Can We Reverse Type 2 Diabetes?

Dr. Mohamed Farghaly

FRCGP(UK).MRCGPI(UK).DIH(IRELAND)

DMSc(UK).MBChB(ALEX)

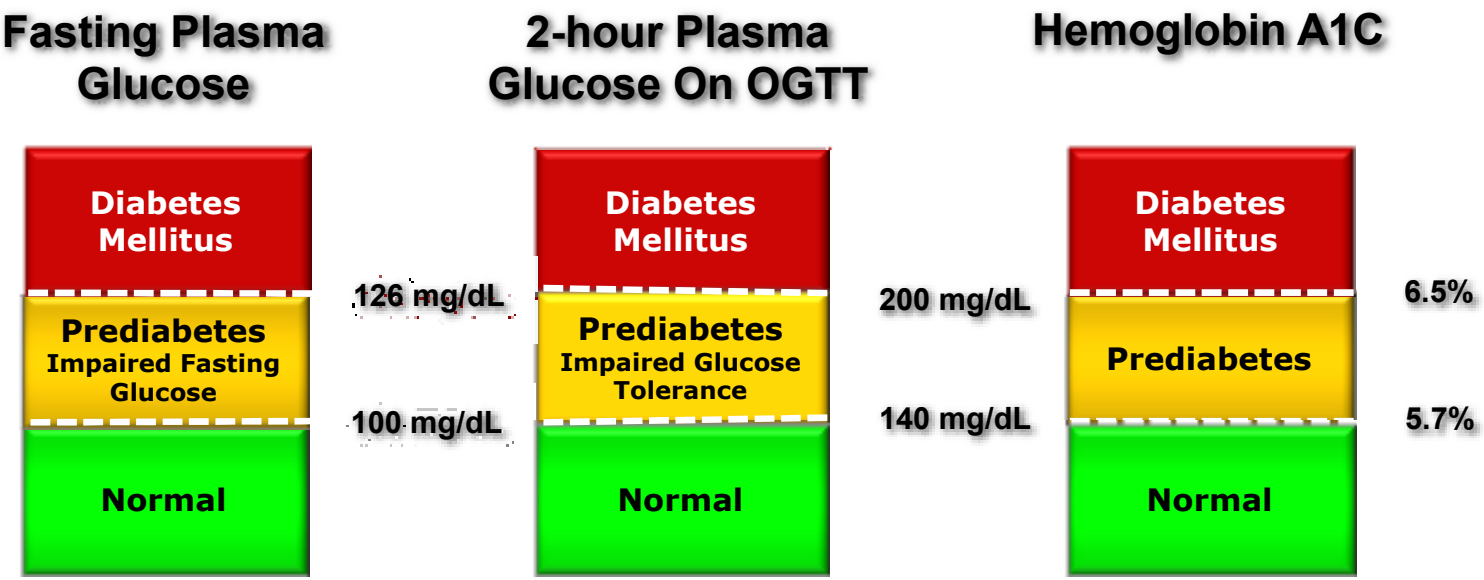
A.Professor Dubai Medical College

Consultant DHIC

Learning Objectives

- Define and know the prognosis of prediabetes
- The Prevalence of T2DM & Obesity
- Definition and classification of obesity
- Prevention Studies in People with IGT Downstream strategies
- How we Reverse Type 2 Diabetes?

What is Prediabetes?



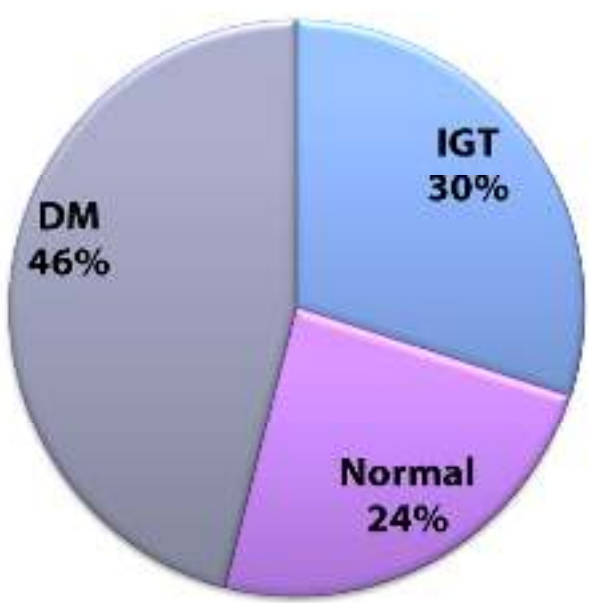
Any abnormality must be repeated and confirmed on a separate day

The diagnosis of diabetes can also be made based on unequivocal symptoms and a random glucose >200 mg/dL

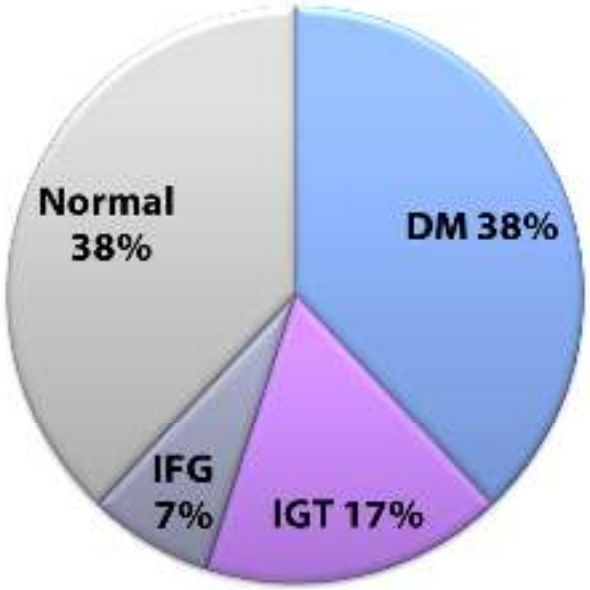
Adapted from:
American Diabetes Association. *Diabetes Care.* 2014;37 Suppl 1:S81-90.

Does Prediabetes Predict Diabetes?

Progression of IGT/IFG to DM in11year follow up



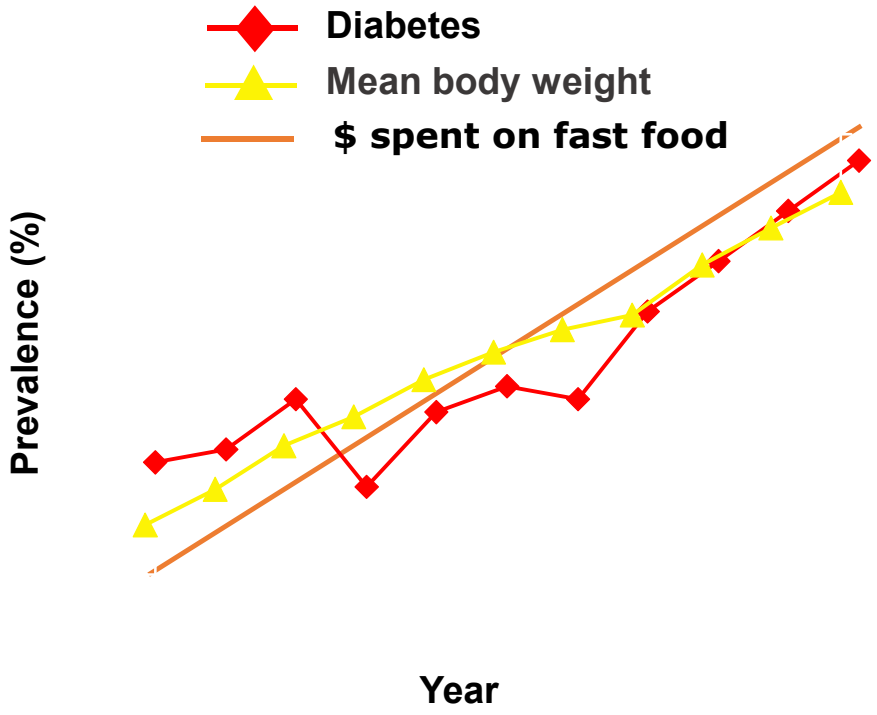
Persons with IGT



Persons with IFG

Stephen Twigg. Pre diabetes Symposium ADS & ADEA Annual Scientific Meeting Sydney 2004

The Prevalence of T2DM & Obesity



Prevalence of obesity, increased by 61% since 1991

65% of US adults are overweight

BMI and weight gain major risk factors for diabetes

JAMA.1999;282:1519-1522 & JAMA.2001;286:1195-1200.

