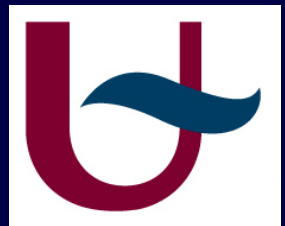


Wereld Nierdag 2017

Obesity and the Kidney

Obesity anno 2017
Epidemio, diagnose, outcome
impact en behandeling.
Geen enkel orgaan ontsnapt !

Luc F Van Gaal, MD, PhD
Dept Endocrinology-Diabetology & Metabolism
Antwerp University Hospital
Antwerp, Belgium

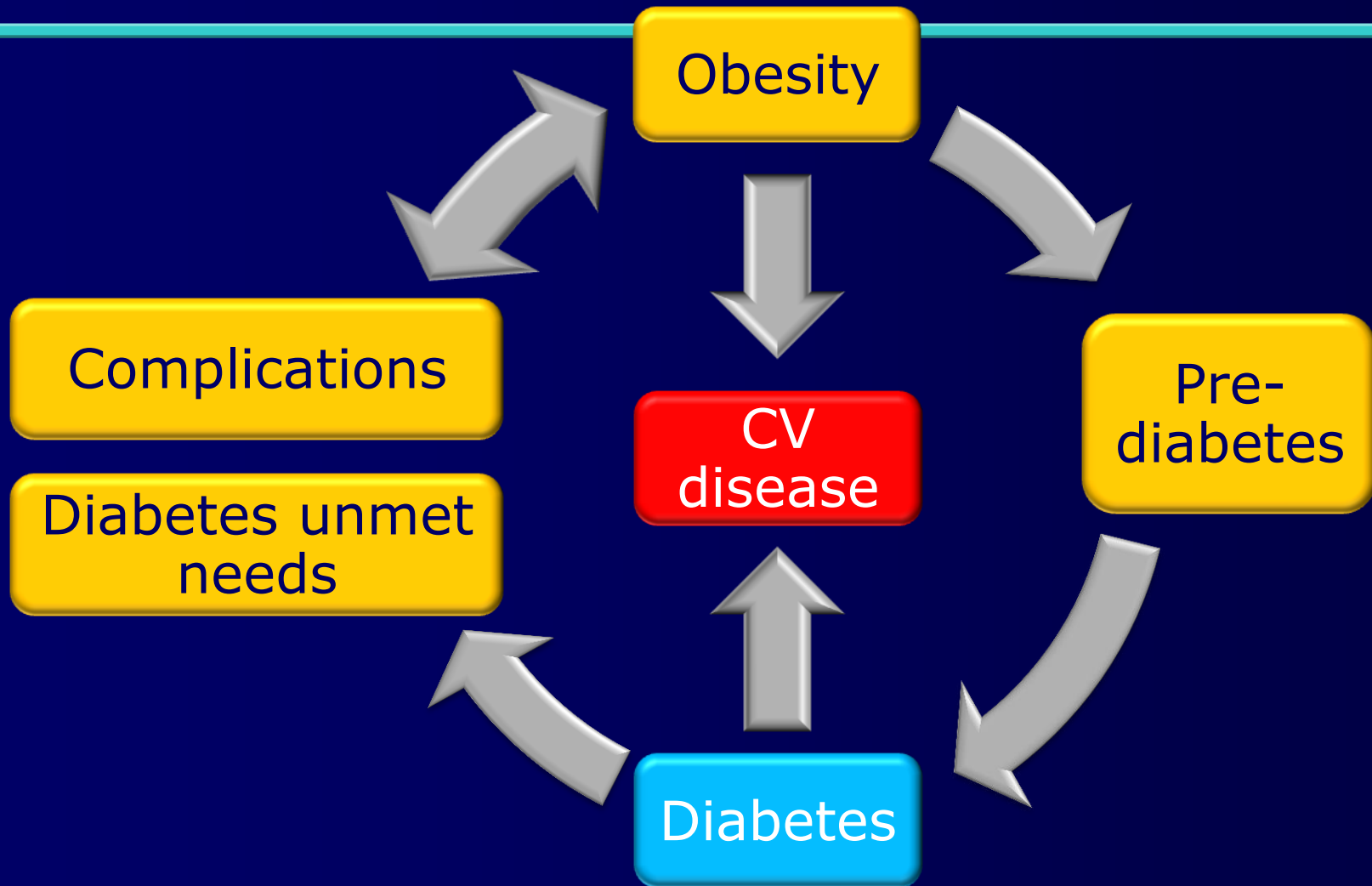


Conflict of Interest Disclosures

- ▶ **Luc Van Gaal is a member of the Advisory Board and/or Speakers Bureau of**
 - ▶ **AstraZeneca**
 - ▶ **Boehringer Ingelheim**
 - ▶ **E. Lilly & Co**
 - ▶ **Janssen-Cilag / J & J**
 - ▶ **Merck Sharp Dohme**
 - ▶ **Novo Nordisk**
 - ▶ **Sanofi**
 - ▶ **Servier**

“The data presented bind the author only. It is possible that this data contains information on unlicensed products or unlicensed usage in Europe and abroad. Do consult the most recent version of the official summary of product characteristics.”

The circle of metabolic risk



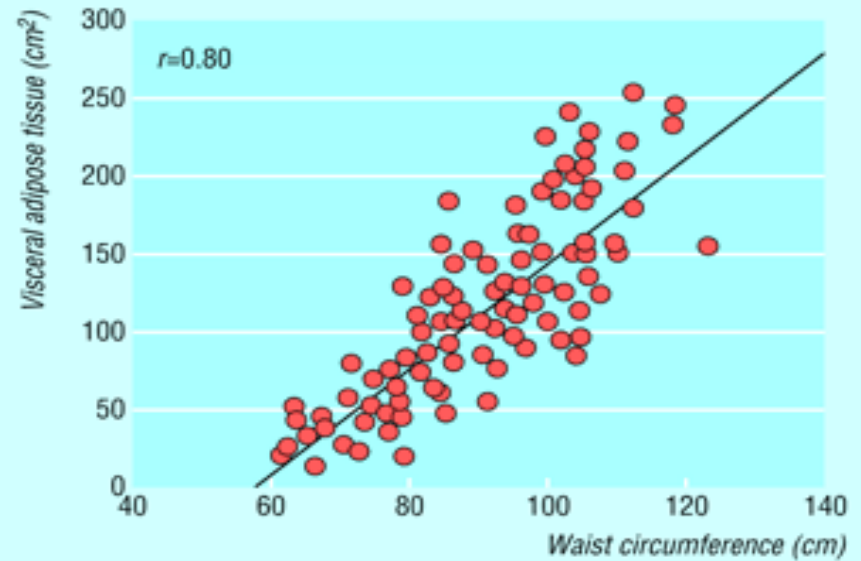
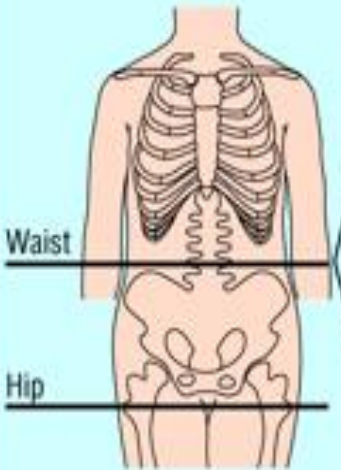
Definition of obesity

