANEMIA
(6) DIABETES
(7) EPILEPTIC FITS
(8) ARTHRITIS
(9) PALPITATION
(10) HEPATITIS (JAUNDICE)
(11) MUSCULAR CRAMPS
(12) OBESITY (OVER WEIGHT)
(13) ANY OTHER SICKNESS THAT MAY BE TRIGGERED BY SEVERE COLD, EXERTION, AND HIGH ALTITUDE.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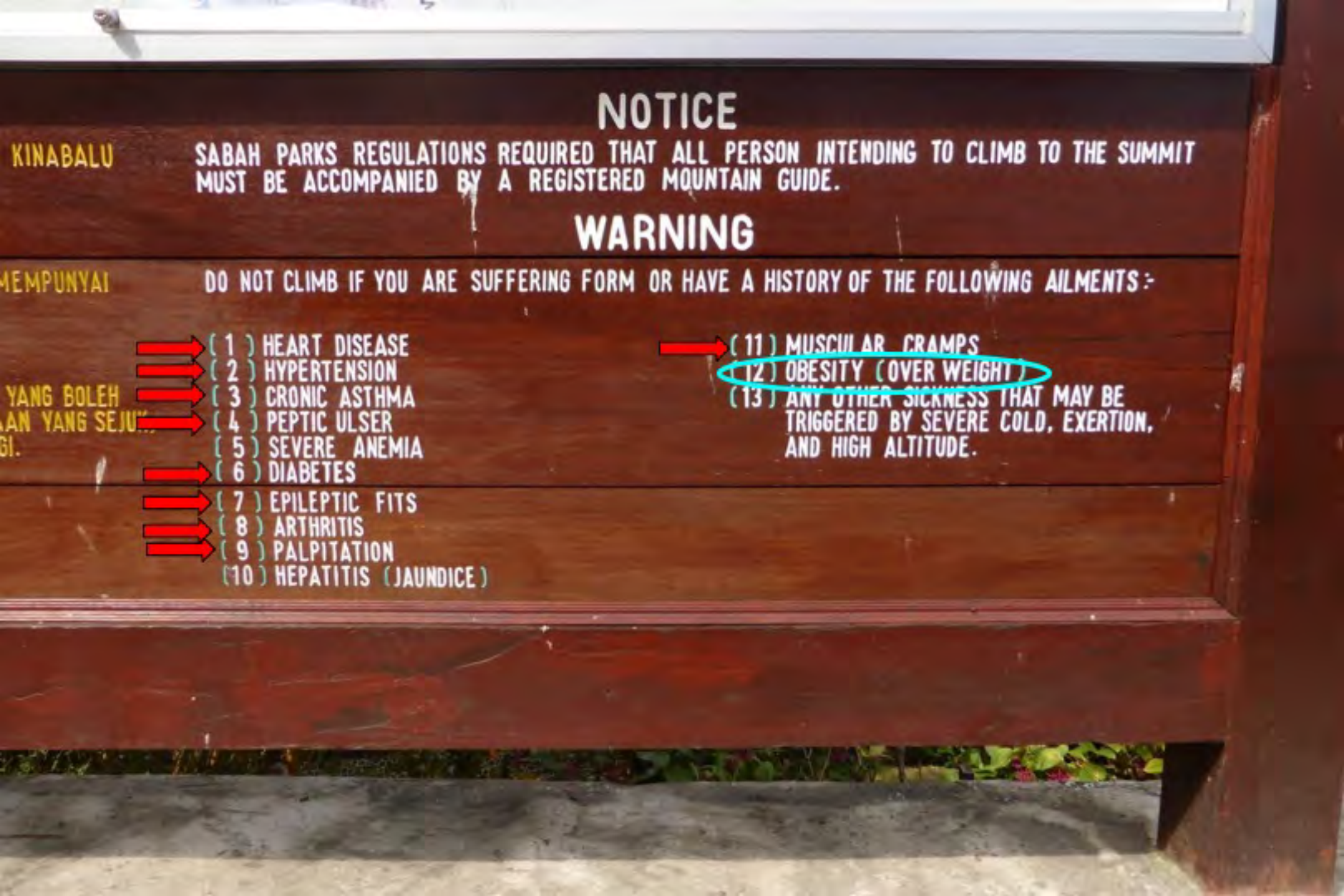
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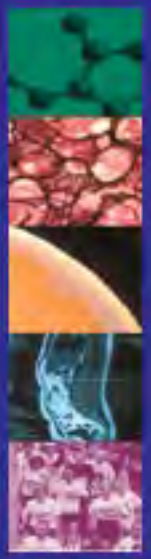

What do people with diabetes actually want?

• **To forget about it…… ….to not be diabetic?**	**???**
• Less complications?	Drugs? **Diet**
• Feel better?	Less drugs **(Diet)**
• Less anxiety?	Less drugs & hypos **(Diet)**
• Weight loss?	**Diet**
• Less problematic issues?	**Diet** **(Grant et al, Adelaide)**

Life-expectancy is still reduced 6-10 years by T2DM, despite all our drug treatments

Age (years)	England life expectancy (2005–2007) males (yrs)	T2DM life expectancy (2000–2007) males (yrs)	England life expectancy (2005–2007) females (yrs)	T2DM life expectancy (2000–2007) females (yrs)
0	77.65	69.58	81.82	71.91
30	48.59	39.86	52.44	41.16
40	39.08	30.82	42.71	32.04
50	29.85	23.14	33.26	24.68
60	21.24	16.92	24.28	17.69
70	13.70	12.60	16.05	12.06
80	7.74	5.98	9.17	7.64
90	3.96	3.68	4.49	6.44

Risk-reduction with current guideline treatment of T2DM (polypharmacy) *Maximum possible =15%*

Echouffo-Tcheugui, Sargeant, Prevost, Williams, Barling, Butler*,Fanshawe, Kinmonth, Wareham & Griffin (Diabetic Medicine 2008)

Model of the effect of treatment combinations	Absolute risk reduction (or risk difference) Estimate (%)	Range
Absolute risk calculated with UKPDS engine		
No additive effect: single most effective treatment (lipid-lowering therapy)	7.2	4.9–9.5
Additive effect of glucose, lipid- and blood pressure-lowering therapies	15.2	13.2–16.9
Additive effect of glucose-, lipid-, blood pressure-lowering therapies and aspirin	18.0	16.7–19.5
Absolute risk calculated with Framingham equation		
No additive effect: single most effective treatment (lipid-lowering therapy)	8.0	5.4–10.5
Additive effect of glucose-, lipid- and blood pressure-lowering therapies	16.9	14.6–18.8
Additive effect of glucose-, lipid-, blood pressure-lowering therapies and aspirin	20.0	18.4–21.6

NB: Aspirin does not prevent new CHD in T2DM. Belch et al, BMJ 2008

Mortality by BMI (general population)

Influence of weight loss on mortality is complicated, especially over long times:

Intentional
vs
Unintentional

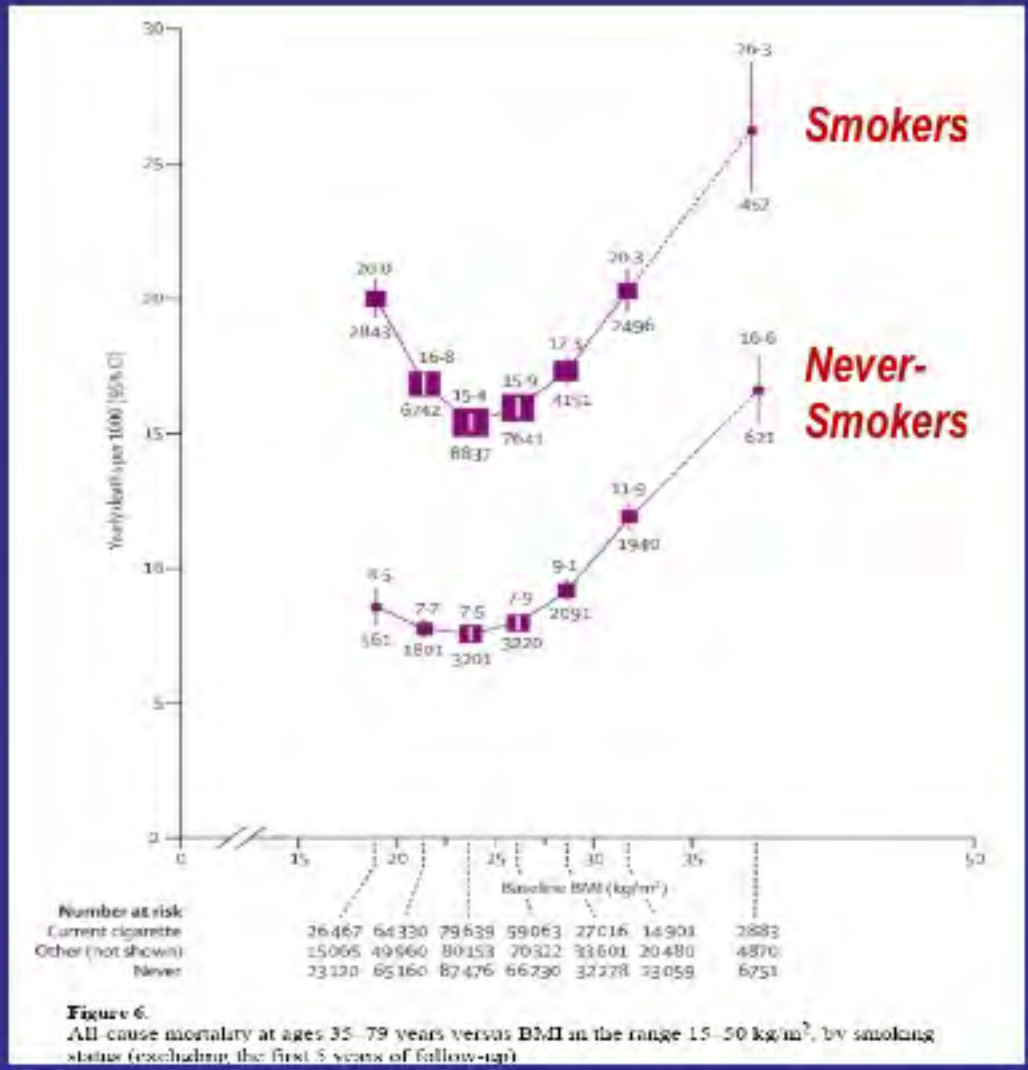

Figure 6.
All-cause mortality at ages 35–79 years versus BMI in the range 15–50 kg/m², by smoking status (excluding the first 5 years of follow-up)

Prospective Studies Collaboration (Whitlock et al)
Lancet 2009

Life expectancy is reduced by obesity:

BMI 30-35: reduced 2-4 years

BMI 40-50: reduced 8-10 years

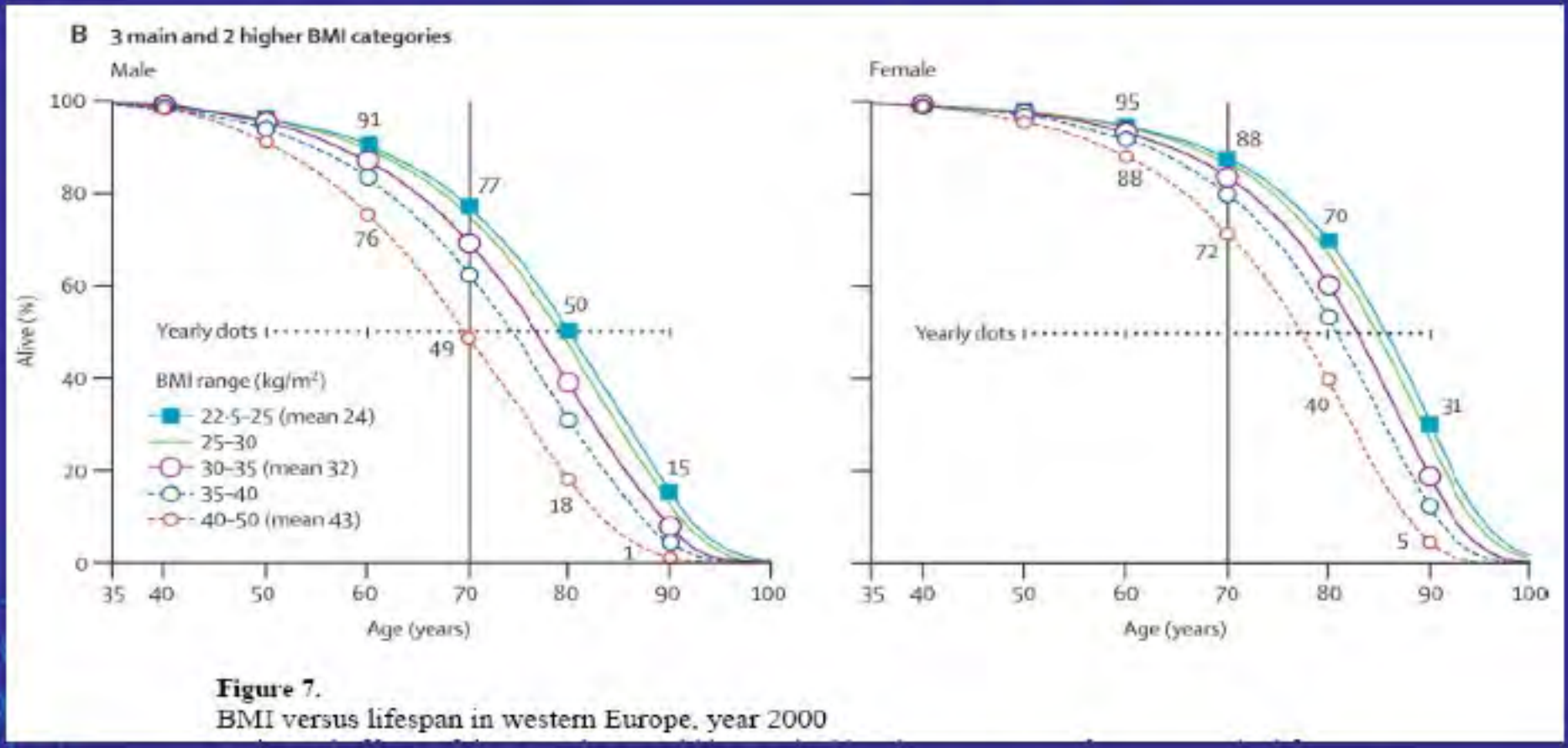

Figure 7.
BMI versus lifespan in western Europe, year 2000

Prospective Studies Collaboration (Whitlock et al)
Lancet 2009 (cf, Fontaine et al 2003)