Definition and classification of obesity

- Obesity is defined as abnormal or excessive fat accumulation that may impair health
- Body mass index (BMI) provides the most convenient population-level measure of overweight and obesity currently available

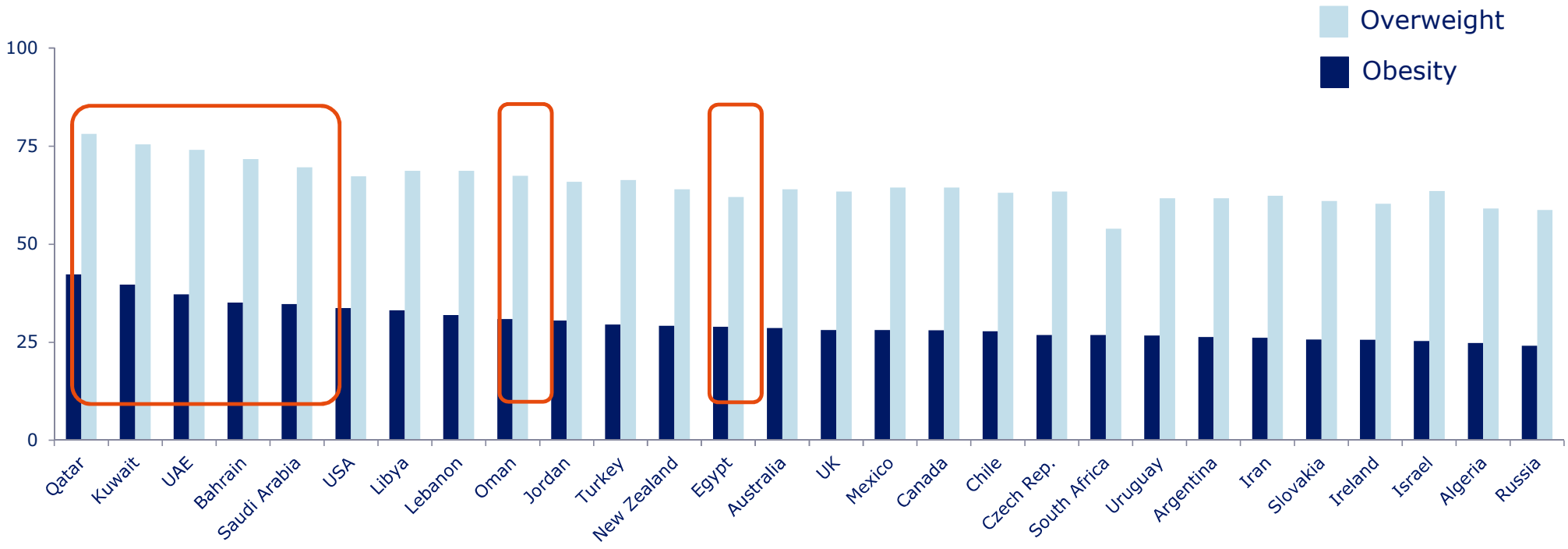
$$BMI = \frac{weight\ (kg)}{height\ (m^2)}$$

Classification	BMI (kg/m²)
Underweight	<18.5
Normal range	≥18.5 and <25
Overweight	≥25 and <30
Obesity	≥30
Obesity class I	≥30 and <35
Obesity class II	≥35 and <40
Obesity class III	≥40

WHO. Factsheet 311. 2014. http://www.who.int/

UAE is among the highest levels of overweight and obesity globally

Age-standardised adjusted estimates for adults with BMI ≥30 kg/m^2 and BMI ≥25 kg/m^2



BMI, body mass index

Mendis *et al.* World Health Organization global status report on noncommunicable diseases. 2014. Saeed *et al. Obesity* 2018;26:474–84; 2. Fahed *et al. J Nutr Metab.* 2012;109037. doi: 10.1155/2012/109037 [Epub 2012 Mar 29]. Khan *et al. BMC Medical Genetics* 2018;19:11

7 Million Moroccans Suffer from Obesity: UN Report

Seven million Moroccans, or an astonishing 20.6 percent of the population, were suffering from obesity as of 2014,

5.4 percent increase compared to 2005, according to UN State of Food Security and Nutrition in their World 2017

United Arab Emirates

In 2014, 31% of adults in the UAE had obesity,[1,2] costing society 8.1 billion UAE for treating its health consequences[2]

3 in 10 ADULTS HAD OBESITY IN 2014[1,2] > **2.3 MILLION** PEOPLE[2]

By 2025 **39%** OF ADULTS WILL HAVE OBESITY IF ACTION IS NOT TAKEN[2] > **3.1 MILLION** PEOPLE[2]

> 15,300 ADULTS DIED FROM OVERWEIGHT AND OBESITY RELATED CAUSES IN 2015 - **42 DEATHS EACH DAY**[3‡]

3,540 UAE[†] was the average healthcare cost of obesity-related complications per person with obesity in 2014[2§]

Investing 154 million UAE[†] between 2014–2025 for treating obesity could **successfully reduce** the adult prevalence of obesity by 1% by 2025[2**]

(Based on calculations from the World Obesity Federation)

In 2017, anti-obesity medication represented only **0.74%** of the total cost of treating the consequences of obesity[2,4††]

1. Risk Factor Collaboration (NCD-RisC). Lancet 2016:387;1377–96 2. World Obesity Federation. World Obesity Day, Our data. 2017 3. The GBD 2015 Obesity Collaborators. New England Journal of Medicine. 2017;377:13–27. 4. IQVIA. Total value of anti-obesity medication in 2017. 2018.

Obesity is recognised as a disease and health issue

American organisations and regulatory bodies

AACE

"…obesity is a primary disease, and the full force of our medical knowledge should be brought to bear on the prevention and treatment of obesity as a primary disease entity"[1]

American Association of Clinical Endocrinologists

FDA

"Obesity is a chronic relapsing health risk defined by excess body fat"[3]

The US Food and Drug Administration

AMA

"Recognizing obesity as a disease will help change the way the medical community tackles this complex issue that affects approximately one in three Americans"[2]

American Medical Association

TOS

"After extensive dialogue and careful consideration, the Council concludes that it is the official position of The Obesity Society that obesity should be declared a disease"[4]

The Obesity Society

1. Mechanick *et al*. *Endocr Pract* 2012;18:642–8; 2. AMA position statement. Available at: http://www.ama-assn.org/; 3. Food and Drug Administration. Guidance for Industry Developing Products for Weight Management 2007 Available here. 4. Council of the Obesity Society. *Obesity (Silver Spring)* 2008;16:1151;

Obesity is recognised as a disease and health issue

Global organisations and major regulatory bodies

WHO

"Obesity is a chronic disease, prevalent in both developed and developing countries, and affecting children as well as adults"[1]

World Health Organization

EMA

"Obesity is recognised as a chronic clinical condition and is considered to be the result of interactions of genetic, metabolic, environmental and behavioural factors, and is associated with increases in both morbidity and mortality"[2]

European Medicines Agency

WOF

"The World Obesity Federation takes the position that obesity is a chronic, relapsing, progressive disease process and emphasizes the need for immediate action for prevention and control of this global epidemic"[3]