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

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

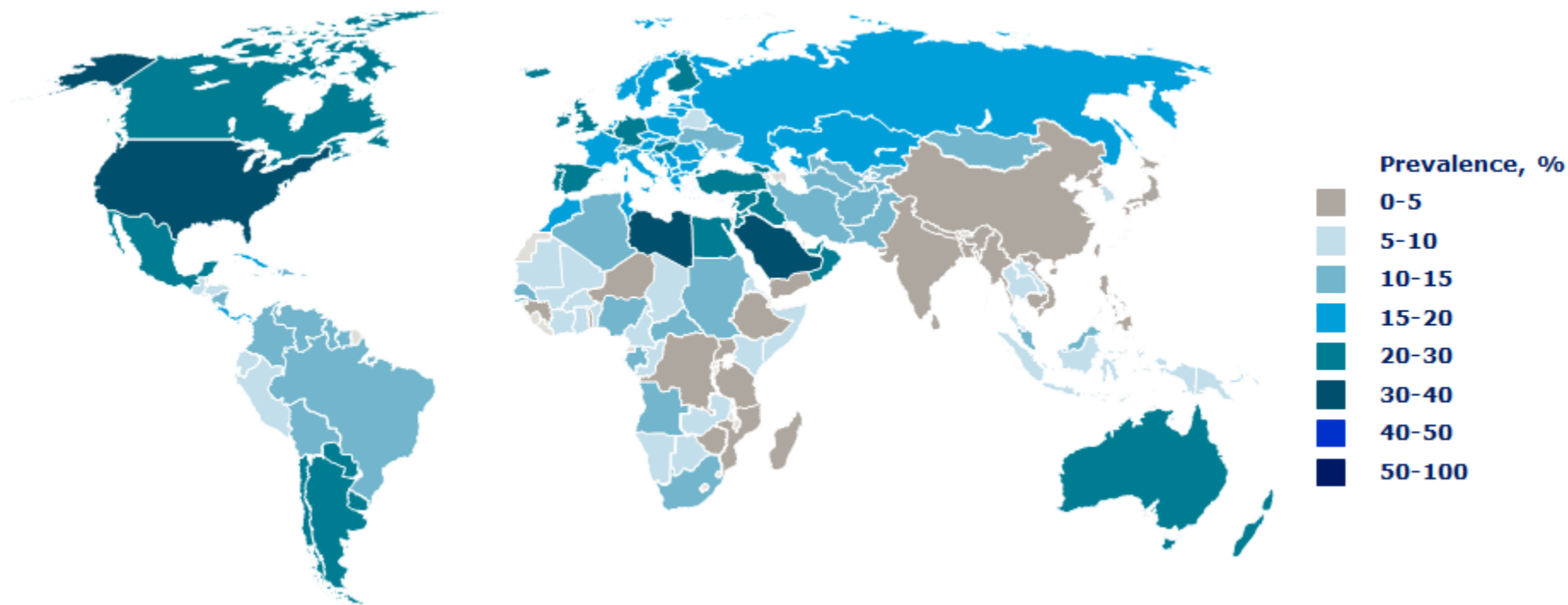
Classification	BMI (kg/m ²)
Underweight	<18.5
Normal range	≥18.5 and <25
Overweight	≥25 and <30
Obese	≥30
Obese class I	≥30 and <35
Obese class II	≥35 and <40
Obese class III	≥40