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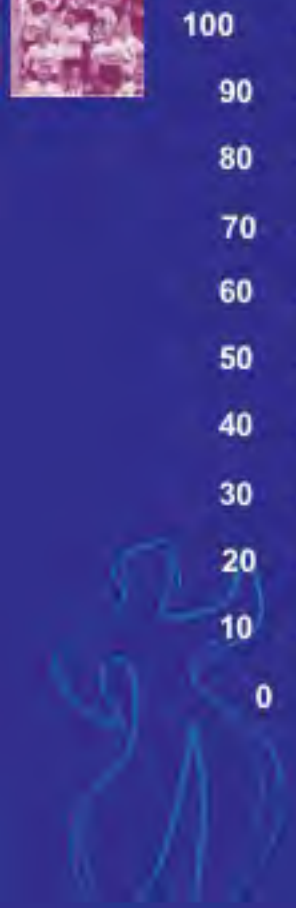
Weight gain/ obesity is the main cause of T2DM - and necessary, whatever the genes: High BMI

Colditz GA et al. Ann Int Med, 1995

Adjusted RR

(BMI <22 = referent)



Most T2DM requires adult weight gain >15kg

Median BMI 30 at diagnosis

100
90
80
70
60
50
40
30
20
10
0

<22 | 22-22.9 | 23-23.9 | 24-24.9 | 25-26.9 | 27-28.9 | 29-30.9 | 31-32.9 | 33-34.9 | >35

BMI (kg/m²)

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Excess fat in key organs – precursor to diabetes

Diet energy > exercise
Sat Fat, Low Fruit & Veg

↑Glucose Output

↑TG → ↑SD. LDL, ↑apoB

ALT
GGT
CRP,
PAI-1

Large insulin-res fat cells

FFAS/
Adiponectin
PAI-1,
IL-6, TNF-α AMGII

↓ Glucose Uptake

↓ Insulin

ALT - Salmeron et al, Diabetes 2001
PAI-1 - Festa et al, Diabetes 2002
Adiponectin - Lindsay et al, Lancet 2002
Leptin, Salmeron et al, AJE
Salmeron Clin Endocr

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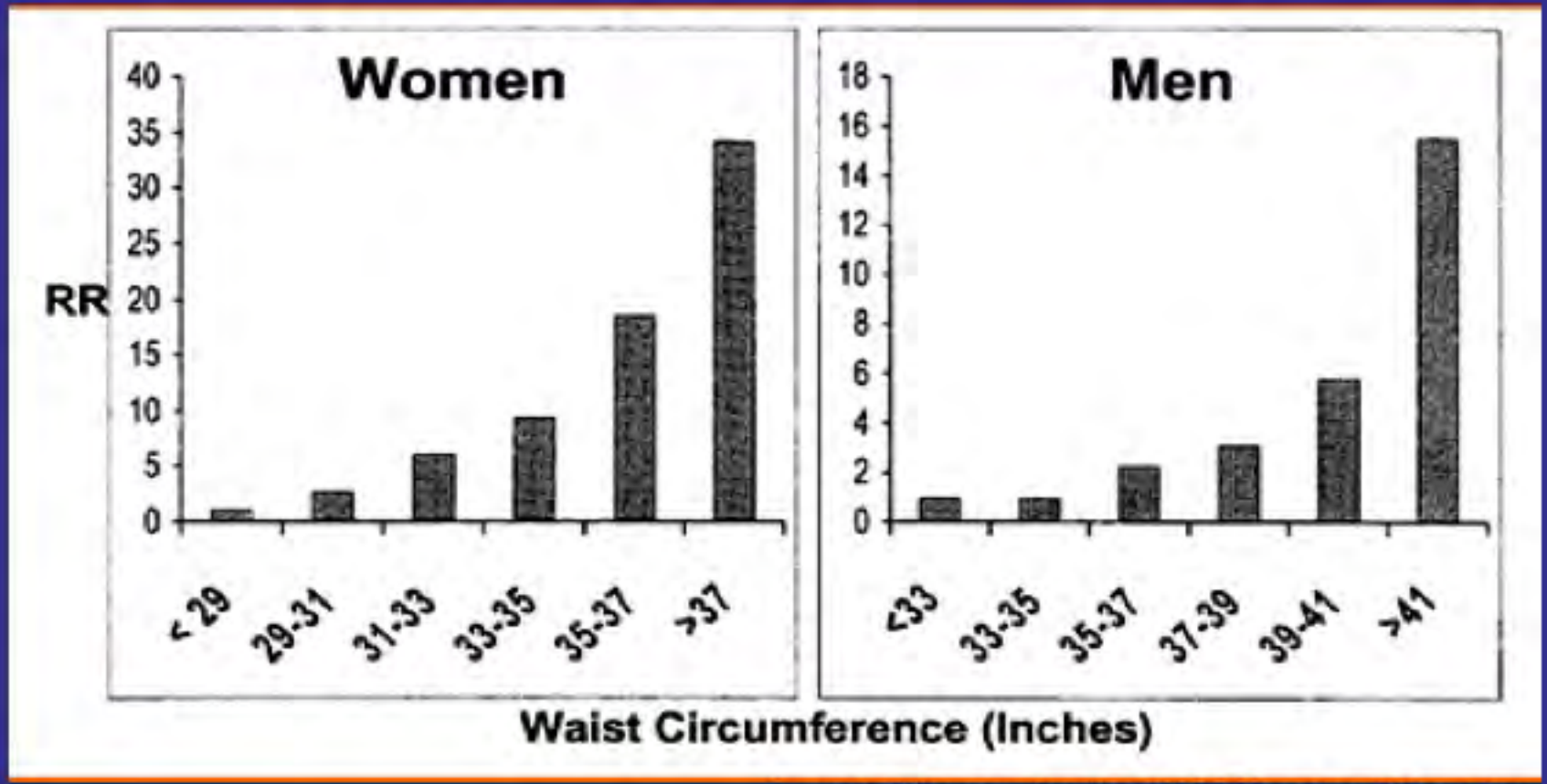
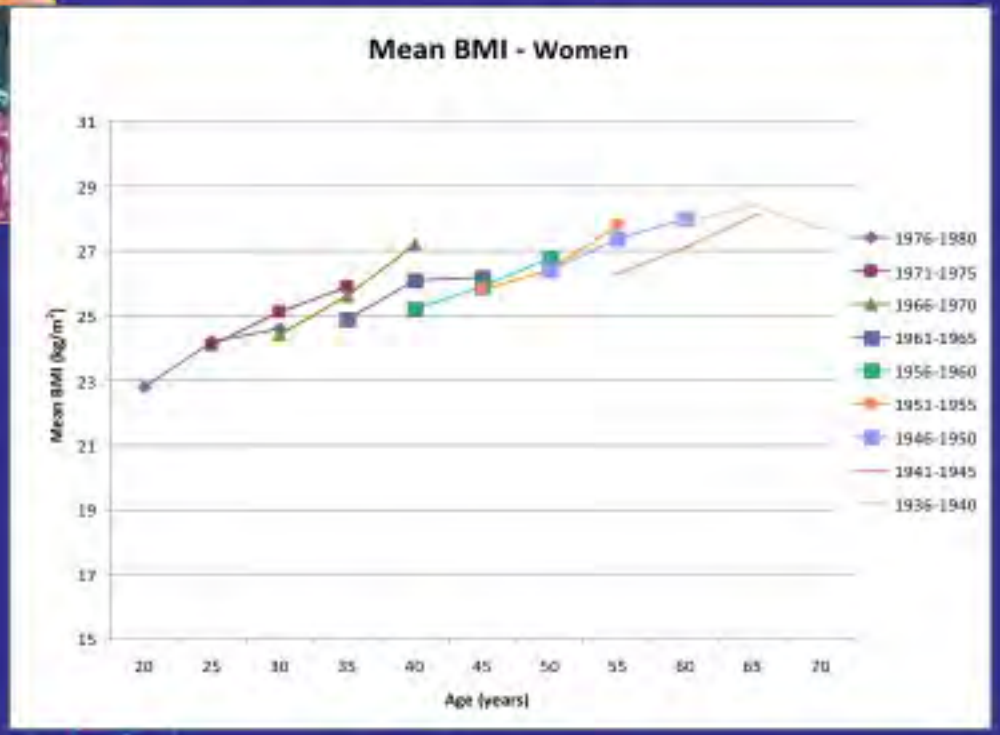
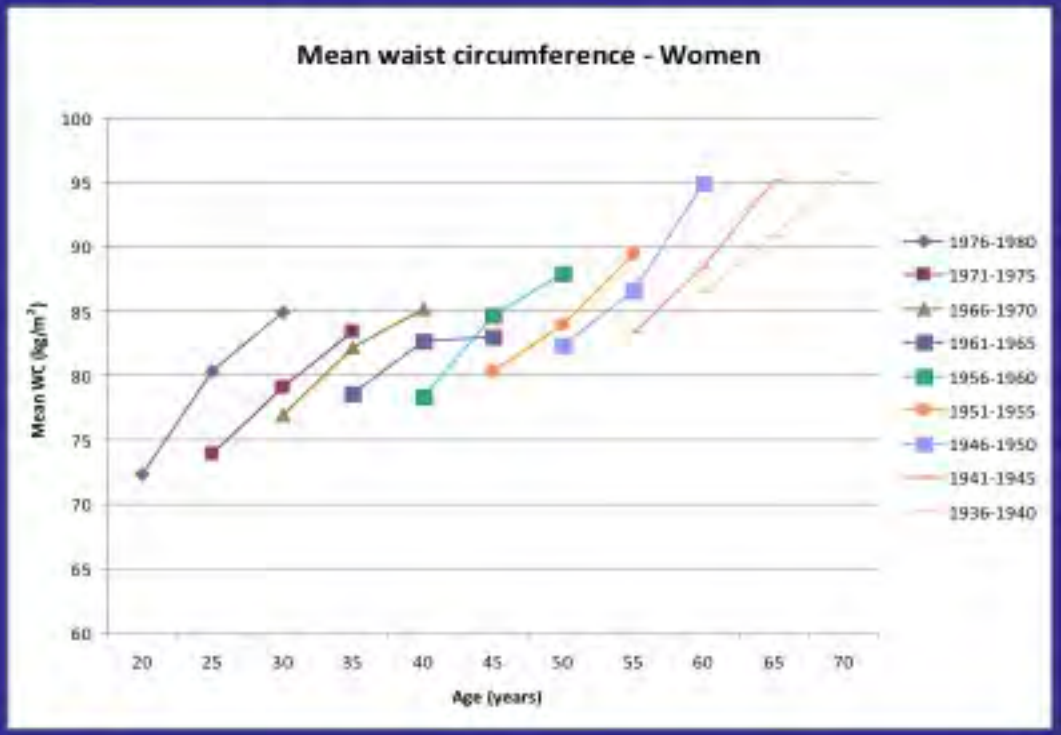
Large waist circumference promotes Type 2 Diabetes (even with normal BMI)



Source: J Womens Health © 2003 Mary Ann Liebert, Inc.

Changing shapes as people age
Scottish Health Surveys 1998-2008





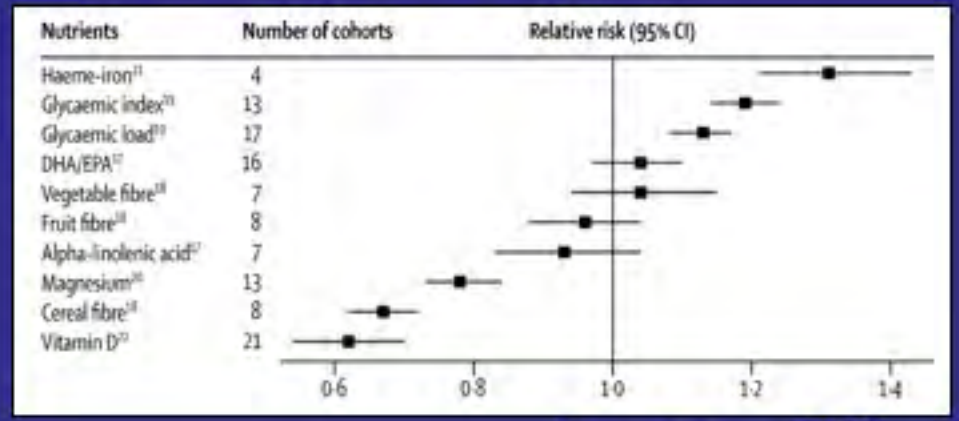
Women are continuing to get fatter even when Weight/BMI is not increasing much - 'Sarcopenic Obesity'

Lean et al, Int J Obesity 2012

Diabetes Prevention: weight control is vital

- DPP and DPS: mean 4kg weight loss and exercise prevented most progression from IGT to T2DM (57% prevented)
  - Weight loss is the dominant element (Torgerson, XENDOS trial)
  - No need for LELD/VLED

- Additional diabetes prevention
  - Regular physical activity (increase type-1 muscle fibres)
  - Low saturated fat diet
  - Fruit and vegetables
  - Magnesium
  - Cereal fibre
  - Low GI



The Counterweight Project

Audit/Needs Assessment
setting priorities

Practice
Training
setting
guidelines

Intervention Programme
measuring performance

Evaluation
improving
performance

Evaluate

Feedback

Improve

(Kai-zen)