World Obesity Federation

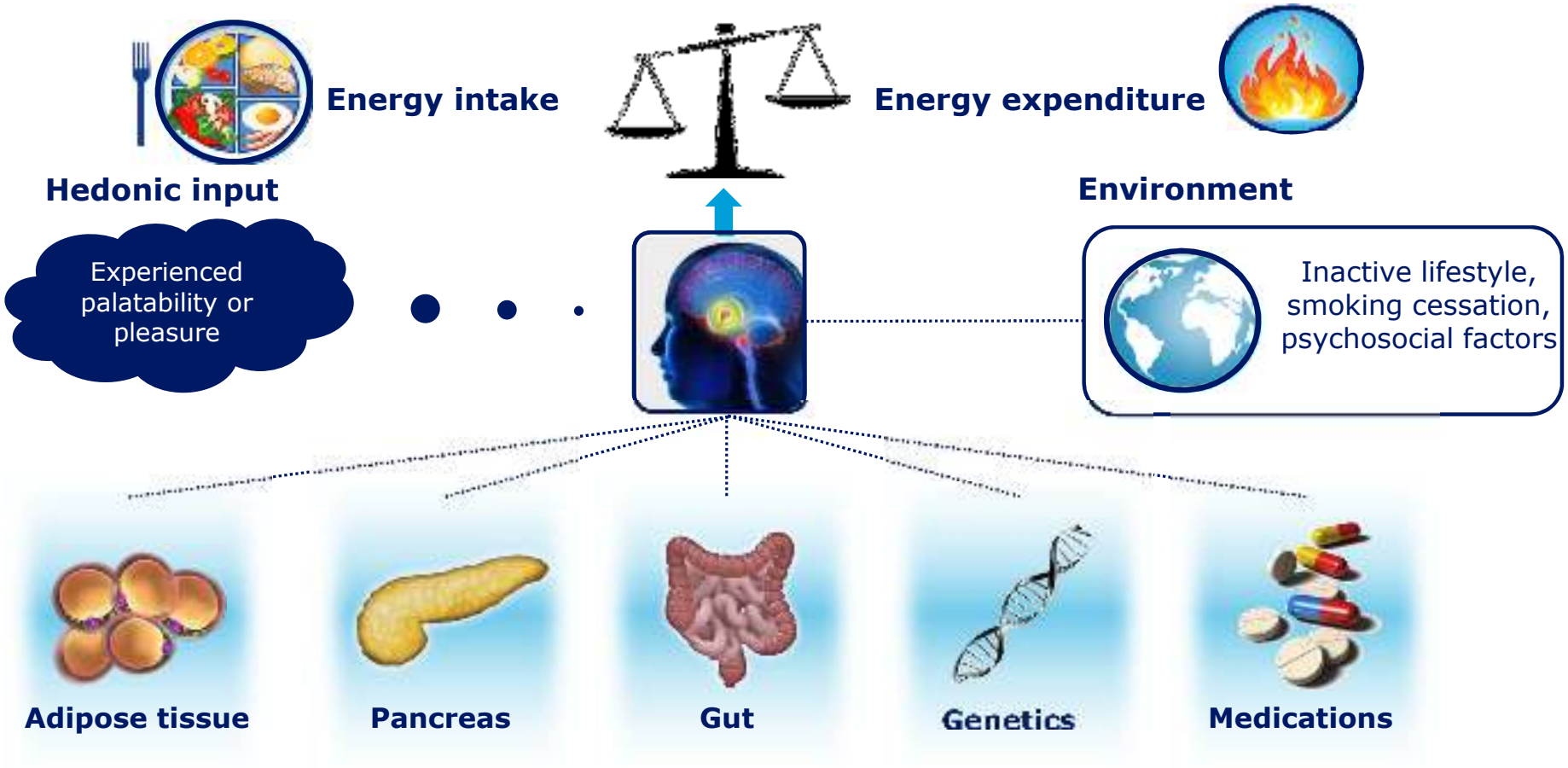
EASO

"A progressive disease, impacting severely on individuals and society alike, it is widely acknowledged that obesity is the gateway to many other disease areas…"[4]

European Association for the Study of Obesity

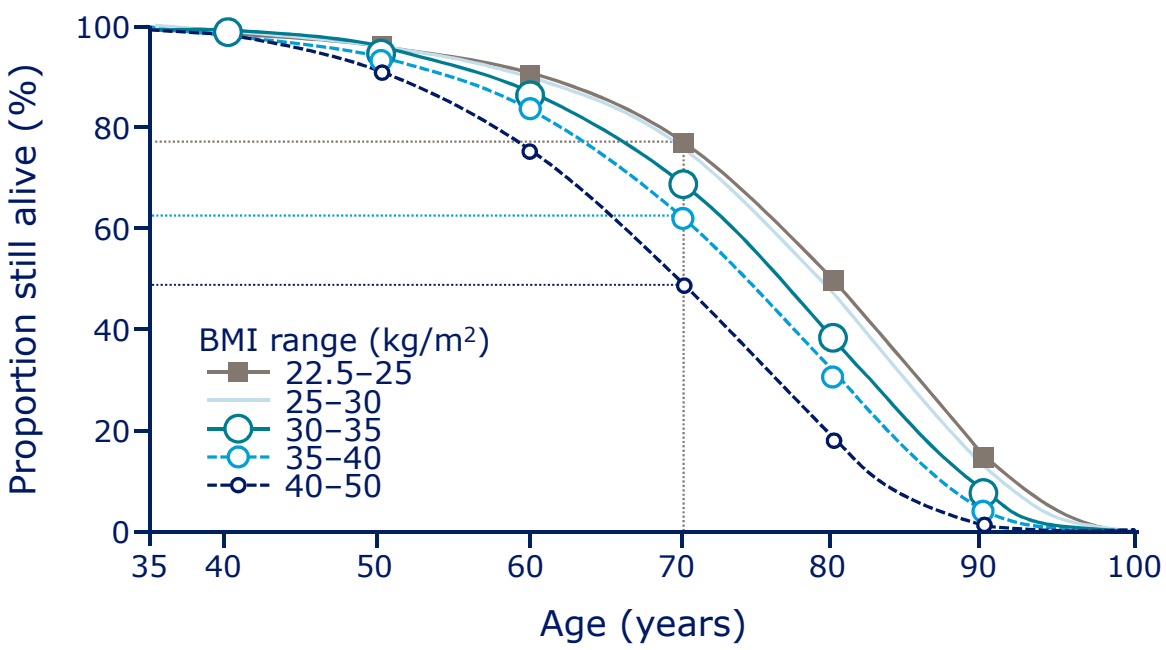
1. World Health Organization. Obesity: Preventing and Managing the Global Epidemic. World Health Organization: Geneva, Switzerland, 1998; 2. EMA Draft Guideline on clinical evaluation of medicinal products used in weight control EMA/CHMP/311805/2014. Available here; 3. Bray GA *et al. Obes Rev* 2017;18:715–723; 4. EASO: 2015 Milan Declaration: A Call to Action on Obesity. Available here

Obesity is a complex and multifactorial disease



1. Badman, Flier. *Science* 2005;307:1909–14; 2. US Department of Health and Human Services, 1998. NIH Publication No. 98-4083

Life expectancy decreases as BMI increases



Normal BMI = almost 80% chance of reaching age 70

BMI 35–40 = ~60% chance of reaching age 70

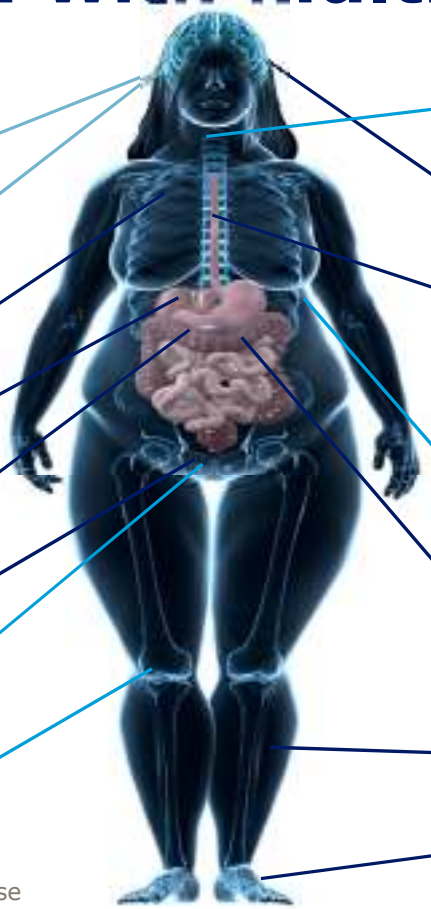
BMI 40–50 = ~50% chance of reaching age 70