Visceral Adipose Tissue Can Be Estimated by Waist Measurement



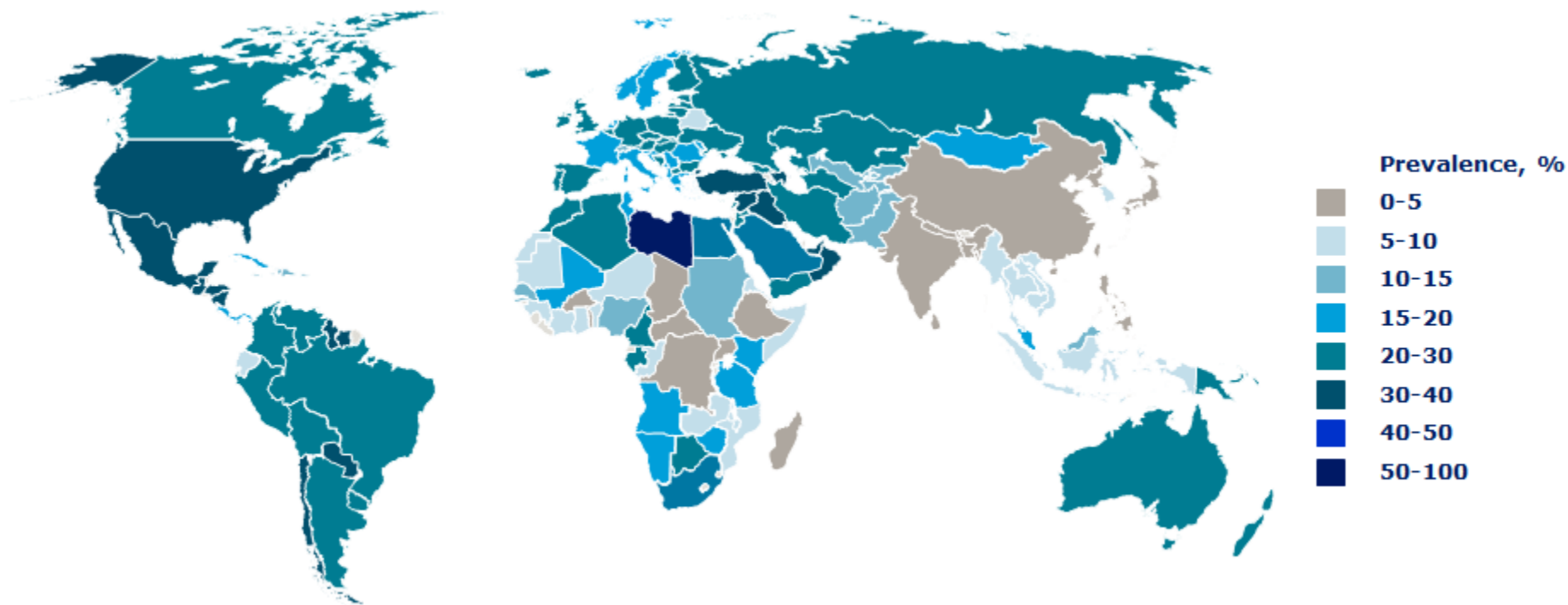
Age-standardised prevalence of obesity

For men aged ≥ 20 years, 2013

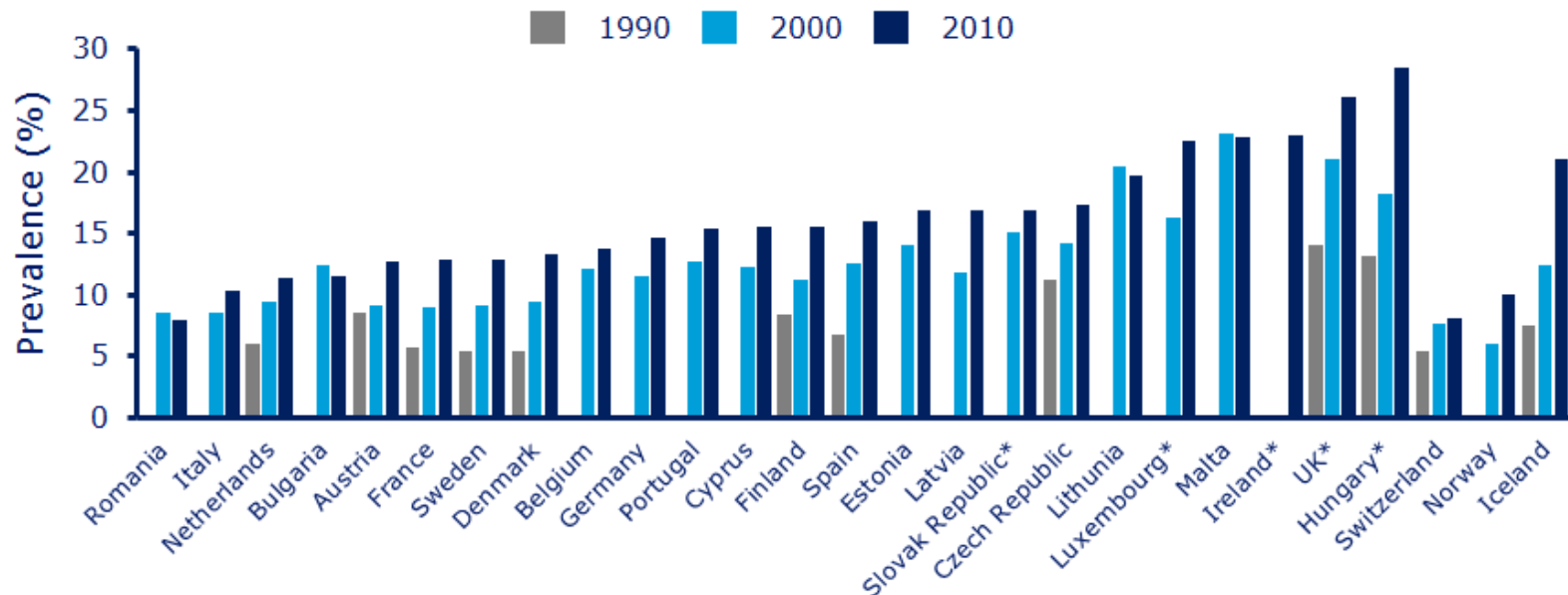


Age-standardised prevalence of obesity

For women aged ≥ 20 years, 2013

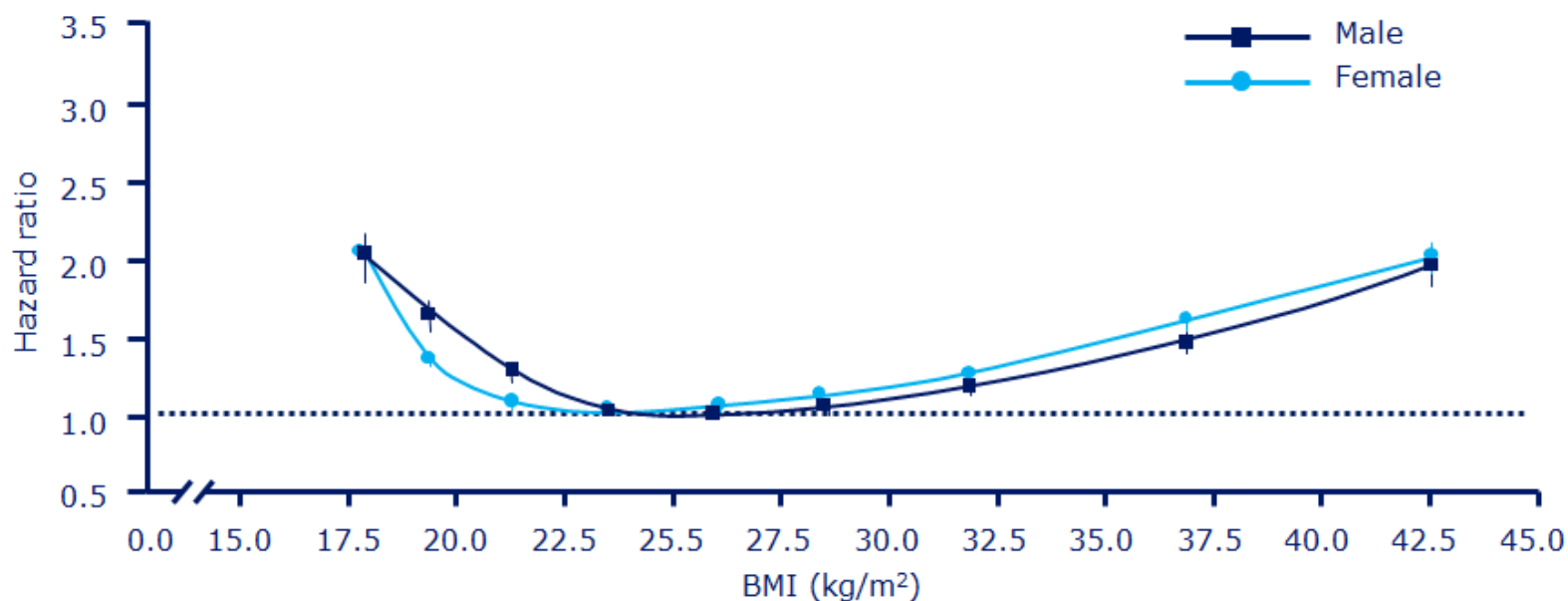


Increasing obesity rates in European countries



Data are from on adults. *Hungary (1988, 2009), Ireland (2007), Luxembourg, the Slovak Republic (2008) and the United Kingdom figures are based on health examination surveys, rather than health interview surveys