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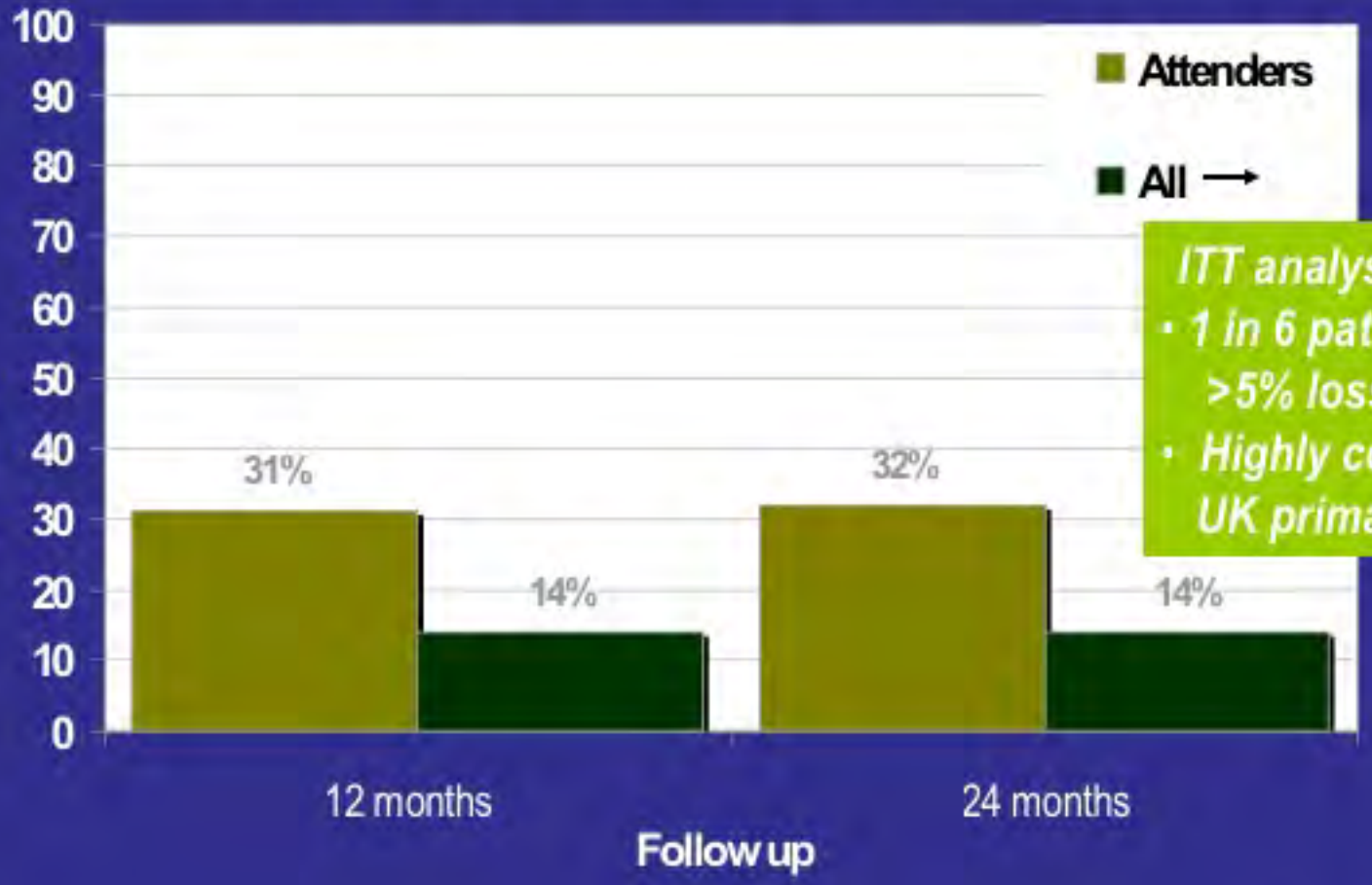
Counterweight: evidence-based multi-facetted programme achieving targets in real life

Ross et al, Br J Gen Practice. 2008; Lean et al, Int J Clin Practice 2010



% achieving ≥5% wt loss target

ITT analysis
- *1 in 6 patients achieved >5% loss at 12m & 24m*
- *Highly cost-efficient in UK primary care*

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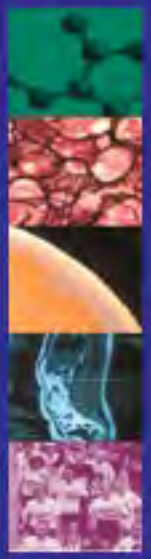

How good are the Counterweight results?

• Original Evaluation: (n = 1906)	1 in 6 maintain >5% weight loss at 12 or 24 months (1 in 3 attenders)
• Scottish Govt. Evaluation: (n = 6715)	1 in 10 maintain >5% weight loss at 12 months (1 in 3 attenders)
c.f. Smoking Cessation	1 in 14 quit at 12 months

What do patients actually want to lose? (And doctors)

'2 or 3 stones' (15-21kg)

Family Practice 2012

Br. J. General Practice 2008

ISD Scotland 2011 May

Int J Obes 1999

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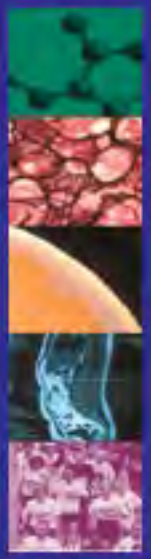
Counterweight: evidence-based multi-facetted programme achieving targets in real life

Ross et al, Br J Gen Practice. 2008; Lean et al, Int J Clin Practice 2010



Only 2% maintain >15kg loss at 12-24 months

% achieving ≥5% wt loss target

ITT analysis

- *1 in 6 patients achieved >5% loss at 12m & 24m*
- *Highly cost-efficient in UK primary care*

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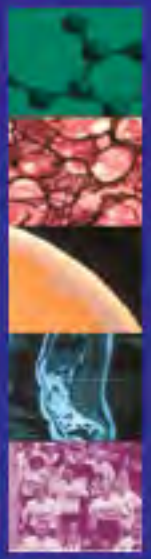
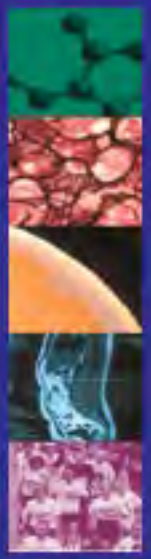


Severe obesity and T2DM prevalence:
estimates from a systematic review

BMI (kg/m^2)	Diabetes Prevalence
30-40	10%
40-50	15%
50-60	15-30%
60-70	20-30%
> 70	30-50%

Grieve, Fenwick & Lean. Obesity Reviews, 2013

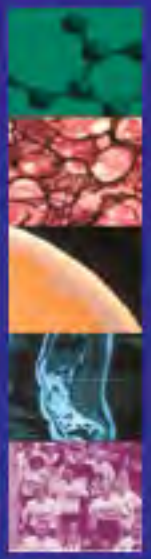


The new epidemic: Severe and complicated obesity

SIGN 115: Management of Obesity 2010

"In patients with BMI>35 kg/m^2 obesity-related comorbidities are likely to be present therefore weight loss interventions should be targeted to improving these comorbidities; in many individuals **a greater than 15-20% weight loss (will always be over 10 kg) will be required to obtain a sustained improvement in comorbidity"**.

Current prevalence of BMI >35 = 9%



The new epidemic: Severe and complicated obesity

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Corrected!

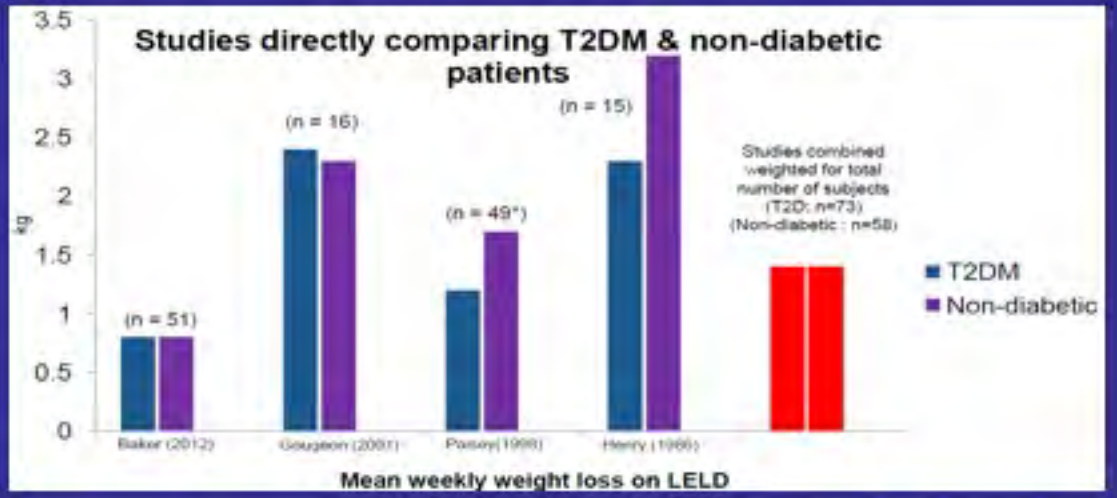
"In patients with BMI>35 kg/m^2 obesity-related comorbidities are likely to be present therefore weight loss interventions should be targeted to improving these comorbidities; in many individuals **a greater than 15-20kg weight loss (will always be over 10%) will be required to obtain a sustained improvement in comorbidity"**.

Current prevalence of BMI >35 = 9%

Weight loss for people with T2DM

- With conventional diets, they lose less than non-diabetic people
  - Already doing their best with diet
  - Distracted by having to take 6-8 different drugs every day
  - Insulin and sulphonylureas increase weight
  - Metabolic rate falls when diabetes is better controlled

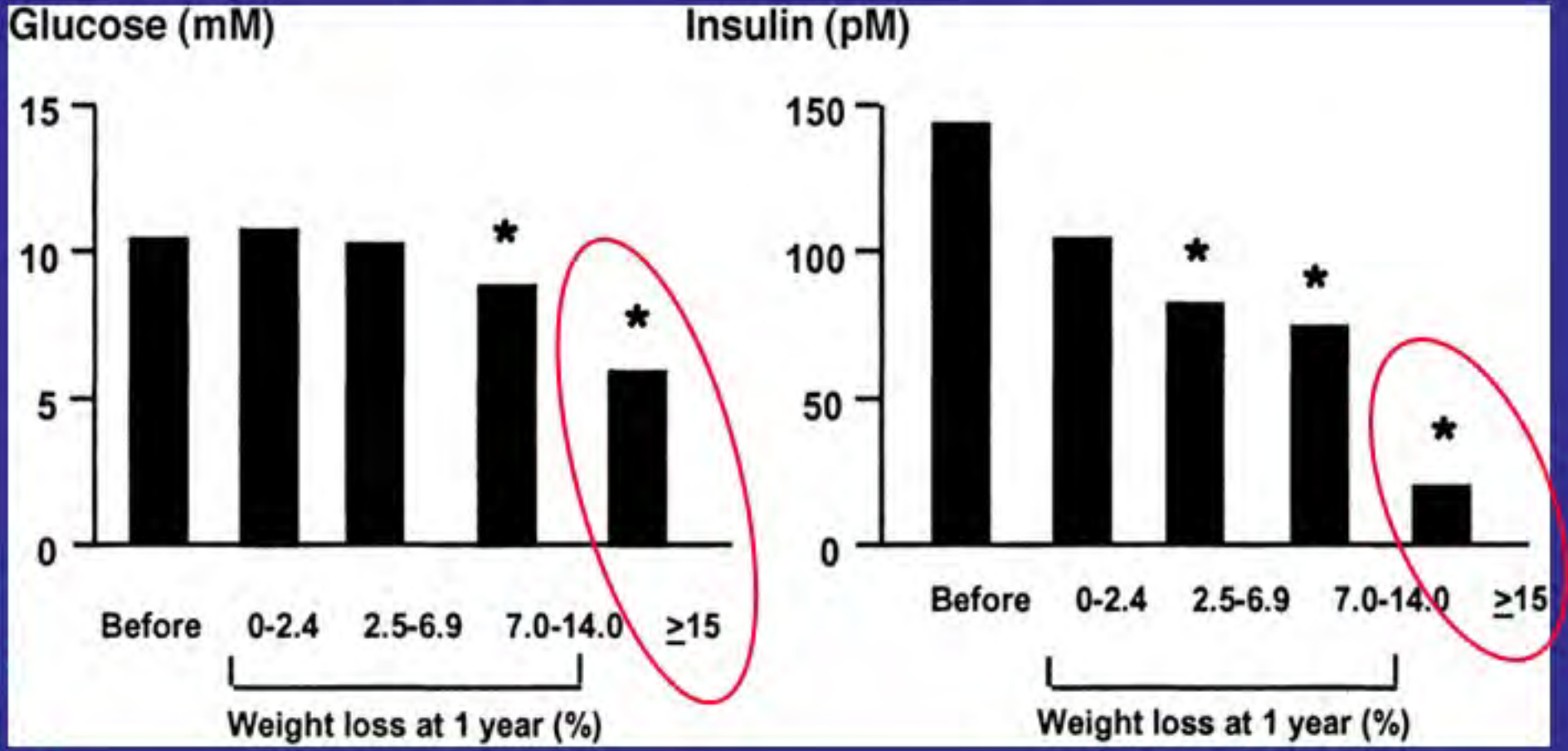
- **With VLCD/ formula diets, they lose the same amount**