Data are based on male subjects; n=541,452

Prospective Studies Collaboration. *Lancet* 2009;373:1083–96

Obesity is associated with multiple complications

Metabolic, mechanical and mental

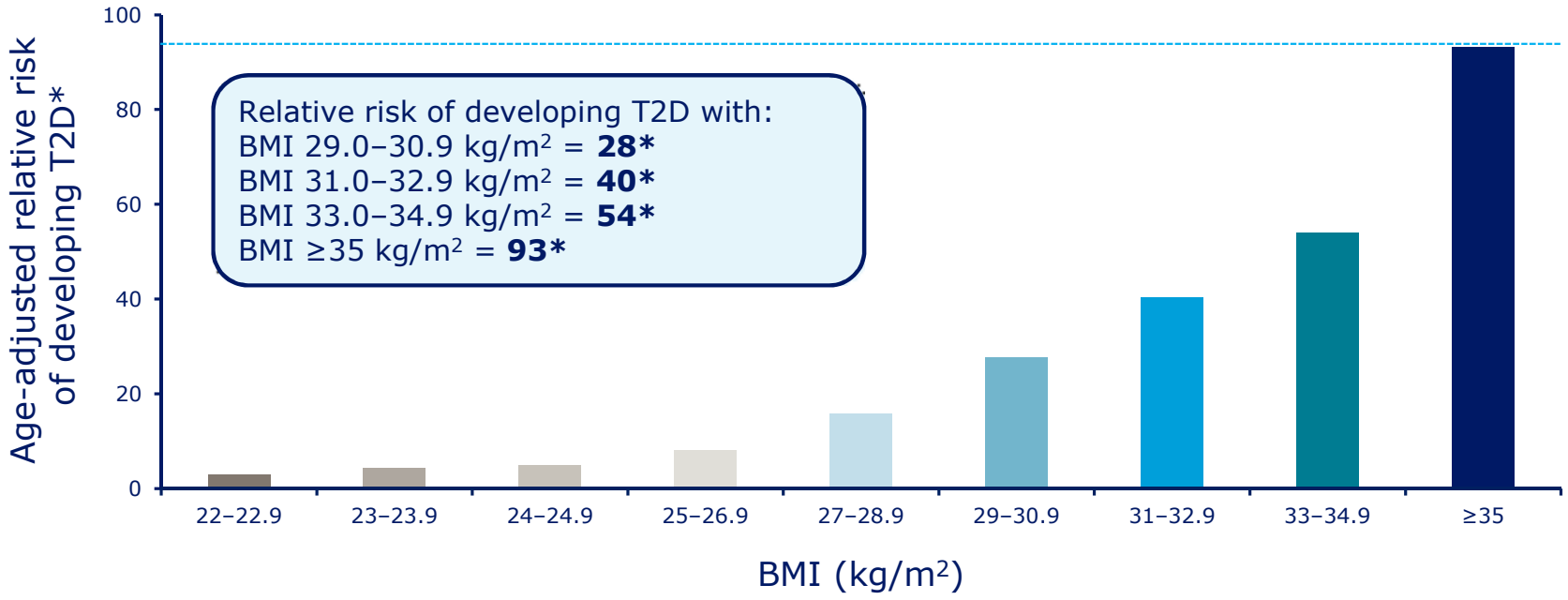


- Metabolic
- Mechanical
- Mental
- Depression
- Anxiety
- Asthma
- NAFLD
- Gallstones
- Infertility
- Incontinence
- Arthrosis
- Cancers*
- Physical functioning
- Sleep apnoea
- CVD and risk factors
  - Stroke
  - Dyslipidaemia
  - Hypertension
  - Coronary artery disease
  - Congestive heart failure
  - Pulmonary embolism
- Chronic back pain
- Type 2 diabetes
  Prediabetes
- Thrombosis
- Gout

CVD, cardiovascular disease; NAFLD, non-alcoholic fatty liver disease
*Including breast, colorectal, endometrial, esophageal, kidney, ovarian, pancreatic and prostate

Adapted from Sharma AM. *Obes Rev*. 2010;11:808-9; Guh *et al. BMC Public Health* 2009;9:88; Luppino *et al. Arch Gen Psychiatry* 2010;67:220–9; Simon *et al. Arch Gen Psychiatry* 2006;63:824–30; Church *et al. Gastroenterology* 2006;130:2023–30; Li *et al. Prev Med* 2010;51:18–23; Hosler. *Prev Chronic Dis* 2009;6:A48

Relative risk of developing T2D by BMI category

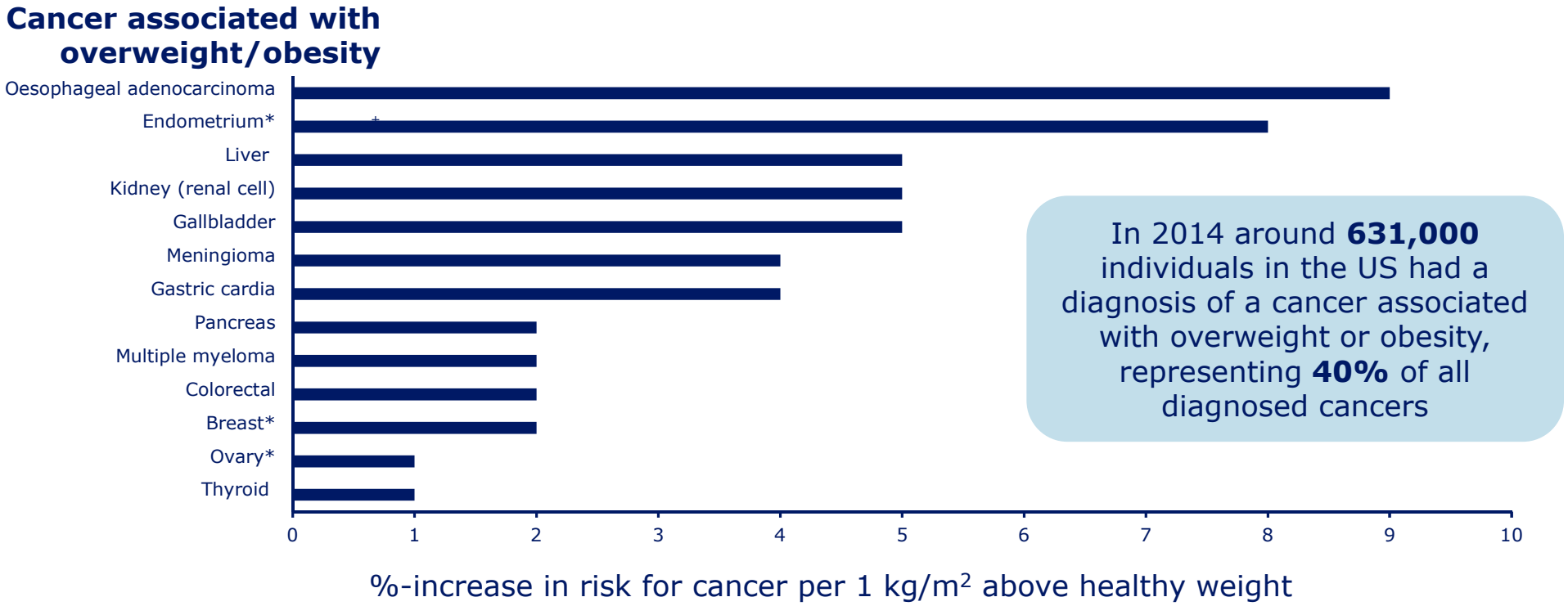


*vs. BMI <22 kg/m²; Data are for women only. n=114,281 female registered nurses aged 30–55 years; T2D, type 2 diabetes

Colditz *et al. Ann Intern Med* 1995;122:481–6

BMI-associated risk increase for specific cancers

Percentage increase in risk per 1 kg/m^2 increase in BMI by cancer type in the US