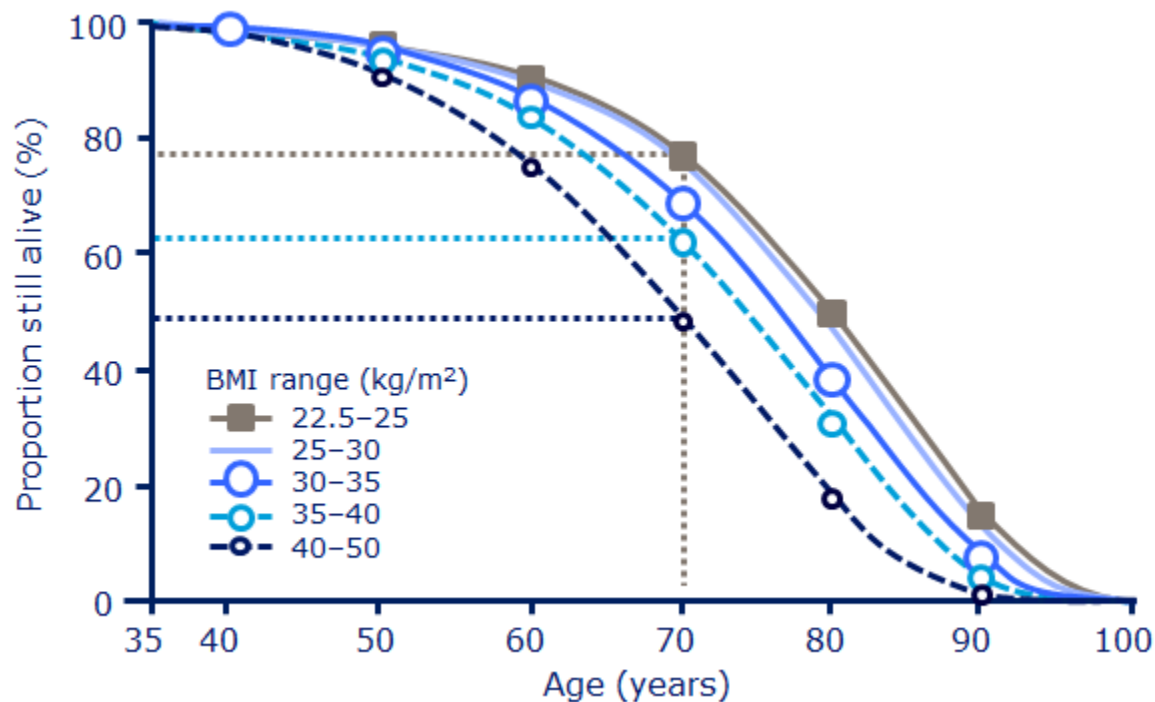
Obesity is associated with increased risk of mortality



Data based on 19 prospective studies encompassing 1.46 million white adults, 19–84 years of age

Berrington de Gonzalez *et al.* *N Engl J Med* 2010;363:2211–9

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

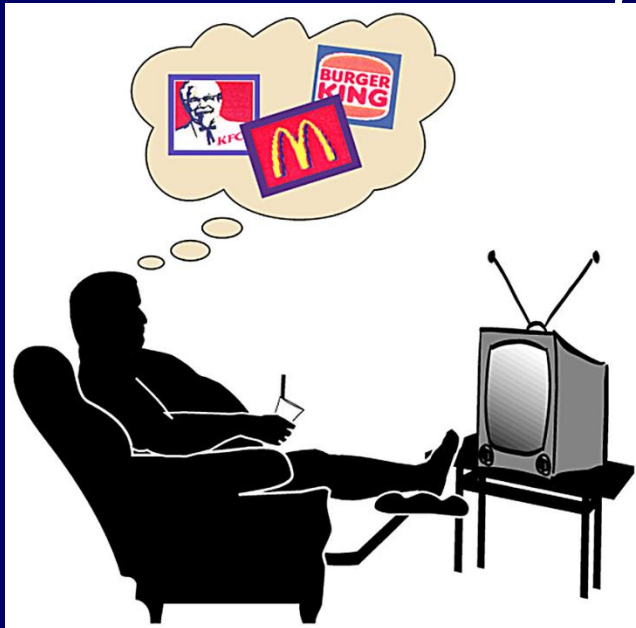
Prospective Studies Collaboration. *Lancet* 2009;373:1083-96