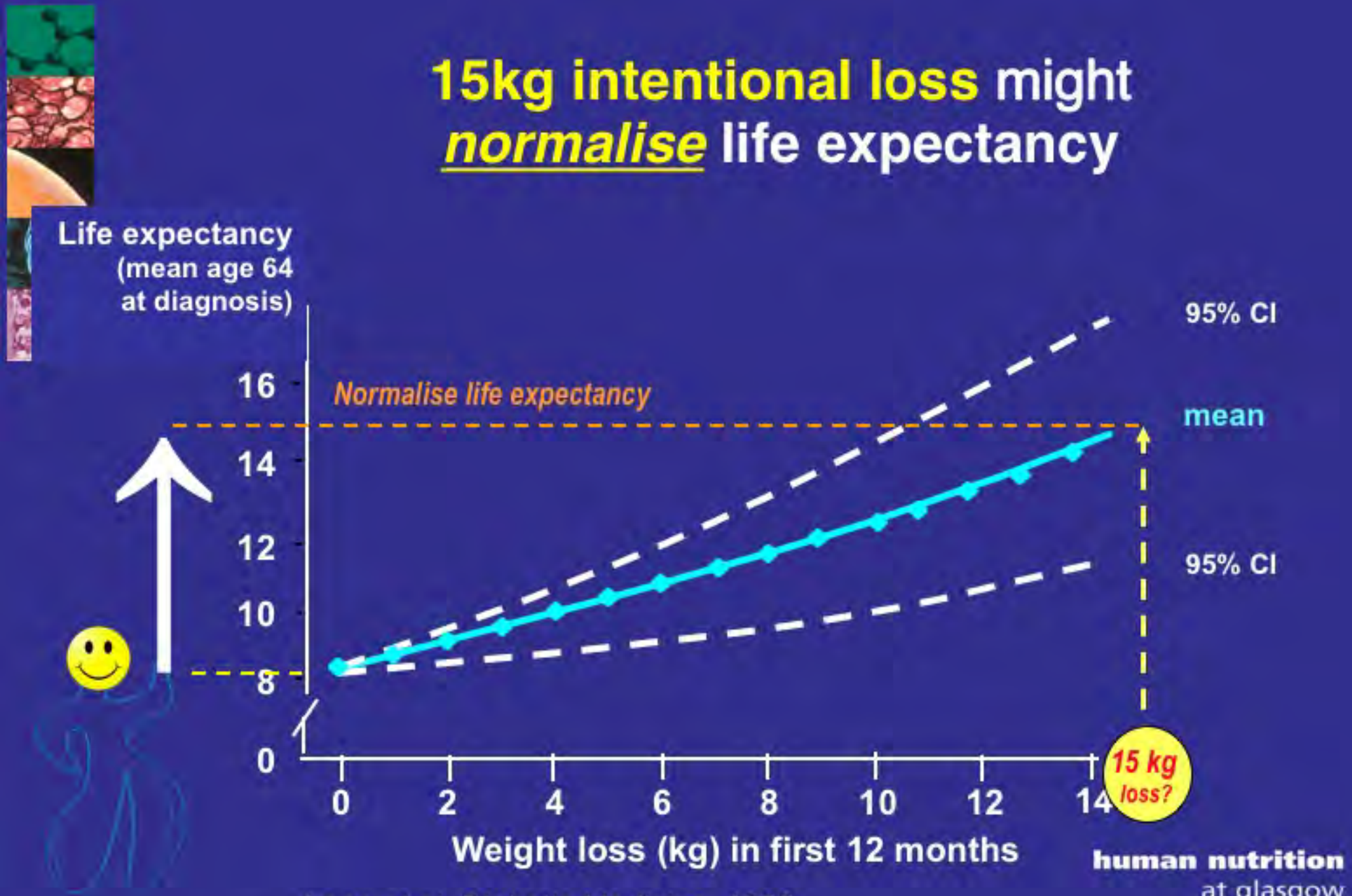
Leslie, Taylor & Lean, 2014 Diabetologia under review

Weight-loss >15% normalises insulin and glucose at 12 months in T2DM patients

Wing et al. Klein, S. Obesity Research (2001)



15kg intentional loss might *normalise* life expectancy



Lean et al. Diabetic Medicine, 1990

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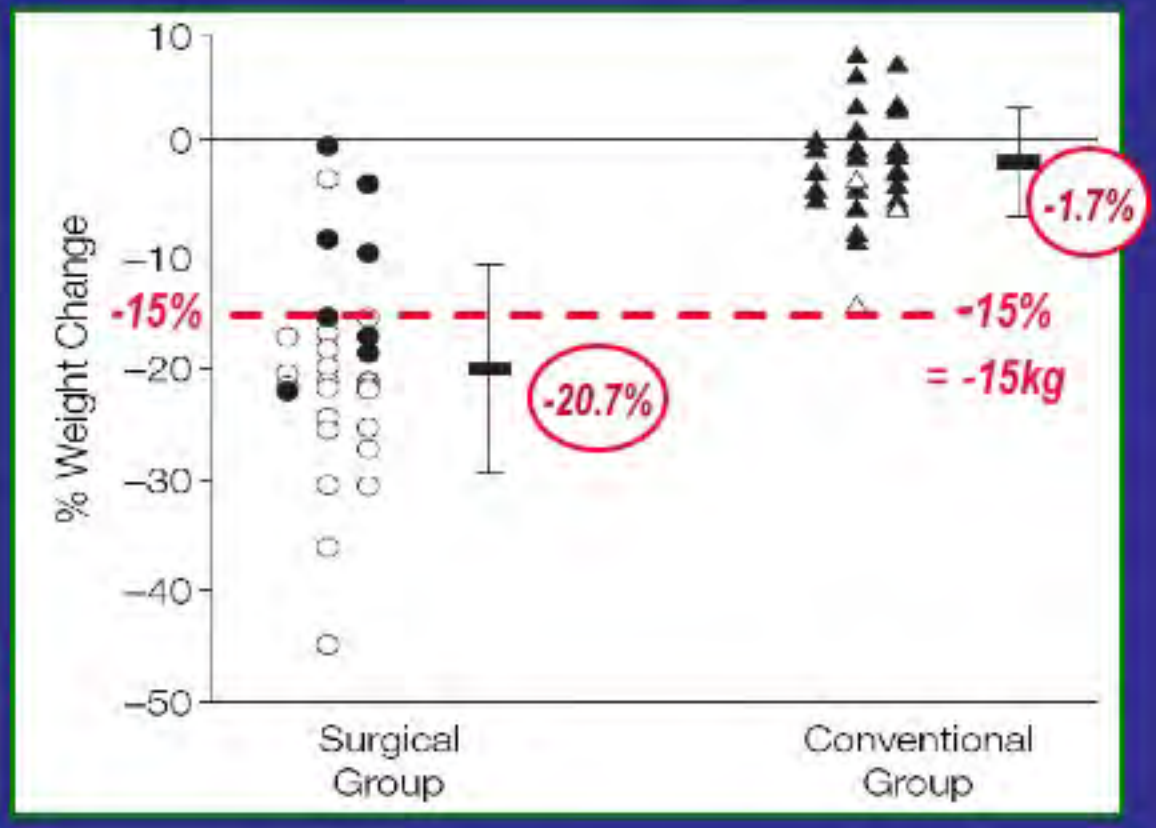
15 kg weight loss normalises glucose tolerance: 2-year RCT, gastric band vs diet advice



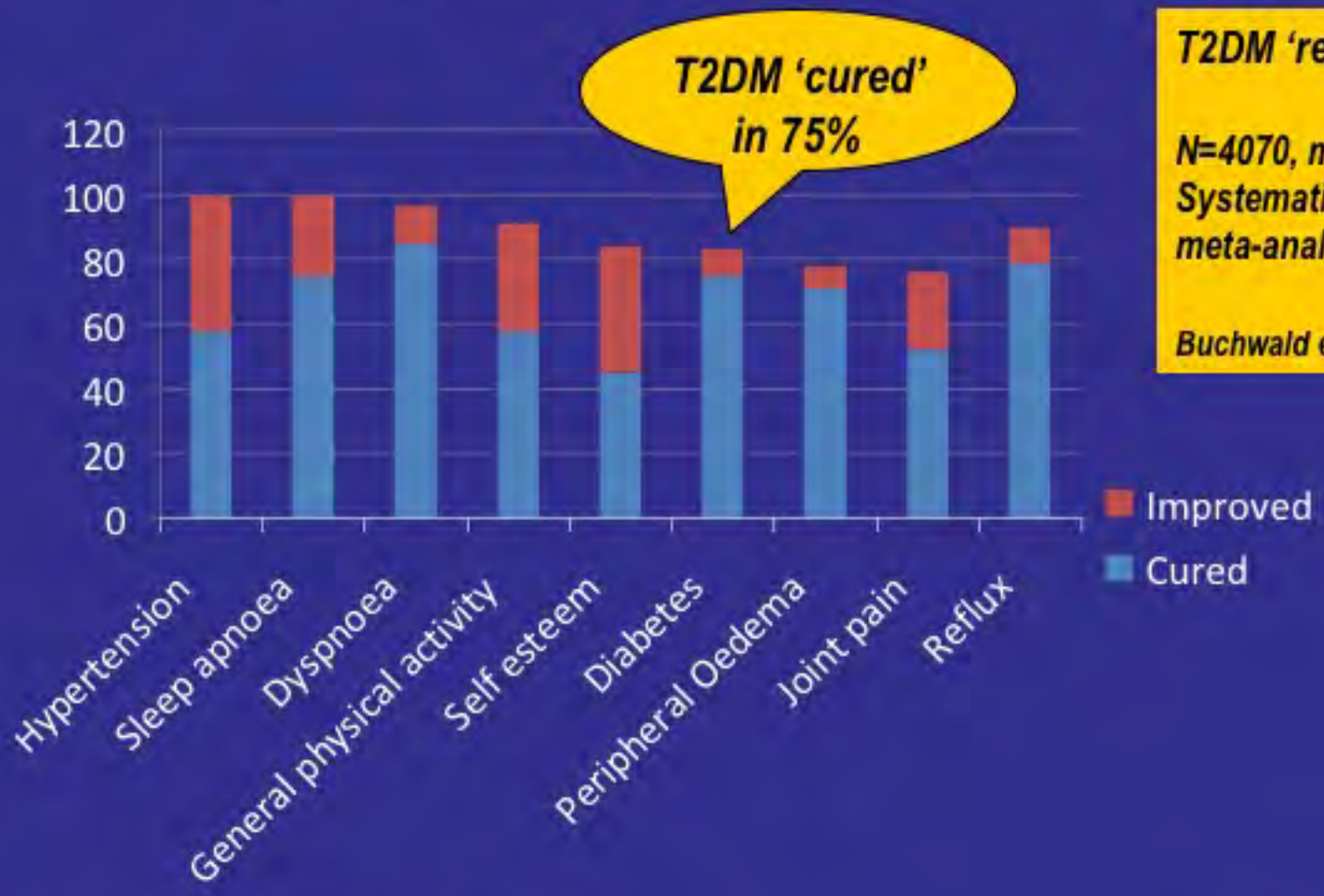
Conventional group
△ Achieved remission of type 2 diabetes — 13%
▲ Did not achieve remission of type 2 diabetes

Surgical group
○ Achieved remission of type 2 diabetes — 73%
● Did not achieve remission of type 2 diabetes

Dixon et al (2008) JAMA

Multiple clinical benefits from major weight loss

4 y after laparoscopic adjustable gastric banding



T2DM 'resolved' in 78%

N=4070, mean age 40, BMI 48, Systematic review and meta-analysis

Buchwald et al Am J Med, 2009

Frigg et al. Obes Surg, 2004

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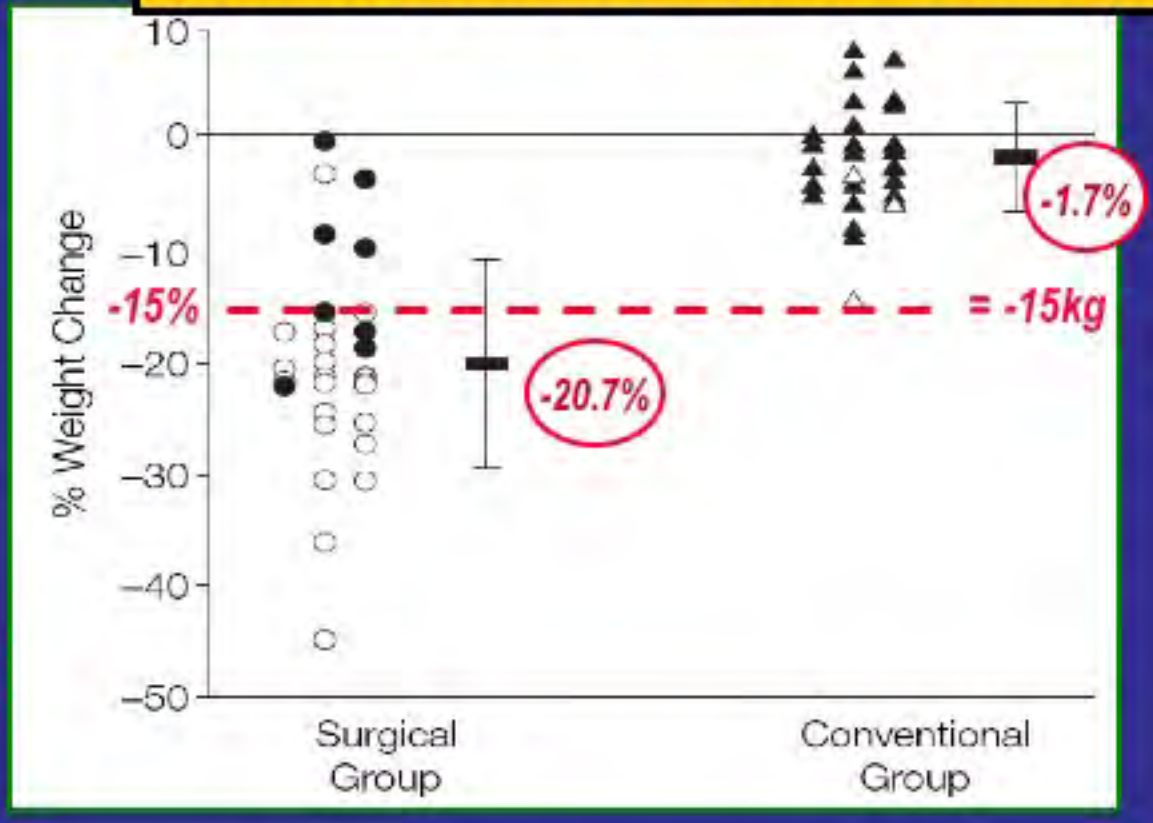
15 kg weight loss normalises glucose tolerance:
2-year RCT, gastric band vs diet advice

Can we achieve similar results without surgery?