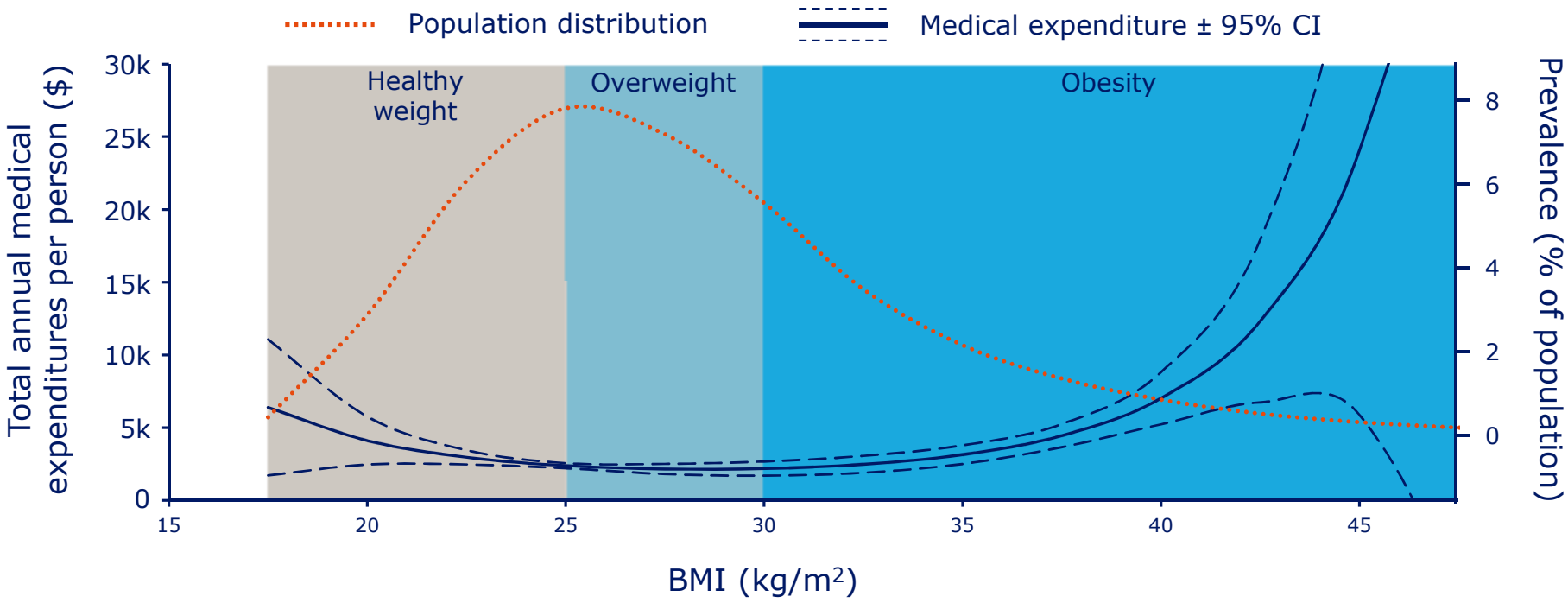
In 2014 around **631,000** individuals in the US had a diagnosis of a cancer associated with overweight or obesity, representing **40%** of all diagnosed cancers

*Female only. †Corpus uterus.
Based on relative risk estimates from pooled epidemiologic studies. Healthy weight, 18.5–25 kg/m^2.

Centre for Disease Control and Prevention. Vital Signs: Trends in Incidence of Cancers Associated with Overweight and Obesity — United States, 2005–2014. https://www.cdc.gov/mmwr/volumes/66/wr/mm6639e1.htm [accessed Nov 2017]

Obesity is associated with significant healthcare costs

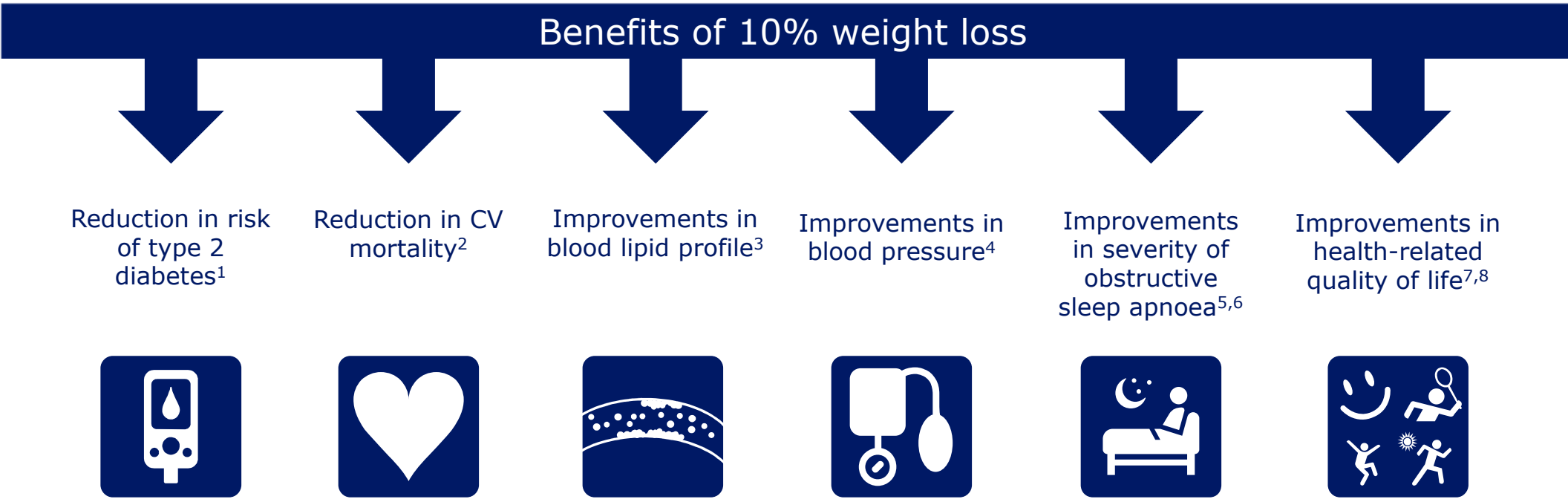
US annual medical expenditure



CI, confidence interval; US, United States

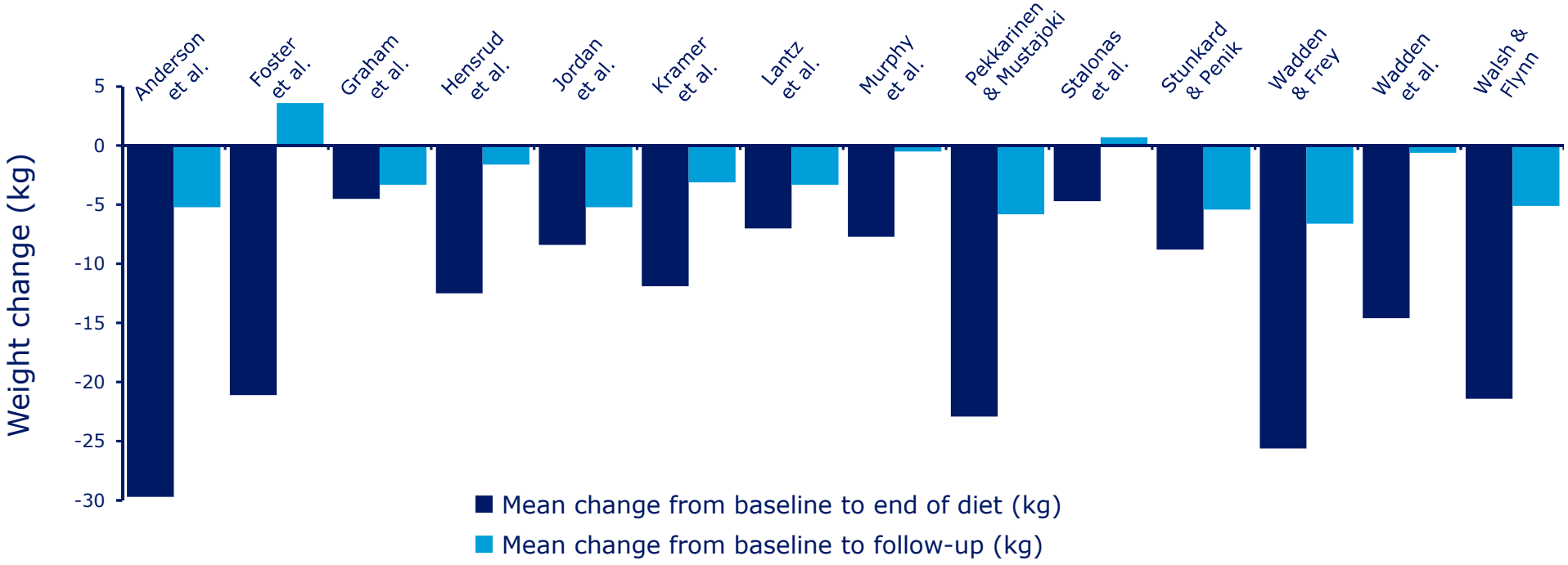
Cawley *et al. Pharmacoeconomics* 2015;33:707–22

Weight loss may improve obesity related complications



1. Knowler *et al*. *N Engl J Med* 2002;346:393–403; 2. Li *et al*. *Lancet Diabetes Endocrinol* 2014;2:474–80; 3. Datillo *et al*. *Am J Clin Nutr* 1992;56:320–8; 4. Wing *et al*. *Diabetes Care* 2011;34:1481–6; 5. Foster *et al*. *Arch Intern Med* 2009;169:1619–26; 6. Kuna *et al*. *Sleep* 2013;36:641–9; 7. Warkentin *et al*. *Obes Rev* 2014;15:169–82; 8. Wright *et al*. *J Health Psychol* 2013;18:574–86