Lifestyle and behavioral therapy



Televisie kijken en prediabetes risico

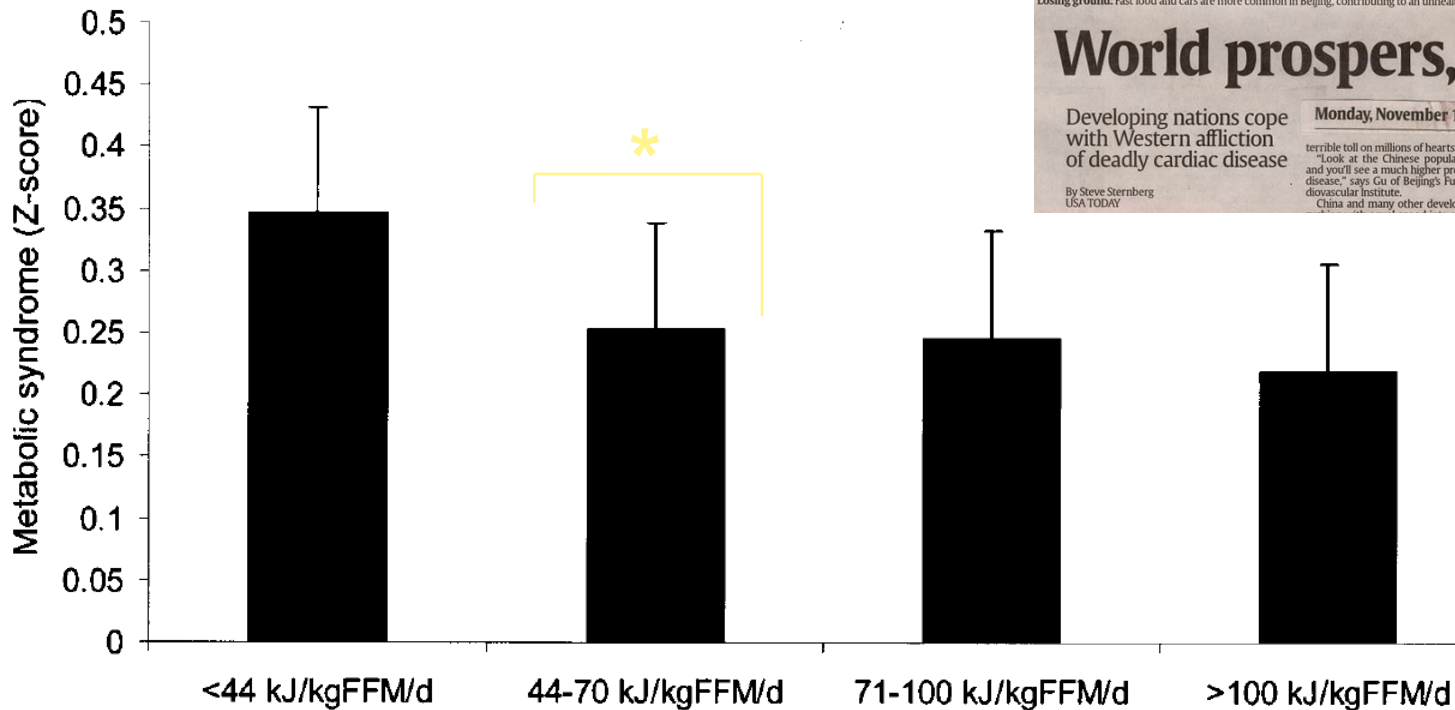
Independent of age, exercise levels, sedentary behaviours, especially TV watching were associated with significantly elevated risk of obesity and type 2 diabetes.



Each 2 h/day increment in TV watching was associated with 23% increase in obesity and 14% increase in risk of diabetes.

Effect fysieke activiteit

PAEE predicts the metabolic syndrome



Losing ground: Fast food and cars are more common in Beijing, contributing to an unhealthy lifestyle. In China, 40% of deaths are from heart disease or strokes.

World prospers, hearts suffer

Developing nations cope with Western affliction of deadly cardiac disease

By Steve Sternberg
USA TODAY

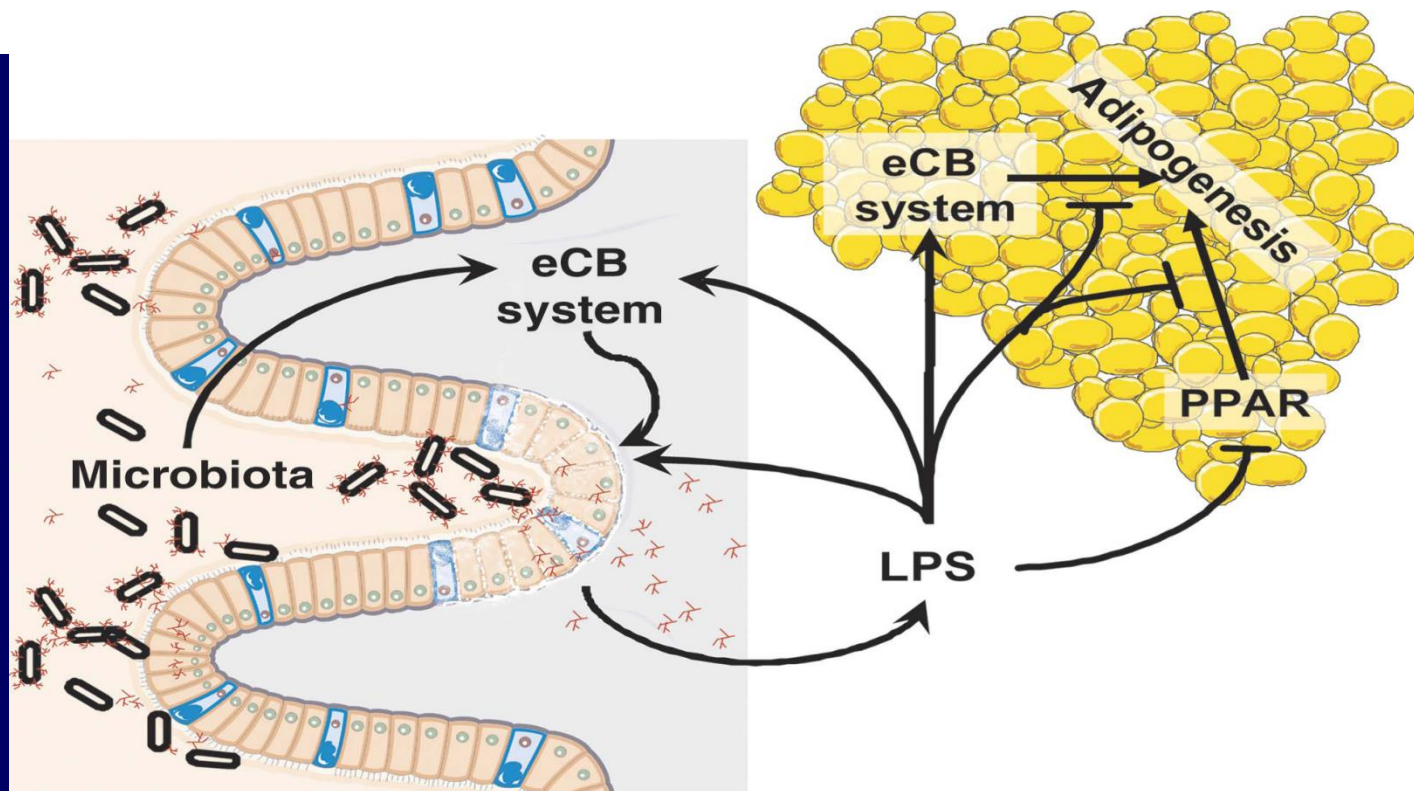
Monday, November 18, 2002

terrible toll on millions of hearts.
"Look at the Chinese population in 10 years and you'll see a much higher prevalence of heart disease," says Gu of Beijing's阜外 Hospital Cardiovascular Institute.
China and many other developing nations are

"disease of any countries in the world."
Heart disease represents an added burden to countries struggling to free themselves from the traditional Third World blights of malnutrition and infectious diseases. Not only does heart disease threaten the health of people in developing countries, experts say, but it also threatens their economies by driving up health costs and sapping the workforce.

Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Jotham Suez¹, Tal Korem^{2*}, David Zeevi^{2*}, Gili Zilberman-Schapira^{1*}, Christoph A. Thaiss¹, Ori Maza¹, David Israeli³, Niv Zmora^{4,5,6}, Shlomit Gilad⁷, Adina Weinberger², Yael Kuperman⁸, Alon Harmelin⁸, Ilana Kolodkin-Gal⁹, Hagit Shapiro¹, Zamir Halpern^{5,6}, Eran Segal² & Eran Elinav¹



And ...

Quid non-caloric sweeteners ?

Clinical Care/Education/Nutrition/Psychosocial Research

ORIGINAL ARTICLE

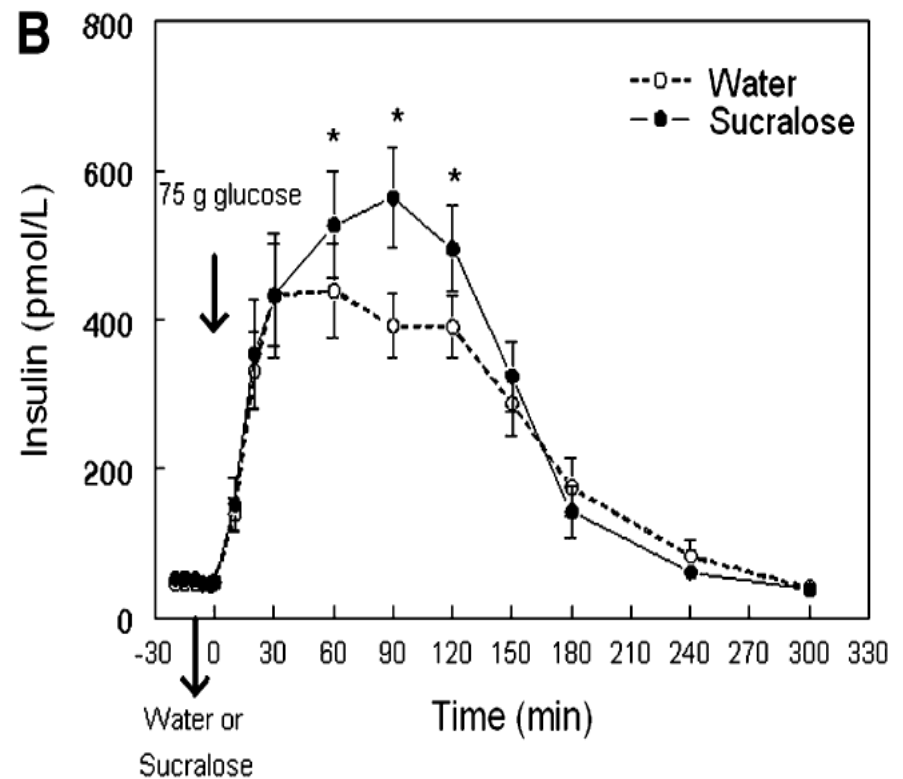
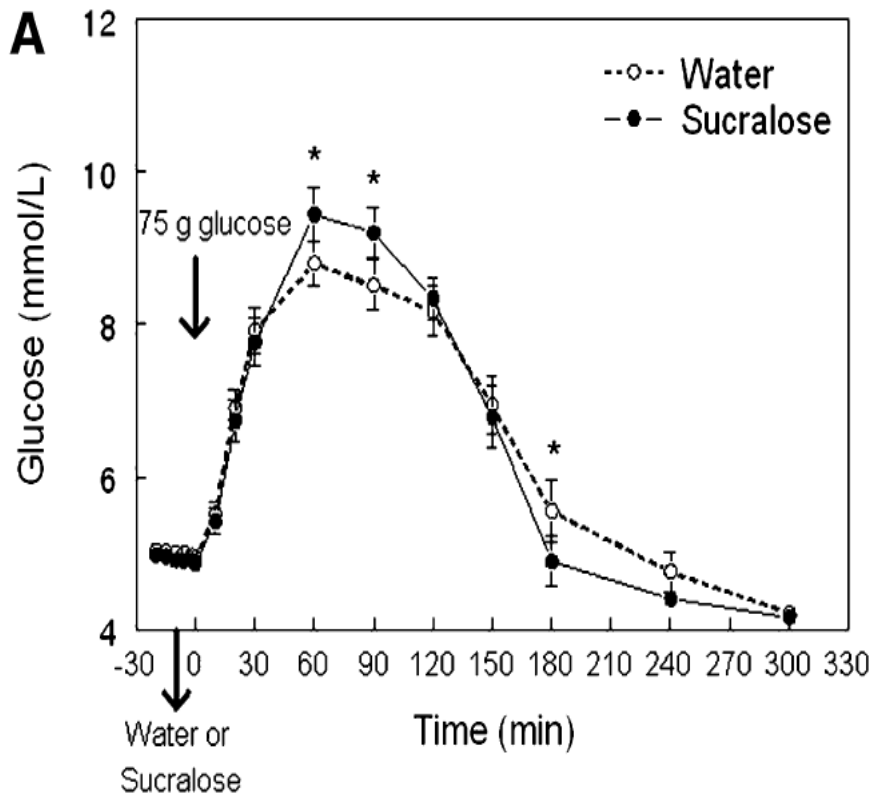
Sucralose Affects Glycemic and Hormonal Responses to an Oral Glucose Load