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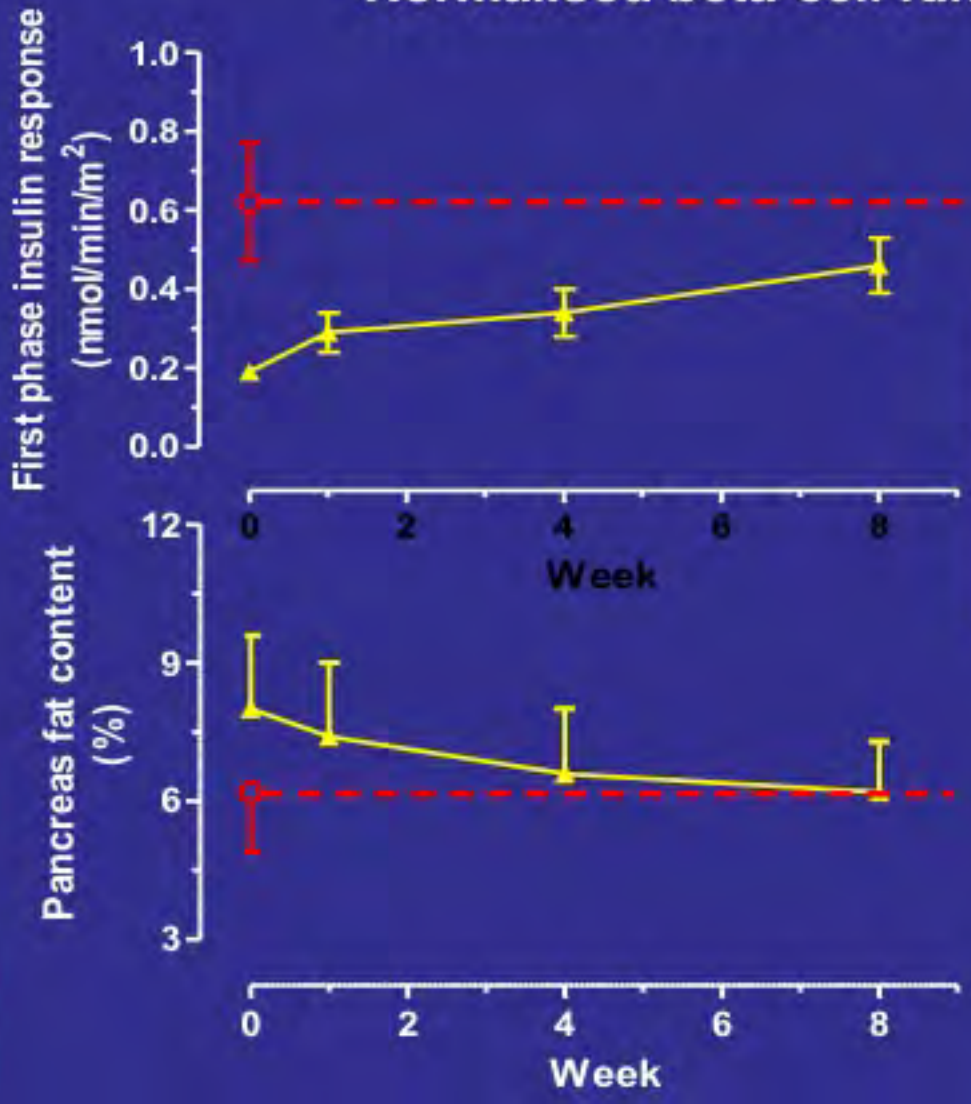
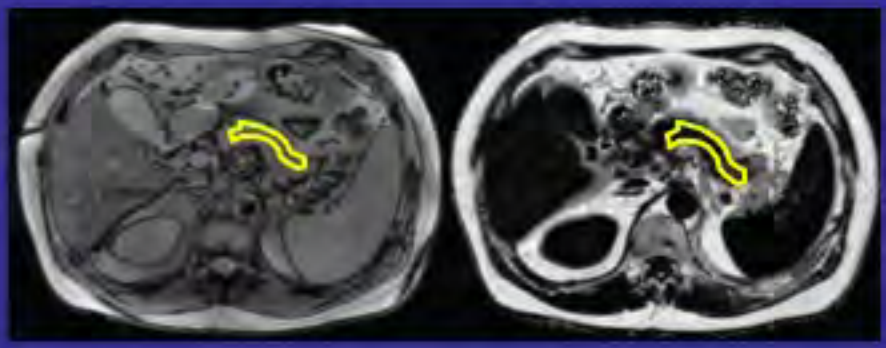
Dixon et al (2008) JAMA

15kg weight loss on 450kcal/d diet

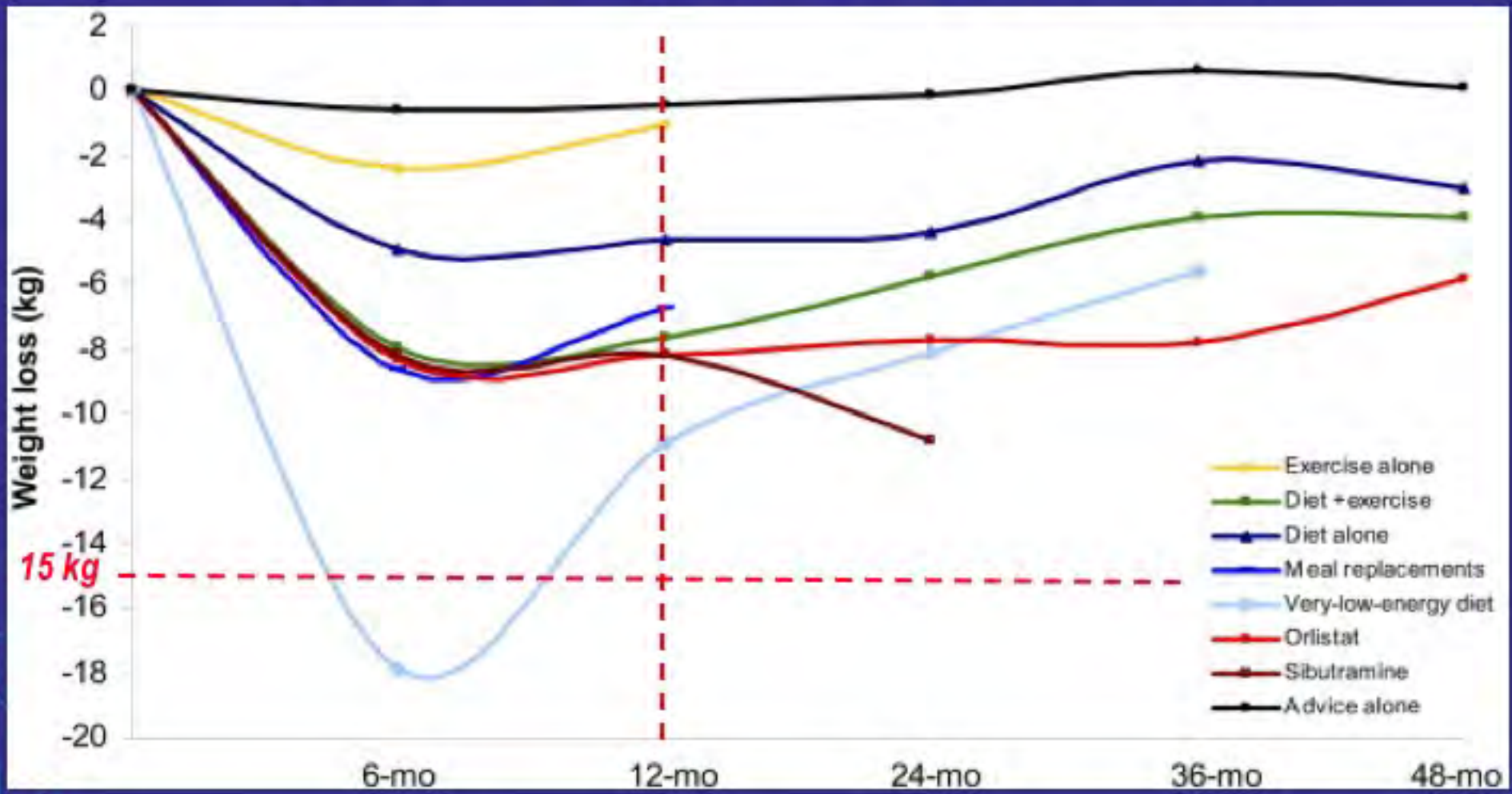
Normalised beta-cell function and pancreas fat





Lim et al, Diabetologia 2011

Meta-analysis of non-surgical trials with 1-year follow-up. (*Franz MJ et al JADA 2007)*



Average weight loss in subjects completing 1-year
80 studies, n = 26,455, completers =18,199 (69%)

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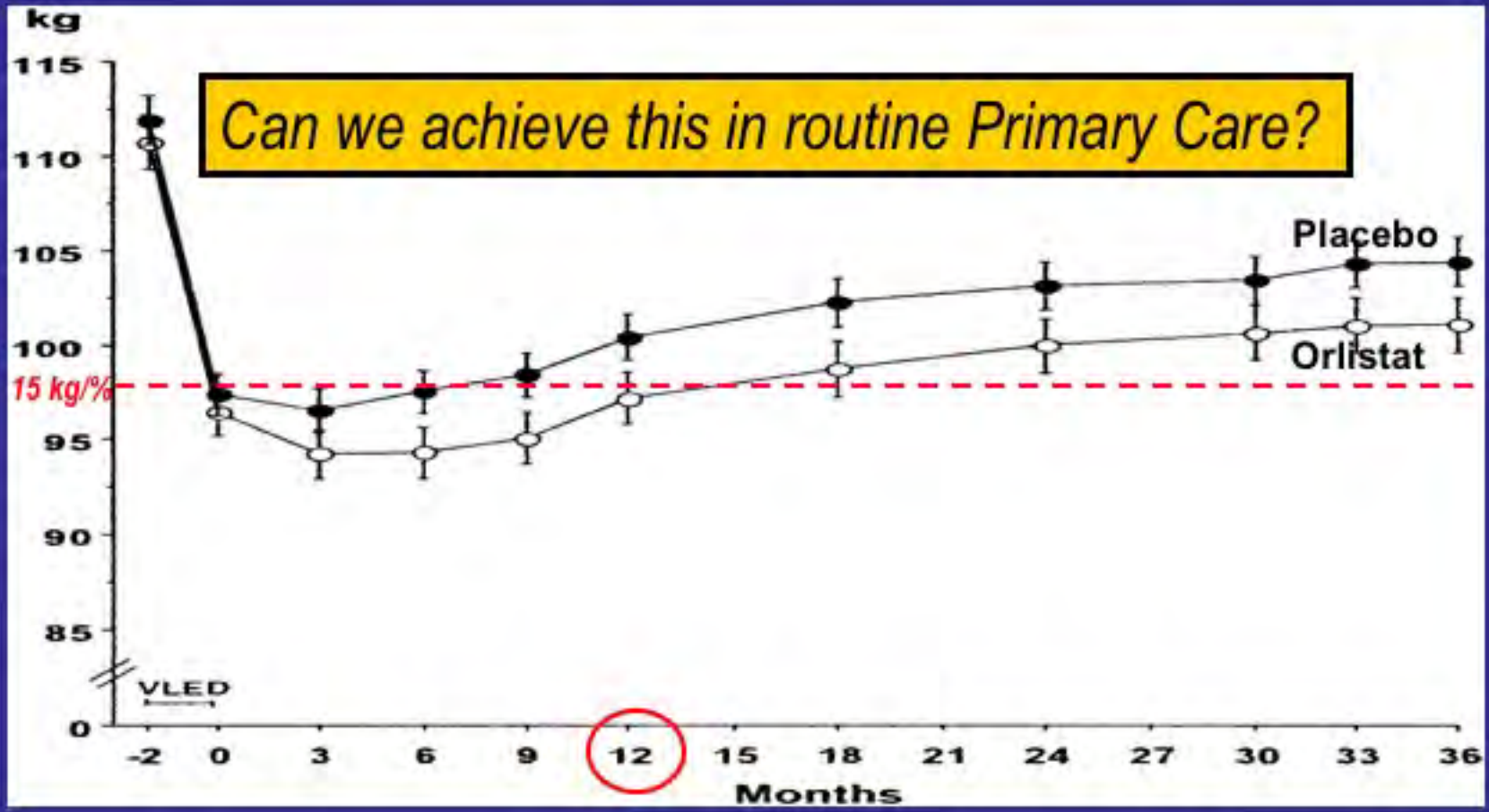
Weight maintenance with orlistat after VLED