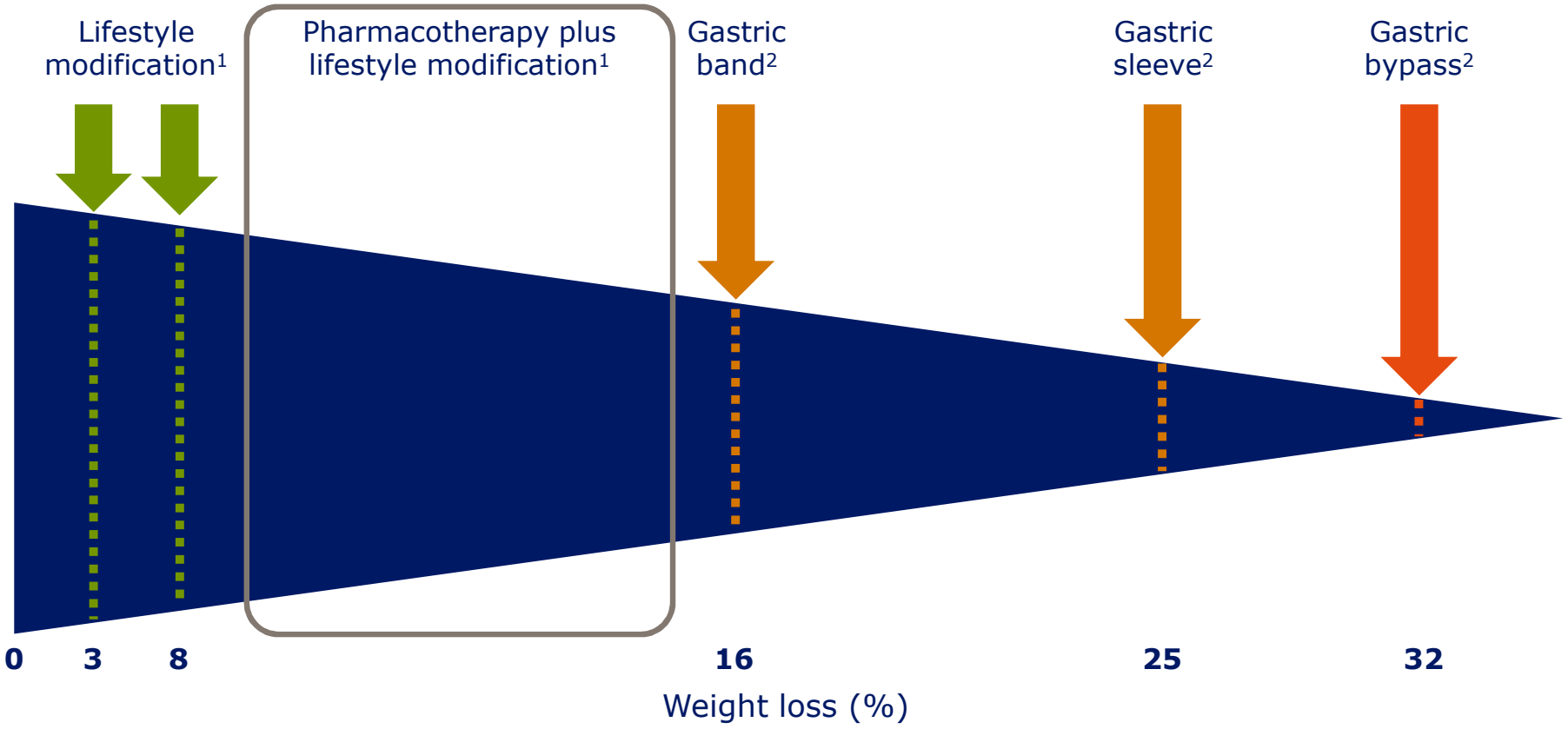
Maintenance of weight loss is challenging



Follow-up range from 4 to 7 years

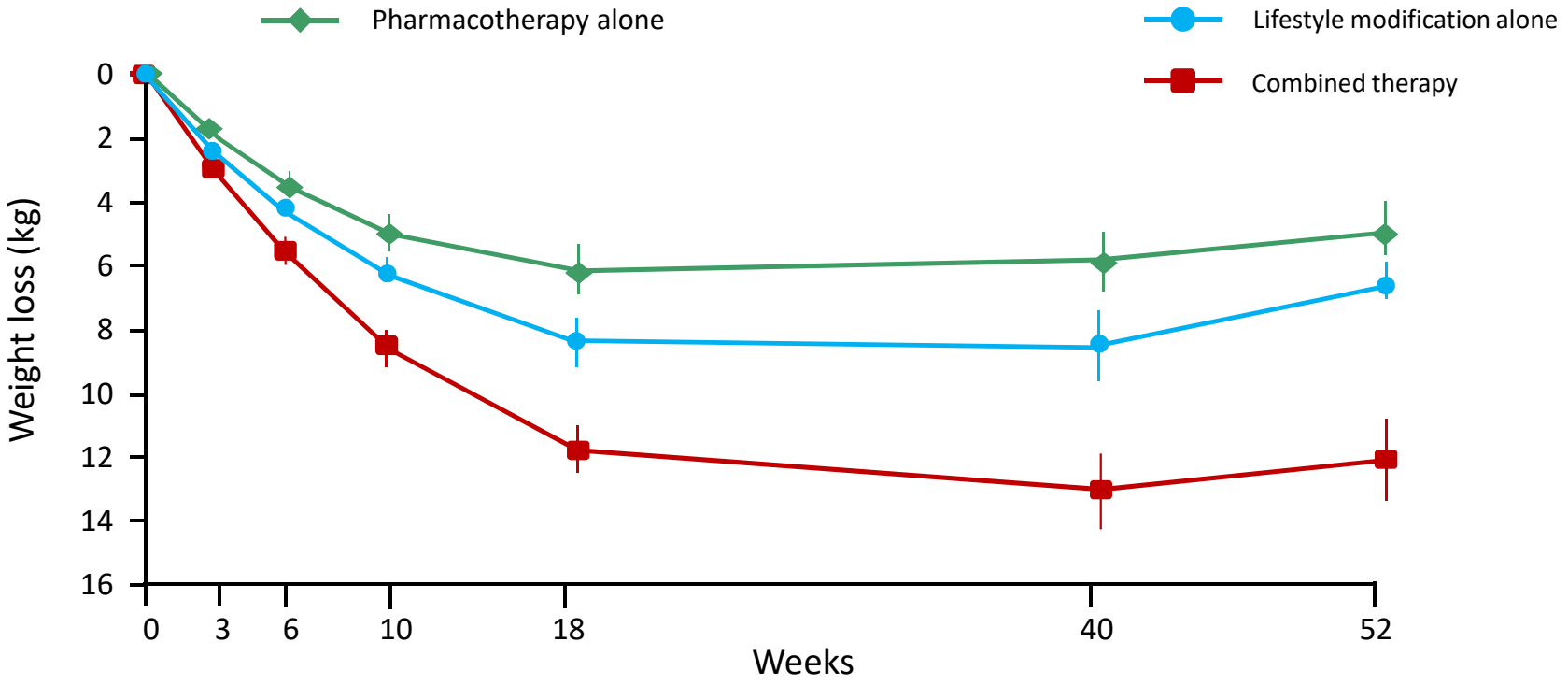
Mann *et al. Am Psychol* 2007;62:220–33

Unmet pharmacological need for obesity treatment



1. Jensen *et al. Circulation* 2014;129(25 Suppl 2):S102–38; 3. Courcoulas *et al. JAMA* 2013;310:2416–25; 3. Obesity Drug Outcome Measures: A Consensus Report of Considerations Regarding Pharmacologic Intervention. Available at: http://sphhs.gwu.edu/pdf/releases/obesitydrugmeasures.pdf (accessed 15 February 2016)

Pharmacotherapy in addition to diet and exercise can help patients achieve clinically relevant weight loss



The marketing authorisation for sibutramine has been suspended by the EMA. Data are mean ± SE. Pharmacotherapy: sibutramine
Pharmacotherapy alone: Patients received a daily dose of 15 mg/day; Lifestyle modification alone: Patients attended 30 lifestyle counselling sessions; Pharmacotherapy + brief therapy: Patients were given sibutramine and received brief lifestyle counselling; Combined therapy: Patients received sibutramine and attended 30 lifestyle counselling sessions.

Wadden T et al. *N Engl J Med*. 2005;353:2111–20.