M. YANINA PEPINO, PHD
COURTNEY D. TIEMANN, MPH, MS, RD
BRUCE W. PATTERSON, PHD

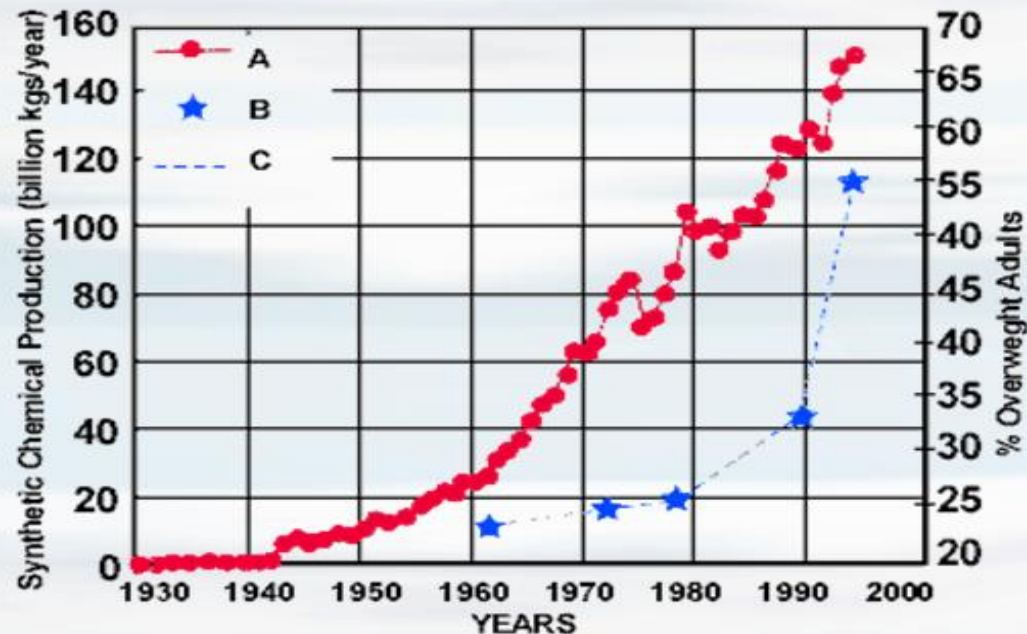
BURTON M. WICE, PHD
SAMUEL KLEIN, MD

Diabetes Care 36:2530–2535, 2013

Metabolic effects of sucralose in humans



Omgevingsfactoren: endocriene dysruptors



A = Synthetic chemical production
B = % Overweight adults, based on survey points
C = % Overweight adults, interpolated

From *The Body Restoration Plan: Eliminate Chemical Calories™ and Repair Your Body's Natural Slimming System™* by Dr. Paula Baillie-Hamilton © 2003 by Dr. Paula Baillie-Hamilton 2000



Association of Brominated Flame Retardants With Diabetes and Metabolic Syndrome in the U.S. Population, 2003-2004

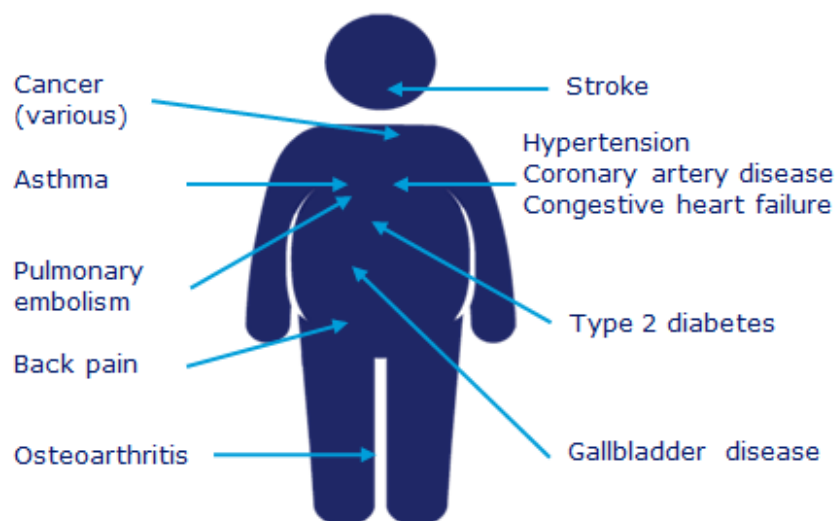
Ji-SUN LIM, MD, PHD¹
DUK-HEE LEE, MD, PHD¹
DAVID R. JACOBS, JR., PHD^{2,3}

Diabetes Care 31:1802-1807, 2008



Obesity is associated with multiple chronic comorbid conditions

Obesity-related comorbidities

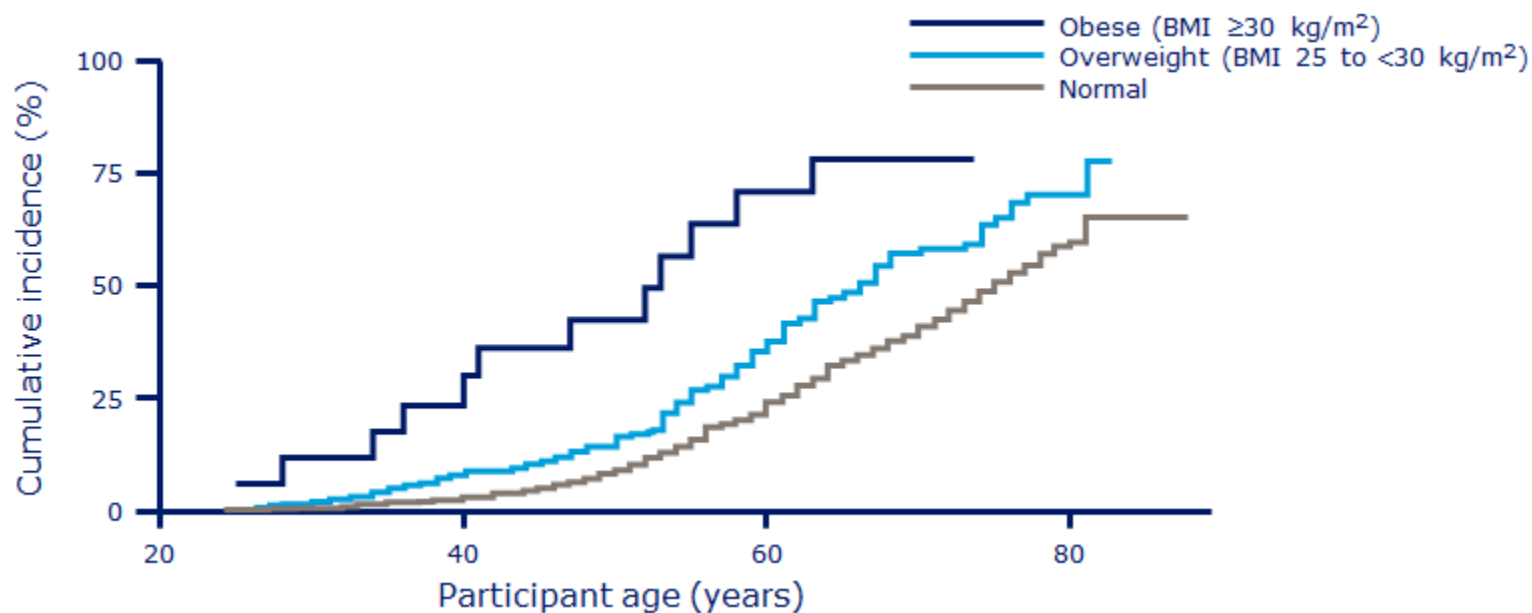


Increased risk of comorbidities with obesity

Comorbidity	RR [95% CI] Male	RR [95% CI] Female
Type 2 diabetes	6.7 [5.6;8.2]	12.4 [9.0;17.1]
Coronary artery disease	1.7 [1.5;2.0]	3.1 [2.8;3.4]
Congestive heart failure	1.8 [1.2;2.6]	1.8 [1.1;3.0]
Hypertension	1.8 [1.5;2.2]	2.4 [1.6;3.7]
Stroke	1.5 [1.3;1.7]	1.5 [1.3;1.7]
Osteoarthritis	4.2 [2.7;6.4]	2.0 [1.9;2.0]
Gallbladder disease	1.4 [1.0;2.0]	2.3 [1.2;4.6]