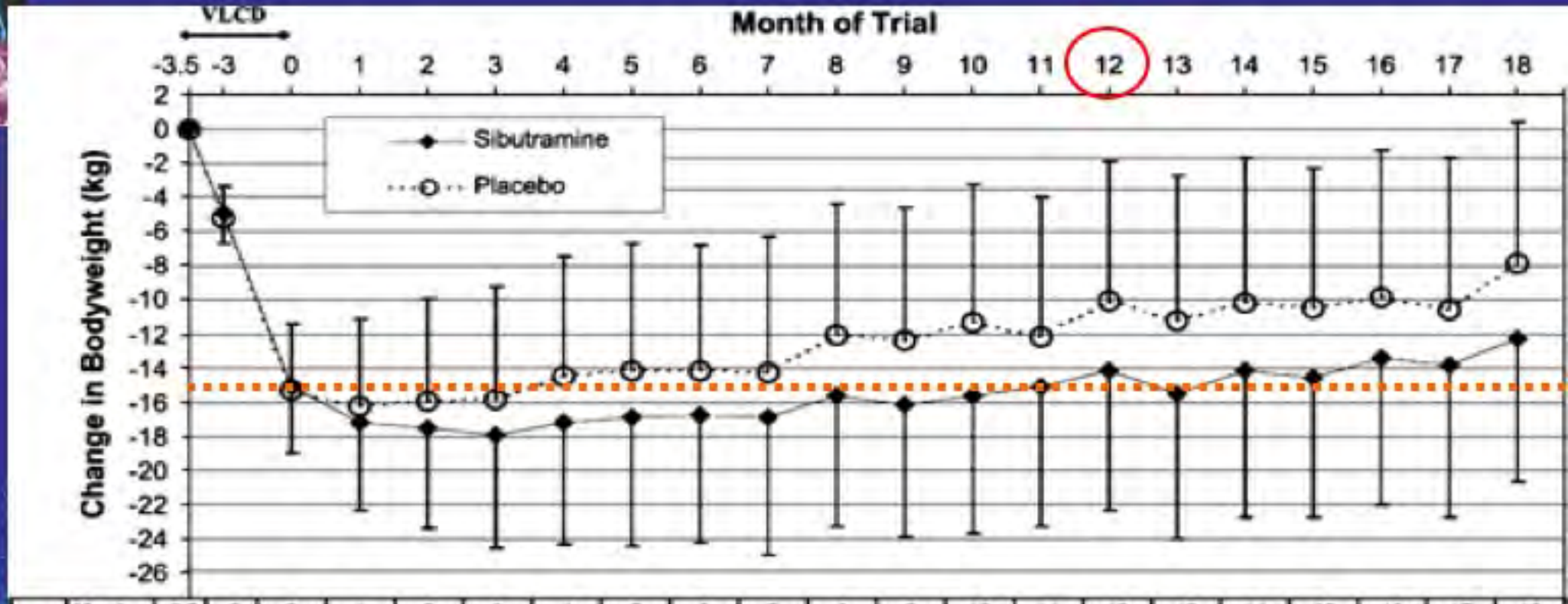
50% of attenders maintained >15kg loss at 12m

Richelsen et al Diabetes Care; 2007



Combining VLED with sibutramine for long-term maintenance, in a GP setting

Mathus-Vliegen EMH for Balance Study Group Eur J Clin Nutr 2005

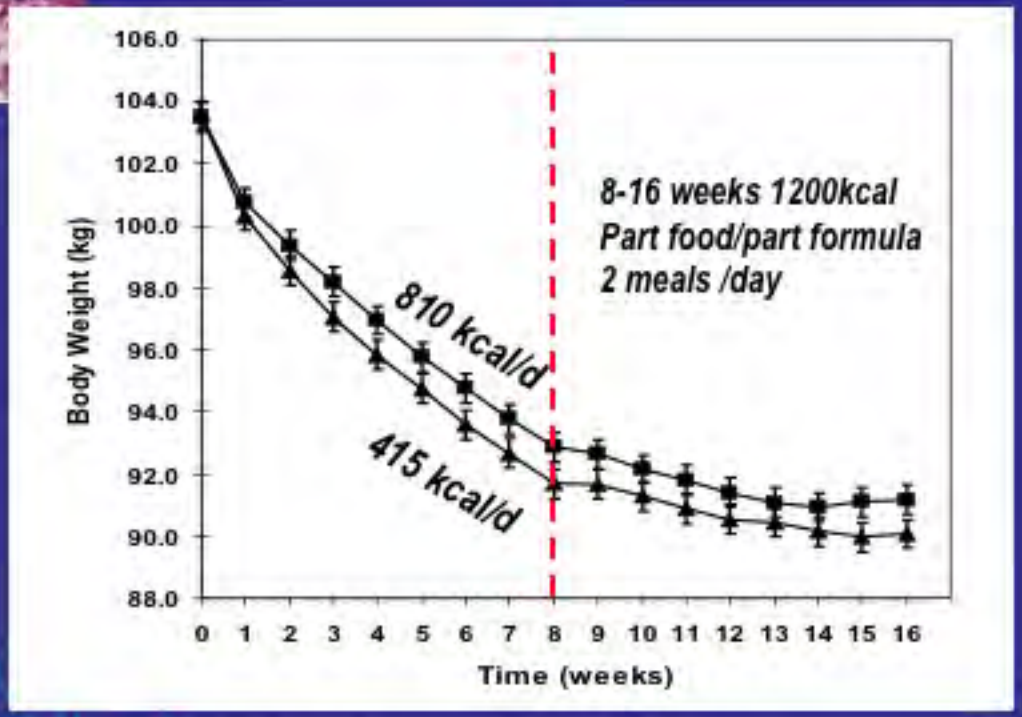


	Month	-3.5	-3	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Sbt	N=	94	94	94	90	90	88	86	81	83	80	74	74	68	67	76	63	61	57	56	49	62
Pcb	N=	95	95	95	93	91	90	88	86	85	78	72	71	68	61	78	56	50	46	47	34	58

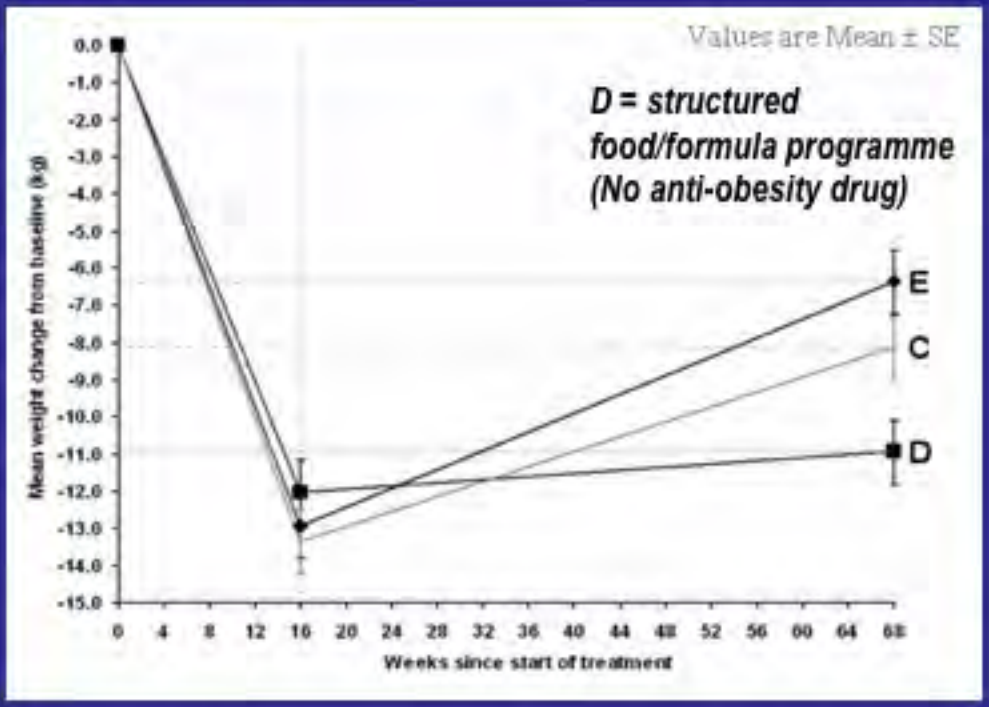
Little difference between 415kcal VLED or 810kcal LED

Copenhagen Weight Loss in Knee Osteoarthritis trial

(Bliddal et al, secondary care, dietitian managed)



No difference in weight loss
n=96 per group



Better maintenance with a structured programme
n=64 per group

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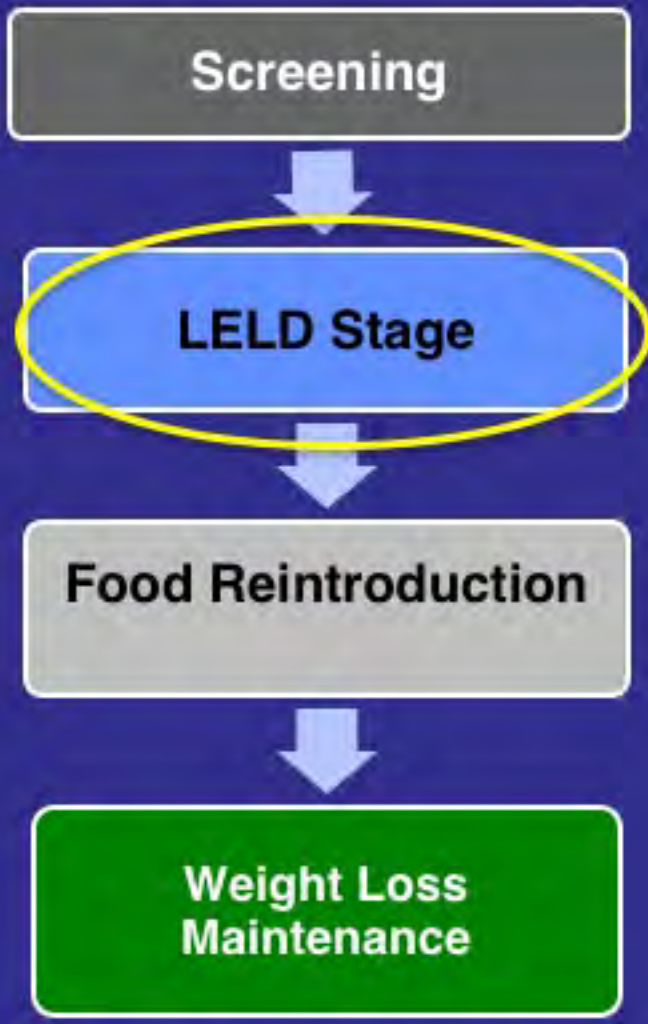
Counterweight-Plus - Protocol

Nutritionally complete LELD either:

1) Homemade (811calories/day)
2) Commercial (832calories/day)
   - Cambridge Weight Plan
3) Mix and match

Plus:

- Structured patient education
  - Step down approach optional
- >2.25l fluid per day (4 pints)
- Fibre supplement



Lean et al , Br J GP (2013)

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Weight Loss Maintenance- Protocol

Stepped Food Reintroduction

- Introduce one 360-400 kcal meal
- Add a meal every two weeks
- Meals based on eatwell plate
- Offer Orlistat

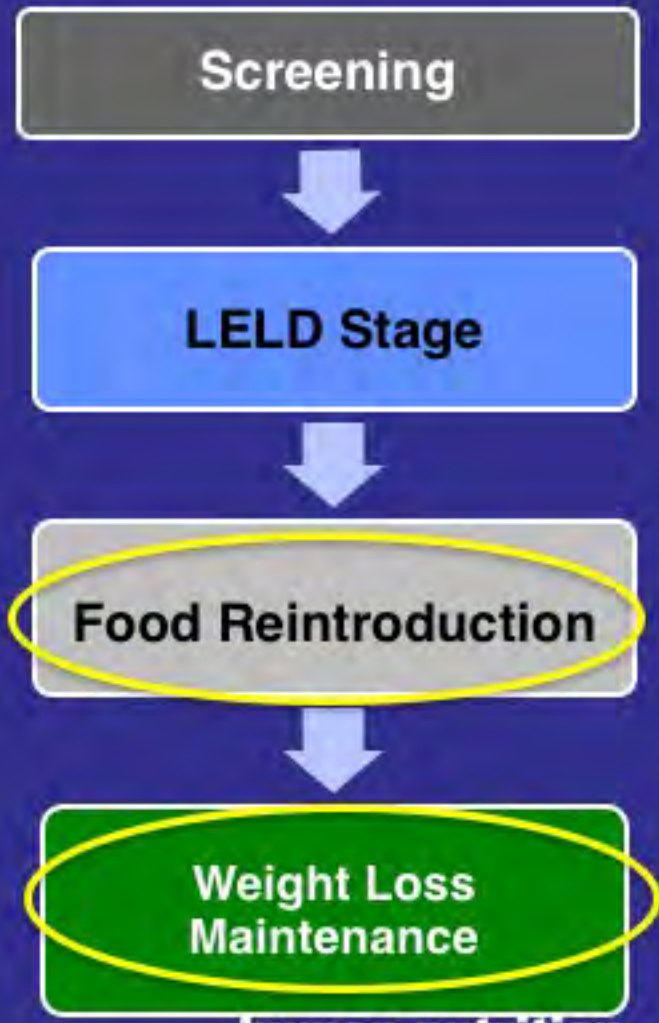
Maintenance

- Low fat diet (30% fat)
- Estimate 500 kcal/d deficit
- 2500 kcal/d upper limit
- Behavioural strategies

Relapse Management

- Offer orlistat
- Second attempt LELD stage

Lean et al , Br J GP (2013)



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Counterweight LELD Feasibility Study