Pharmacotherapy helps with adherence to a lifestyle change

- Increase the **number** of patients responding to lifestyle modification
- Increase the **magnitude** of the response
- Increase the **duration** of the response

Adapted from Lau et al. Can Med Assoc J 2007;176:S1–S13

Feasibility of Preventing T2DM

- There is a long period of glucose intolerance that precedes the development of diabetes
- Screening tests can identify persons at high risk
- Predicts high risk for development of diabetes
- Predicts high risk for development of atherosclerotic vascular disease
- There are safe, potentially effective interventions that can prevent the above modifiable risk factors such as lifestyle and pharmacologic interventions

Prevention Studies in People with IGT Downstream strategies

- Lifestyle interventions
  - Da Qing : Diet and Exercise
  - Malmo study : Diet and exercise
  - Finish Diabetes Prevention Study Lifestyle
  - DPP (Diabetes Prevention Study) Lifestyle, MF (Glitazone)
- Lifestyle interventions with pharmacological agents
  - FHS (Fasting Hyperglycaemia Study) Healthy Living & SU
  - EDIT (Early Diabetes Intervention Study): Acarbose and MF
  - STOP NIDDM : Acarbose

Diabetes Prevention Programme (DPP)

- 27 centres
- 3234 participants
- > Or = 25 years
- BMI > or = 24 (22 for indo Asian)
- IGT
- 45%
  - American Indian, African American, Hispanic American, Asia American, pacific islanders

DPP

Average Age 51 Years
BMI 34

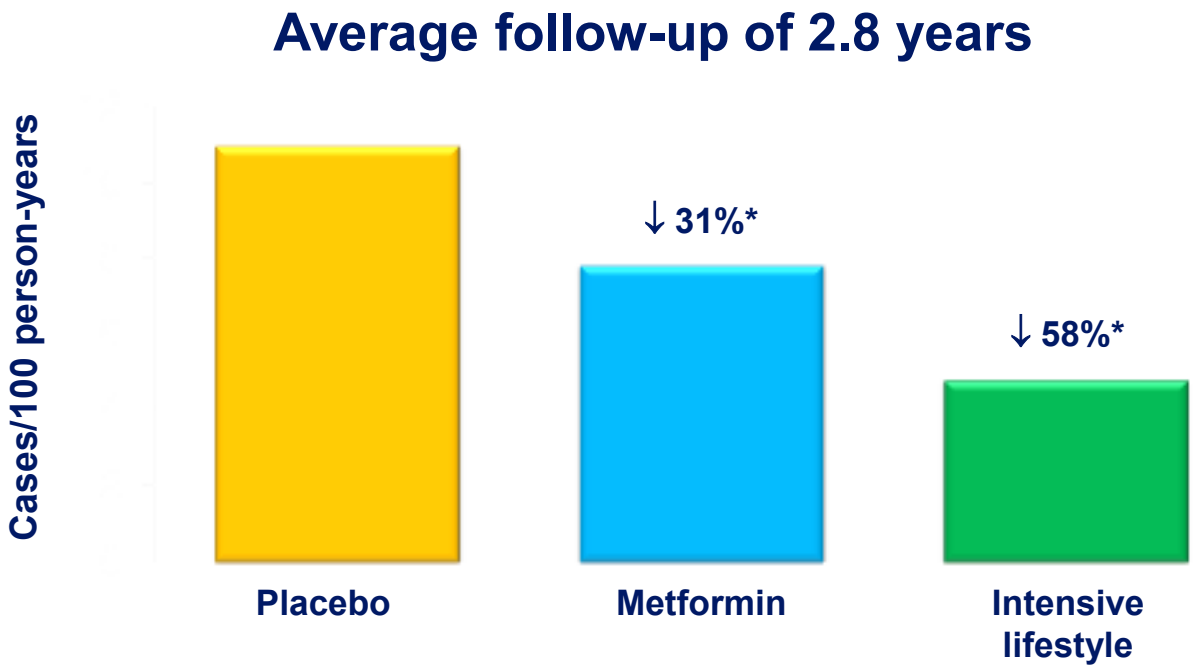
Lifestyle intervention

Weight reduction 7%

- Low fat diet
- Exercise for 150 mins per week

OR metformin 850mgs BD

Diabetes Prevention Program DPP Progression to Type 2 Diabetes



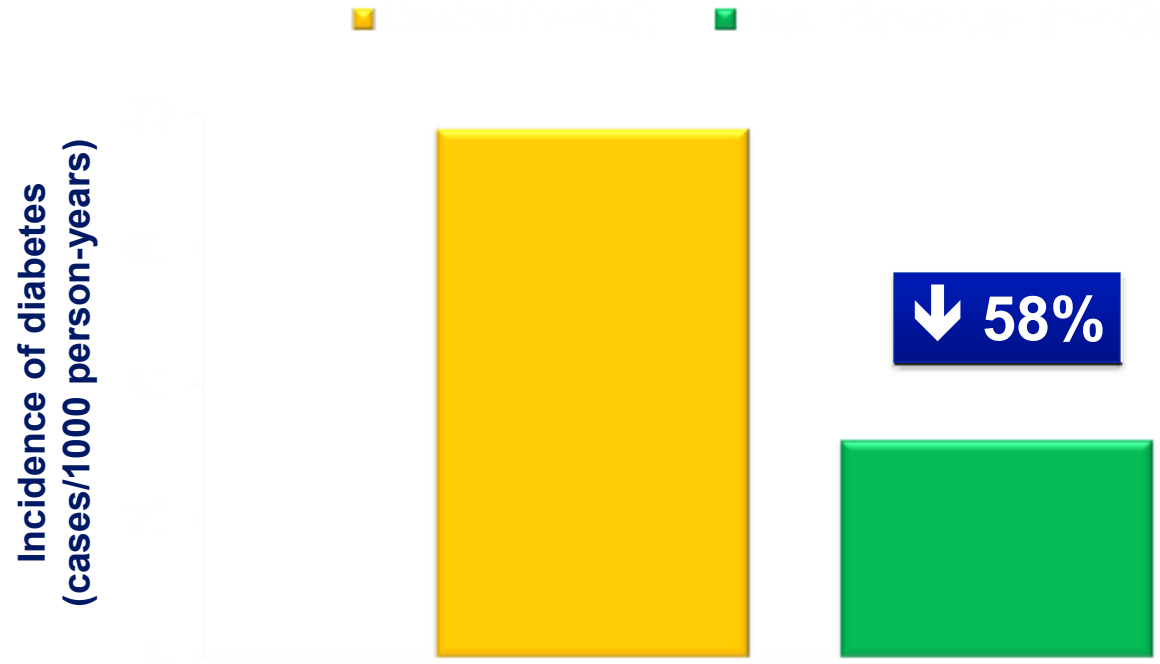
*All pairwise comparisons significantly different by group;

The Diabetes Prevention Program Research Group. N Eng. J Med. 2002;346:393.

Finish Diabetes Prevention Study

- Dietary and Exercise Intervention
- Goals
  - 5% weight loss
  - Total fat intake < 30%
  - Saturated fat intake <10%
  - Fibre >15gm per 1000 kcal
  - Moderate exercise for 30 mins every day
    - Seven sessions in first year,1 session nutritionalist every 3 months throughout 4 year study

The Finnish Diabetes Prevention Study Lifestyle Modifications (cont'd)



Tuomilehto et al. N Engl J Med. 2001;344:1343.

DiRECT
(Diabetes Remission Clinical Trial)

First time randomized trial shows remission of T2DM with dietary and lifestyle intervention

Lean MEJ, Leslie WS, Barnes AC, *et al.* Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. The Lancet 2017

DiRECT: Background & objective

Background

- T2DM management is focused on pharmacological treatment
- Caloric restriction is beneficial for T2DM patients, but not tested in routine primary care.

Study objective

The DiRECT study was designed to assess whether intensive weight management can produce sustained remission of T2DM in the primary care setting.