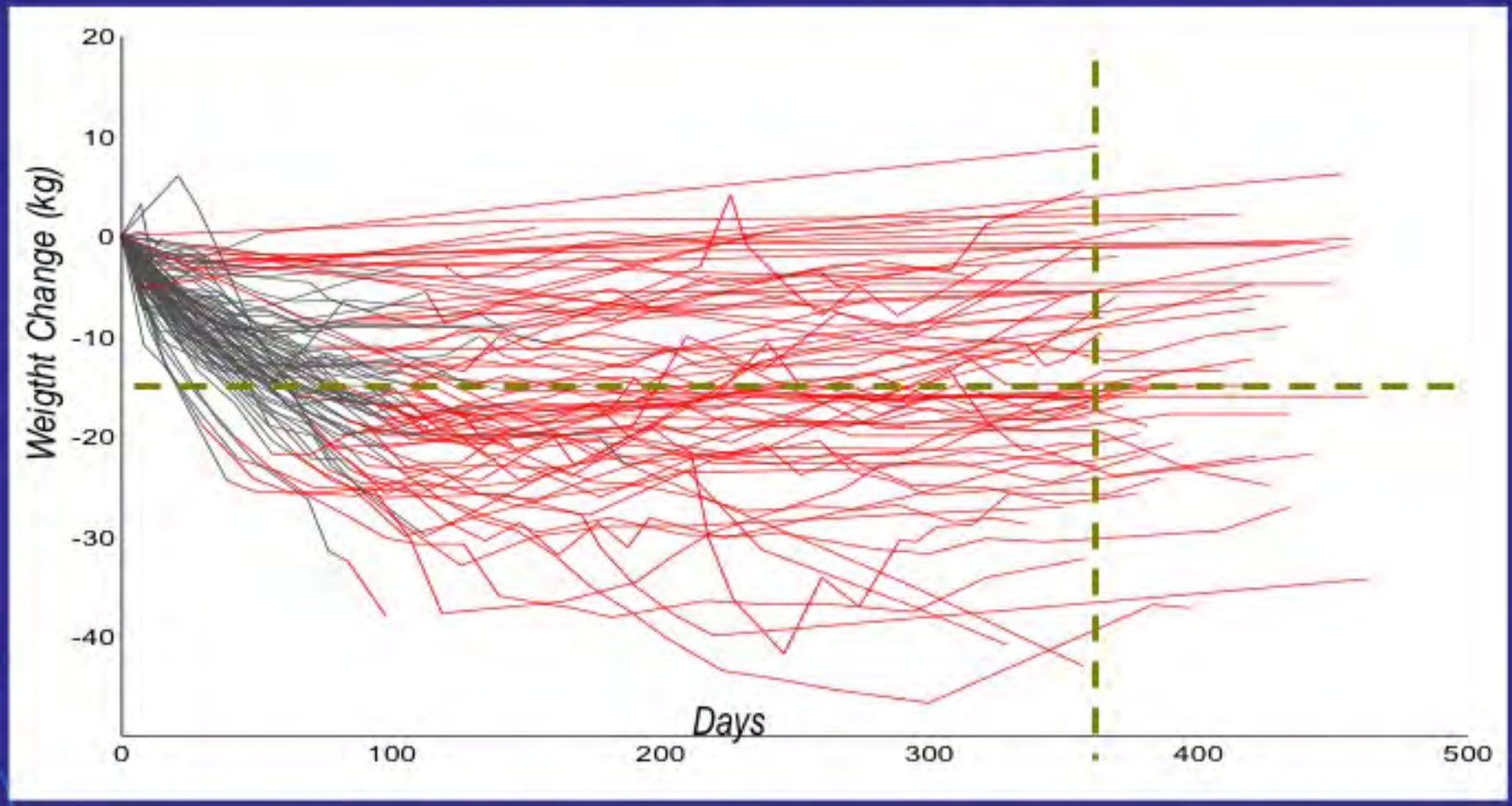
- 22 general practices in 7 Scottish Health Boards took part
- 6 practice nurses and 8 dietitians trained to deliver it
- No extra funding

- 91 patients entered over 6 months
- 78% women, mean BMI 48 (131kg)
- Average 14 visits, mean 5 hours contact, over 12 months

- Feasible to deliver in routine primary care
- Highly acceptable to both patients and practitioners
- Demands high personal responsibility, but well supported

Lean et al , Br J General Practice (2013)

Initial weight loss is the main determinant of long-term results



Lean et al , Br J General Practice (2013)

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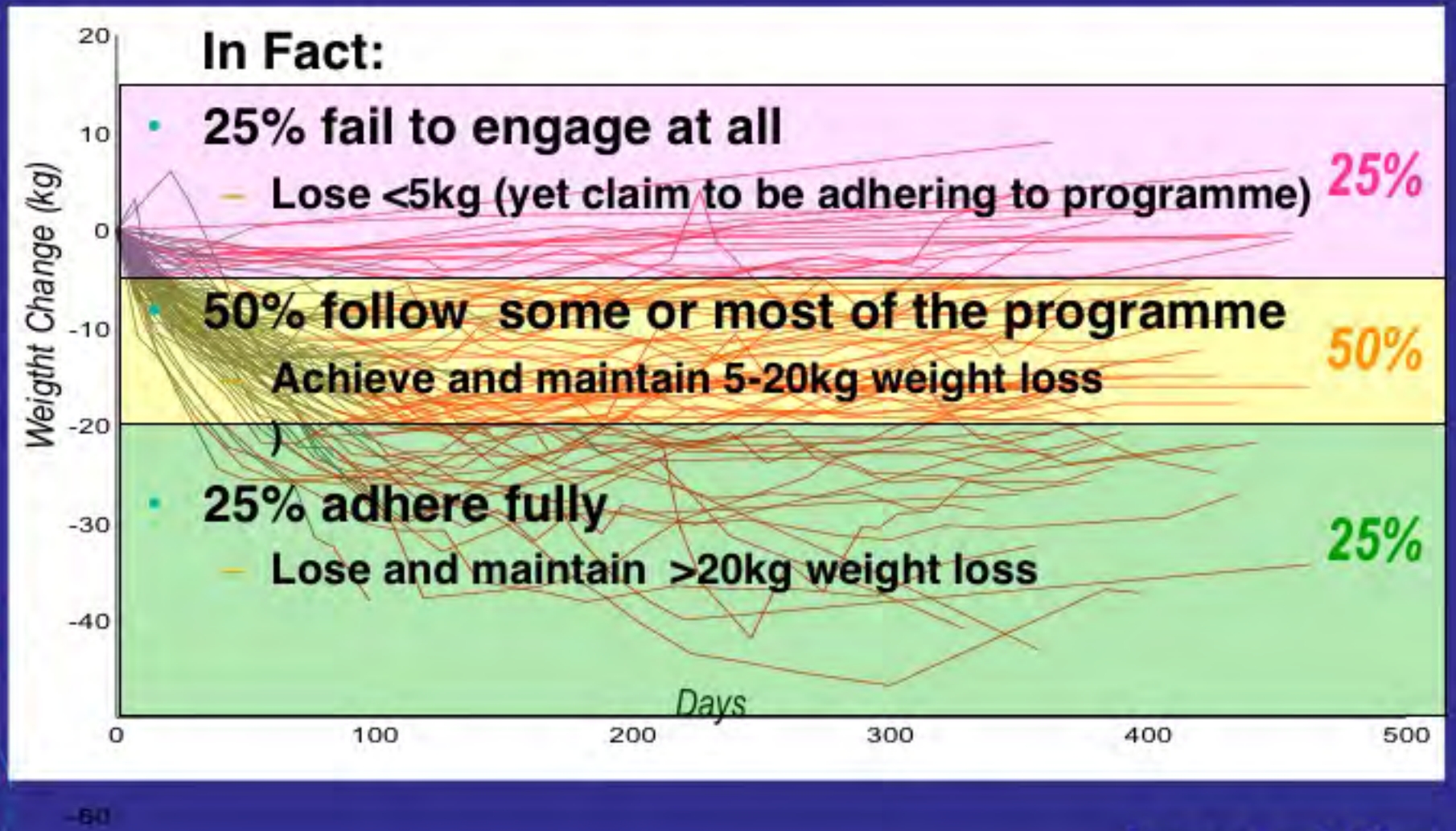
Popular Belief: Patients regain all the weight, or more



Lean et al , Br J General Practice (2013)

'Total Diet Replacement' and structured long-term weight maintenance: Counterweight-Plus

Maintaining weight loss ≥15kg at **12 months:**

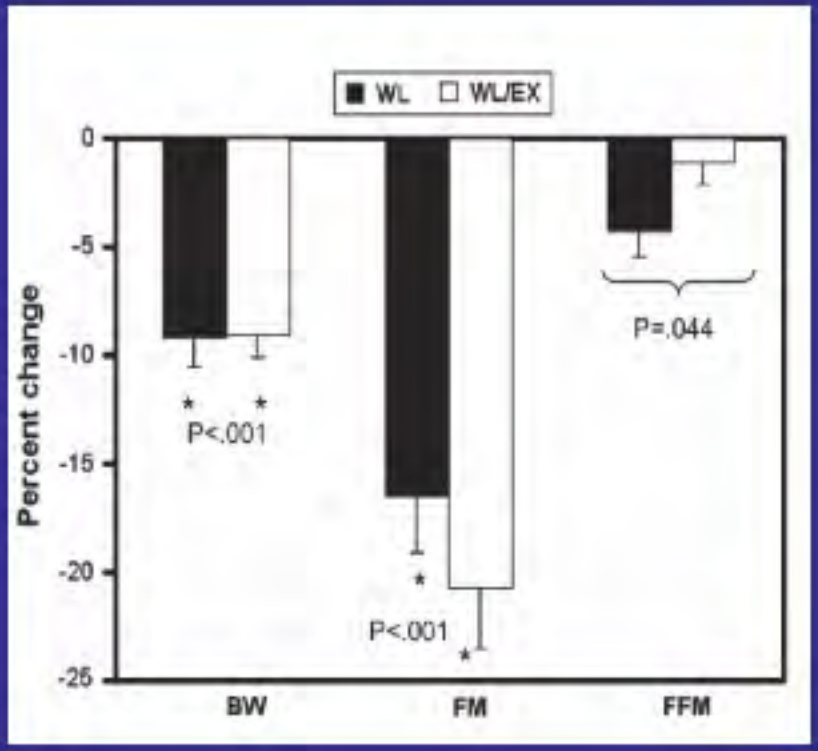
- 33% of all 91 patients
- 44% of patients with a known 12-month weight
- 57% of those who lost >15kg on LELD

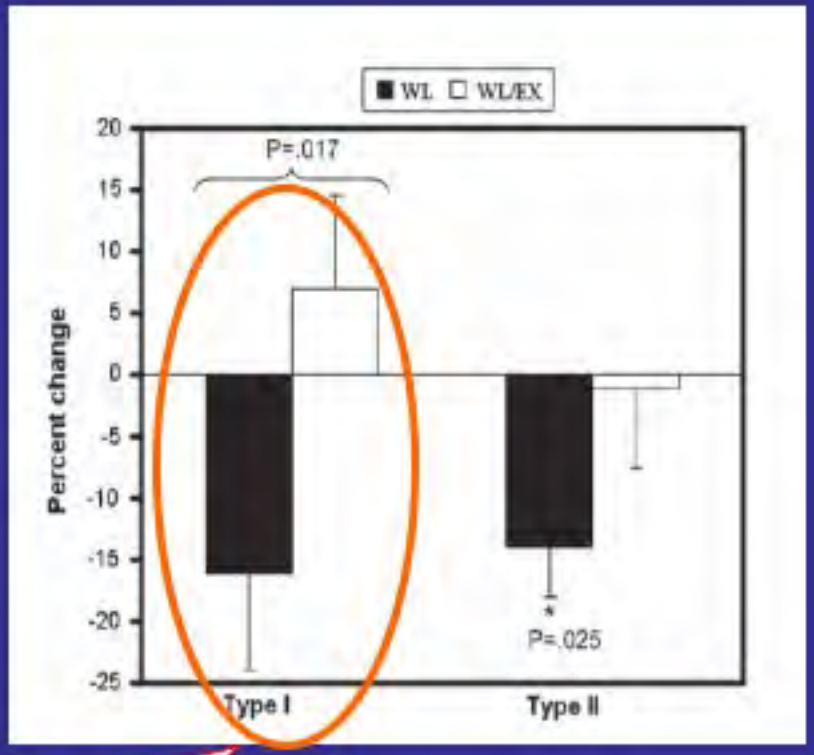
- **Highly cost-effective:**
  - 3-5 times as many can lose >15kg as with bariatric surgery

Lean et al, Br J General Practice (2013)

Weight loss depletes muscle mass and function if exercise is not included

(Chomenowski et al, LOOKAHEAD)





Oxidative, slow-twitch type-1 muscle fibres

Population response to information on reversibility of Type 2 diabetes

- T2DM people want to be non-diabetic
- Many can lose 15kg
- Most become non-diabetic

S. Steven, E. L. Lim and R. Taylor

Magnetic Resonance Centre, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK

Accepted 10 January 2013

Abstract

Aims Following publication of the Counterpoint Study (on the reversibility of Type 2 diabetes using a very low energy diet), the extent of public interest prompted the authors to make available, on a website, general information about reversing diabetes. Shortly thereafter, individuals began to feed back their personal experiences of attempting to reverse their diabetes. We have collated this information on the effects of energy restriction in motivated individuals with Type 2 diabetes that has been achieved outside a research setting.

Methods Emails, letters and telephone communications received between July 2011 and September 2012 were evaluated (n = 77: 66 men, 11 women). Median diabetes duration was 5.5 years (3 months–28 years). Reversal of diabetes was defined as achieving fasting capillary blood glucose < 6.1 mmol/l and/or, if available, HbA_{1c} less than 43 mmol/mol (6.1%) off treatment.

Results Self-reported weight fell from 96.7 ± 17.5 kg at baseline to 81.9 ± 14.8 kg after weight loss ($P < 0.001$). Self-reported fasting blood glucose levels fell from 8.3 mmol/l (5.9–33.0) to 5.5 mmol/l (4.0–10.0) after the weight loss period ($P < 0.001$). Diabetes reversal was considered to have occurred in 61% of the population. Reversal of diabetes was observed in 80, 63 and 53% of those with > 20, 10–20 and < 10 kg weight loss, respectively. There was a significant correlation between degree of weight loss and reported fasting glucose levels (Rs −0.38, $P = 0.006$). Reversal rates according to diabetes duration were: short (< 4 years) = 73%, medium (4–8 years) = 56% and long (> 8 years) = 43%.

Conclusion These data demonstrate that intentional weight loss achieved at home by health-motivated individuals can reverse Type 2 diabetes. Diabetes reversal should be a goal in the management of Type 2 diabetes.

DiRECT

Diabetes Remission Clinical Trial

2013-2018
funded by DiABETES UK
to Mike Lean and Roy Taylor

- Cluster-Randomised Trial: Counterweight-Plus* 810kcal/d LELD and weight maintenance programme vs usual care
  - Both arms follow current clinical guidelines
  - 280 patients, BMI >27, diagnosed T2DM <6 years, not on insulin
- Co-primary endpoints: weight loss >15kg and non-diabetic HbA1c
  - at 12 & 24 months off all drugs (plus life-long clinical monitoring)

- Mechanistic and Magnetic Resonance studies
- Qualitative and process evaluation

- Planned economic analyses

* Supported by Cambridge Weight Plan

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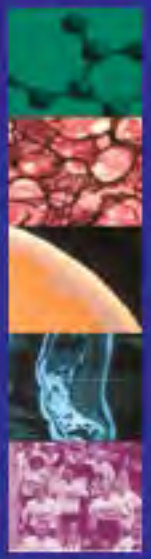

DiRECT
Diabetes Remission Clinical Trial

Mechanistic Studies – Newcastle

(n = 88, at baseline, 3 &12m)

Day 1

Pancreas and liver fat	Abdominal Magnetic Resonance scanning
Beta-cell function	Stepped hyperglycaemic clamp & arginine stimulation, to measure maximal insulin

Day 2

Whole body glucose & lipid oxidation	Indirect calorimetry (fasting & rested)
$VLDL_1$ and VLDL-apoB100 secretion	Intralipid (fat) infusion
PNPLA3 genotyping	

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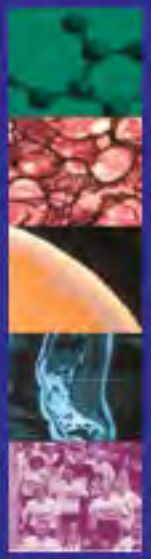

DiRECT
Diabetes Remission Clinical Trial

Qualitative Evaluations

During WL, FR and Maintenance phases

Participants:

Cognitive, affective and social predictors of adherence	Mobile phone based Ecologic Momentary Assessment (EMA)
Barriers, facilitators & strategies for self-control	Semi-structured theory domain interviews
Quality of Life	EQ-5D questionnaire

Health Professionals:

Barriers to implementation & ease of engagement with the intervention	Semi-structured theory domain interviews

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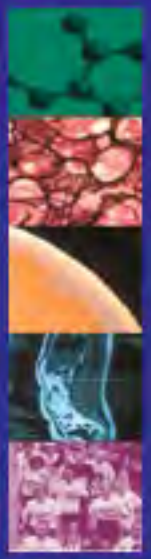

DiRECT
Diabetes Remission Clinical Trial

Team

Principal Investigators

Professor Mike Lean
Professor Roy Taylor

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Louise McCombie
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Partners:
Glasgow University, Newcastle University,
Diabetes UK, Counterweight Ltd, Cambridge Weight Plan

NHS
Greater Glasgow and Clyde

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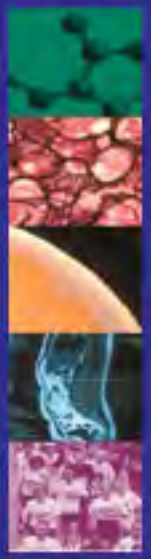


Conclusions

1. 'Well-treated' type 2 diabetes is not a well-treated patient
   - Still a devastating disease, despite drugs and guidelines

2. Being non-diabetic is now a reasonable goal
   - Maintain waist <80 cms (women), <94cms (men)
   - If pre-diabetic: lose 5kg and maintain weight loss
   - If diabetic: lose >15kg and maintain weight loss

3. Personal commitment to weight control is essential
4. Matched professional commitment and training is essential

5. Public Health responsibility is essential to oppose obesogenic commercial and political activities

Routine management of T2DM

1st priority - reduce dietary fats (esp. saturated fat)
and lose >15kg weight, maintaining physical activity

- Not just sugar avoidance
- Not primarily drugs
- Formula diets are more effective than conventional lifestyle advice, and more cost-effective than bariatric surgery

2nd priority - prevent weight gain/ treat obesity in pre-diabetic family members

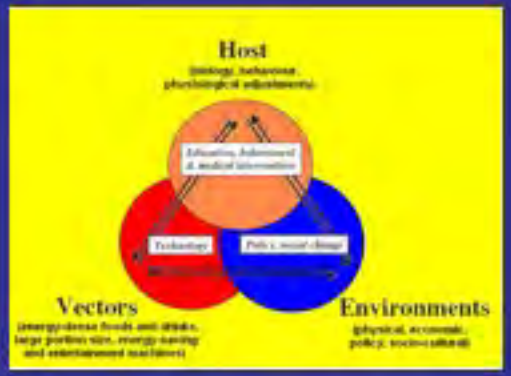
So - Doctors and nurses must be trained, and resourced, to offer:

- Optimal evidence-based diets, for weight loss
- Lifestyle advice & support for long-term weight maintenance

Ethics of treatments for diabetes

- No drug should be prescribed without urging personal responsibility, with professional support, for diet and lifestyle change
- No clinical trial in T2DM patients should be permitted unless optimal diet and lifestyle advice is given to both intervention and placebo arms
- Prescribing physicians should have training and resources to provide optimal evidence-based diet and lifestyle advice
    - AND ACCEPT THAT NOT ALL WILL SUCCEED

Epidemic!*



Medical Responsibility

Optimal medical treatment within available resources

- Diet & lifestyle
- Drugs
- Surgery

Political Responsibility

Government interventions to remove primary causes

- Catering outlets — increasing
- Meals/snacks outside home — increasing
- Portion sizes — increasing

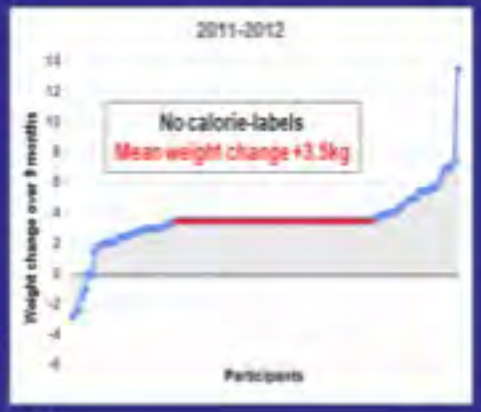
- Physical inactivity……

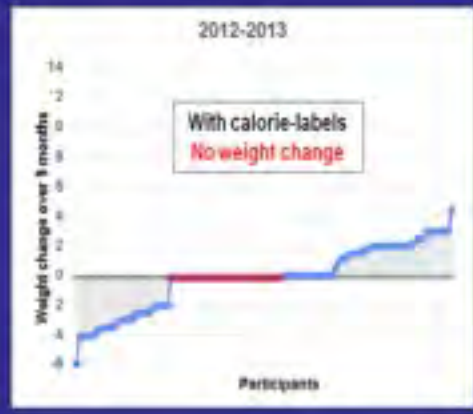
*** WHO: 'Critical Threshold for Intervention'**

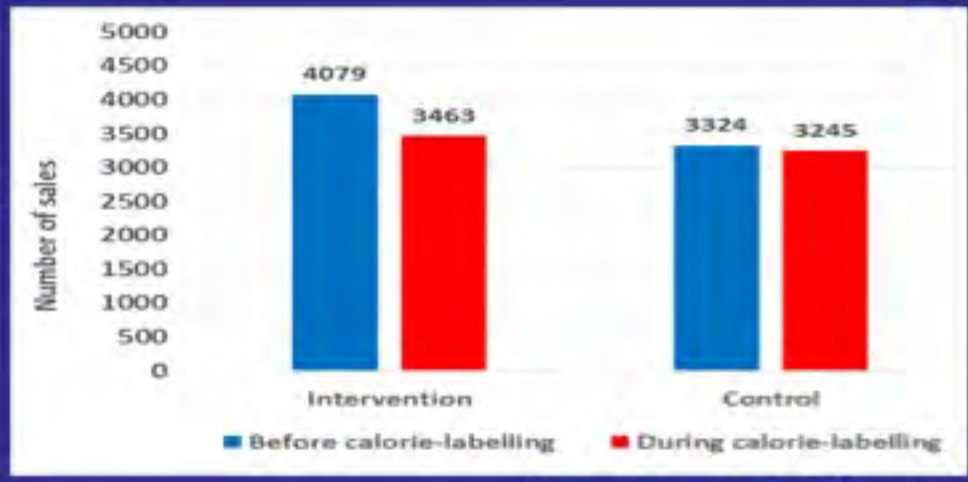
New evidence for primary prevention of obesity:
---------- prominent Calorie-Labelling

- Systematic Review: Overall no effect of calorie labelling, but -124kcal for those who noticed the labels (Nikolaou et al, IJO, 2014)
- Meals currently supplied to young adults are excessively calorie-rich (Nikolaou et al Int J Obesity, 2014)
- Prominent main-meal calorie-labelling prevents weight gain over 9 months in young adults (Nikolaou et al, Obesity 2014)
- Prominent calorie-labelling at self-serve food outlets leads to lower-calorie choices (Nikolaou et al Preventive Medicine, 2014)

(all: Nikolaou, Hankey & Lean, 2014)







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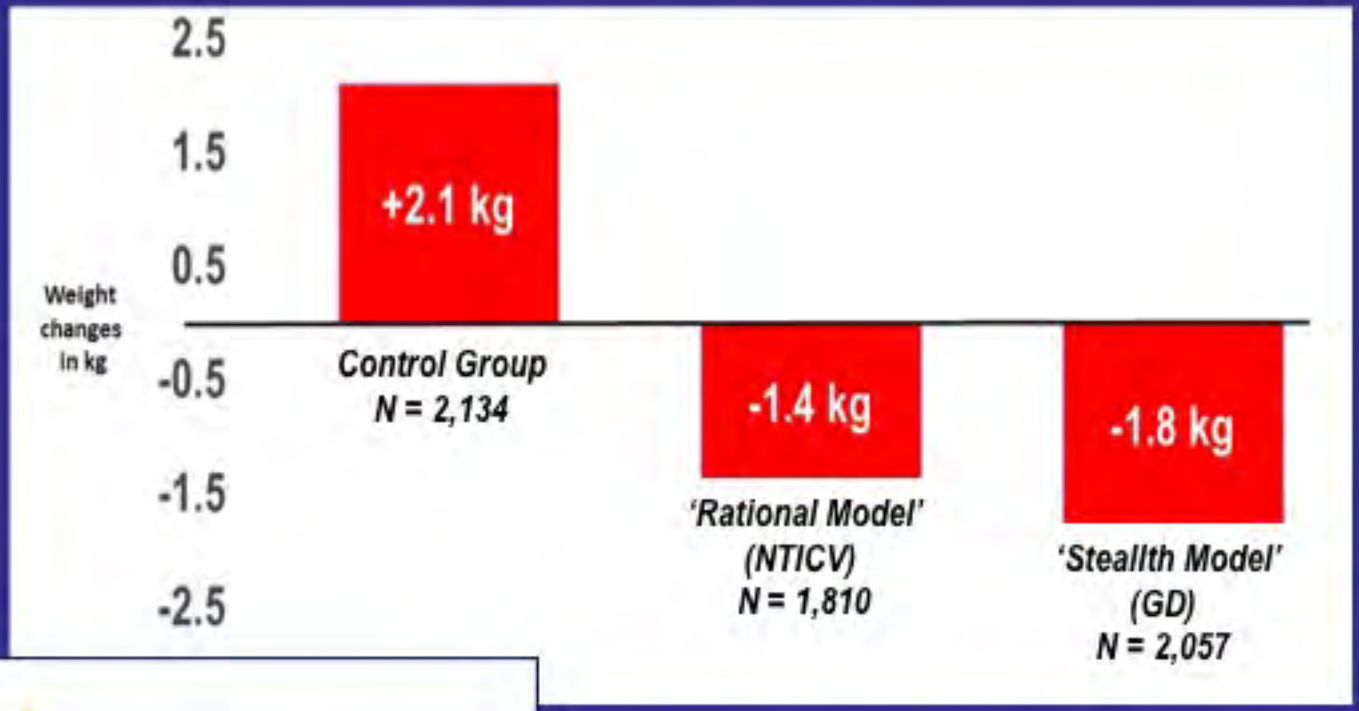
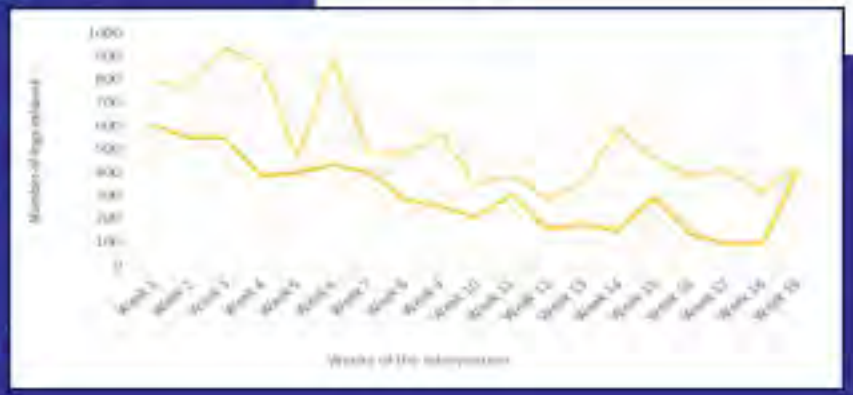
9-month weight changes in 20,975 young adults randomised to an on-line public health intervention





(Nikolaou, Hankey & Lean, under review, 2015)

human nutrition
at glasgow

You can all help prevent obesity/diabetes

You can all help prevent obesity/diabetes

(Completely out of Order)

(Completely off the map)