Study design (1)

Main inclusion criteria

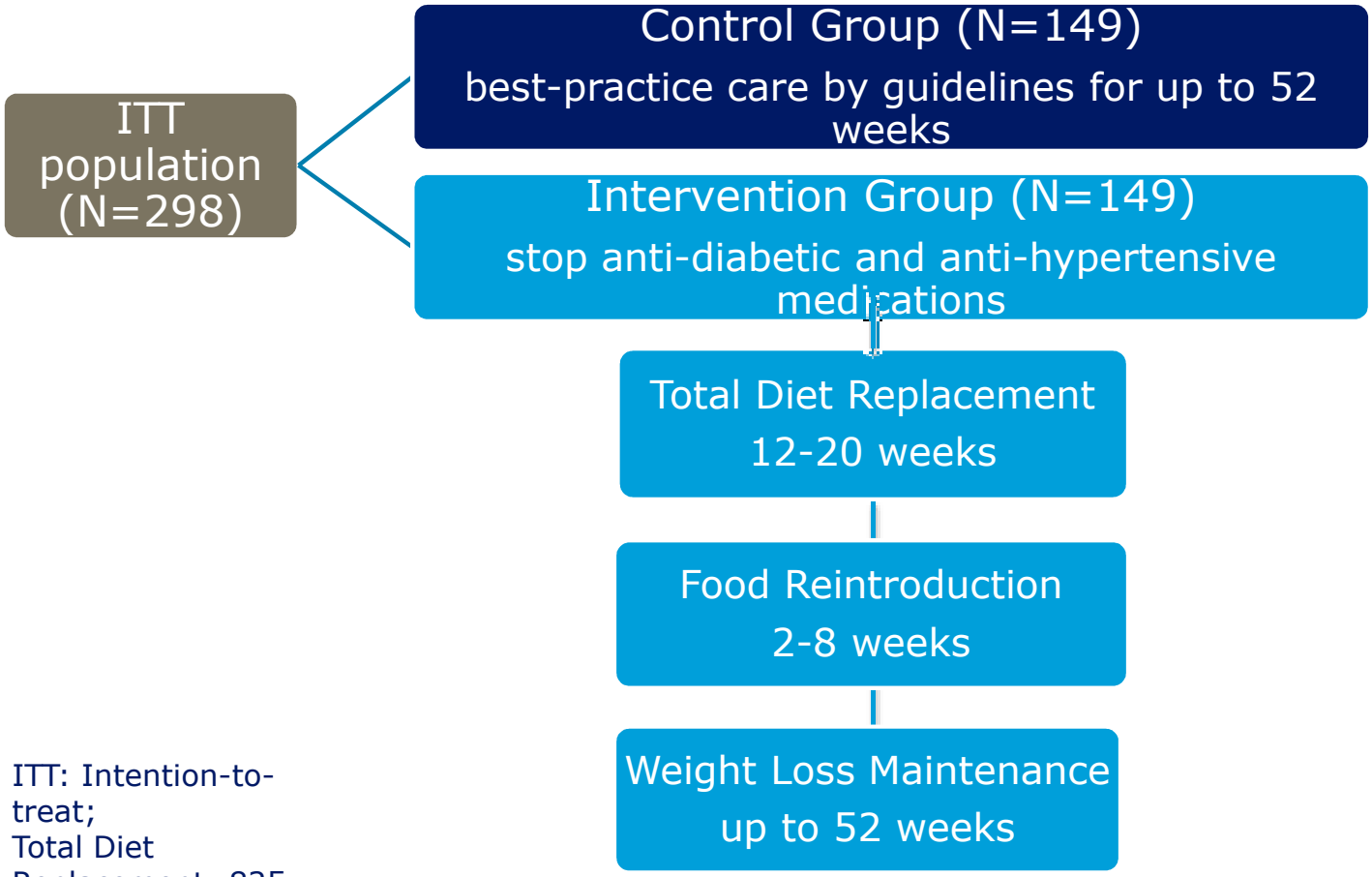
- T2DM diagnosis within the previous 6 years(*)
- age 20–65 years
- BMI: 27 - 45 kg/m^2

Endpoint at 12 months

- Weight loss ≥15 kg
- DM remission defined as HbA1c <6.5% (<48 mmol/mol) after 2 months without antidiabetic medications

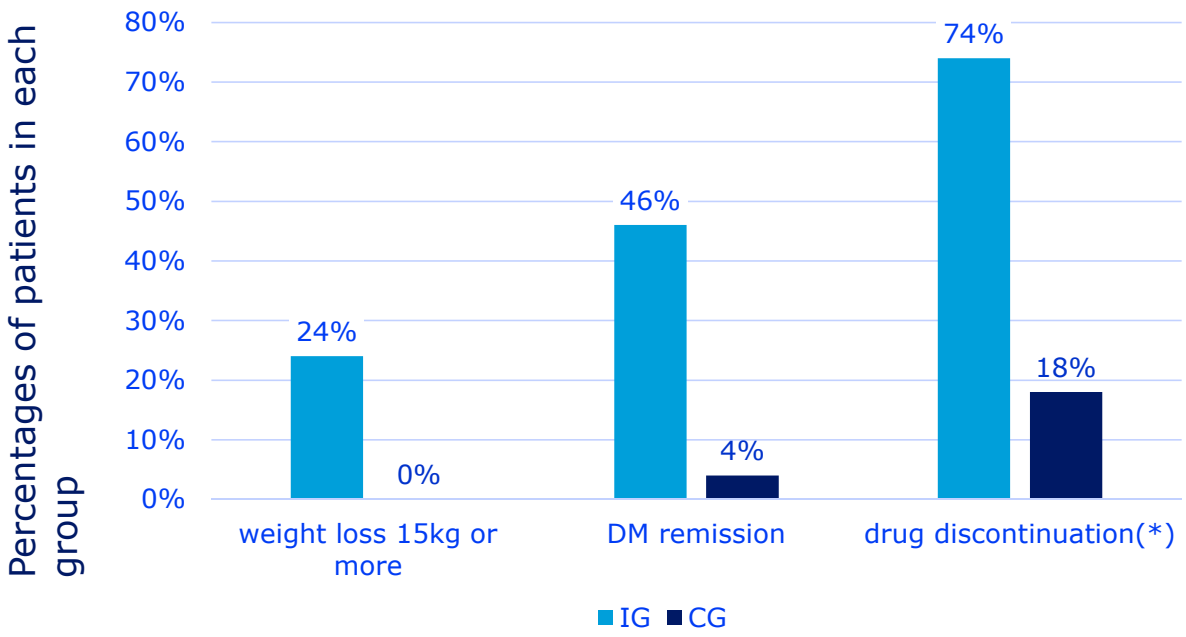
(*) most recent HbA1c value > 6.0%, if HbA1c <6.5% antidiabetic medication was continued

Study design (2)



ITT: Intention-to-treat;
Total Diet Replacement: 825-853 kcal/day formula;

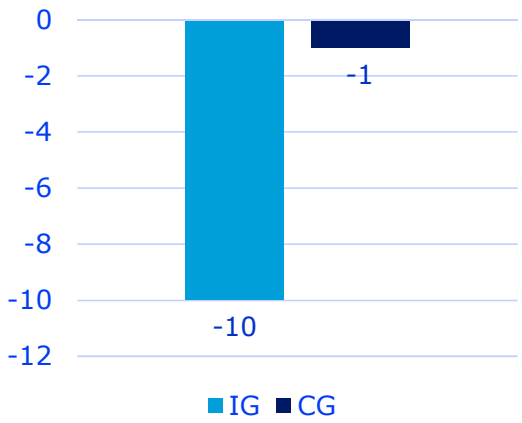
Main results (1/2)



IG: Intervention group; CG: Control group; DM: Diabetes Mellitus;
(*) Additionally, 5% in the CG started antidiabetic medications

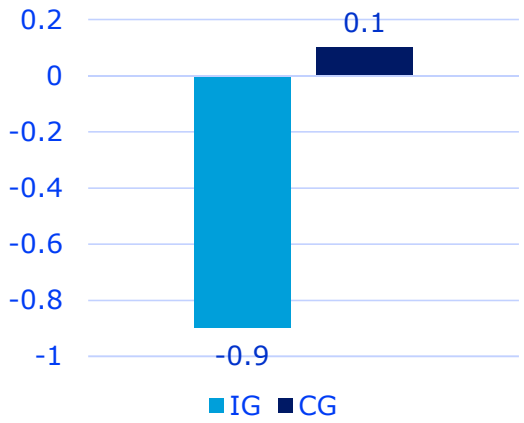
Main results (2/2)

Mean change in weight (kg)



P<0.0001

Mean change in HbA1c (%)



P<0.0001

IG: Intervention group; CG: Control group;

Lean MEJ, et al. Lancet 2017

Conclusions

- **T2DM of up to 6 years' duration can be reversed by weight loss with help of an evidence-based structured weight management program delivered in a community setting, by routine primary care staff.**
- **Almost a quarter of participants who followed the intervention achieved at least 15 kg of weight loss at 12 months.**
- **Almost half of patients in the intervention group showed remission of diabetes, and were off antidiabetic medication.**

Q&A