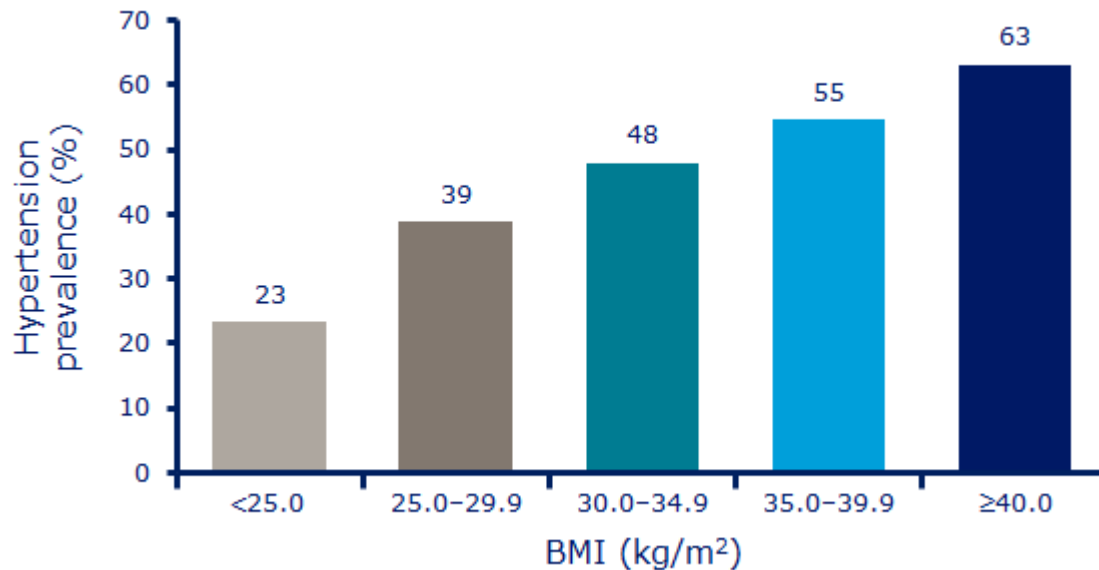
RR = relative risk

Cumulative incidence of hypertension increases with baseline BMI



Prospective cohort study of white men (n=1132) from the Johns Hopkins Precursors Study
BMI, body mass index

The prevalence of hypertension increases with increasing BMI



Based on data from the NHANES III survey; n=7689 (women)
BMI, body mass index

Must *et al.* JAMA 1999;282:1523–9



MOVING AHEAD: Hillary's new bike has helped her lose 11 kg. A combination of diet, exercise and medication has stabilized her glucose level

HEALTH

WHY SO MANY ARE GETTING DIABETES

Never have doctors known so much about how to prevent or control this disease, yet the epidemic keeps on raging. How you can protect yourself

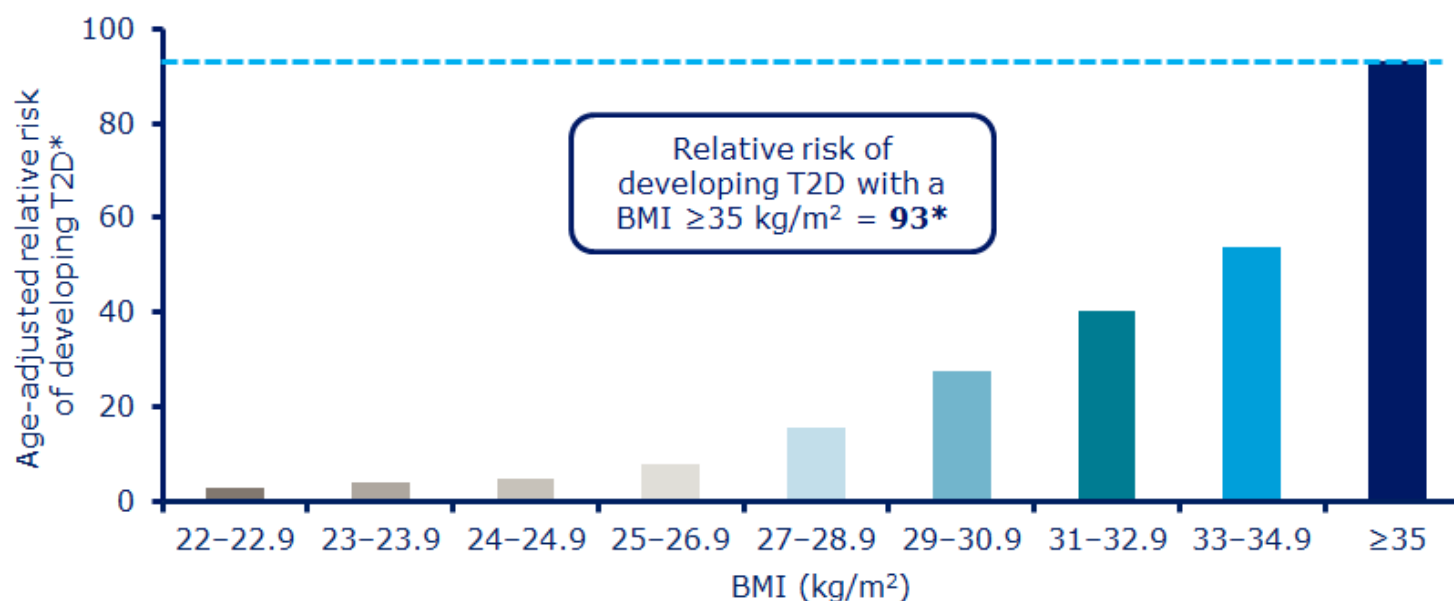
By CHRISTINE GORMAN

HILLARY CARROLL KNEW SOMETHING WAS AMISS. SHE had spent the day happily frolicking in her grandmother's swimming pool, but by that evening she was doubling over in pain every time she went to the bathroom. Her mother figured it was probably an infection and the next day took Hillary, then 10, to the pediatrician. Instead of getting a prescription for an antibiotic, however, the 100-kg youngster was immediately admitted to the hospital. Lab tests showed that she had something far more serious—Type 2 diabetes.

Hillary is not the first overweight child to learn she has this form of diabetes, a chronic metabolic disorder that used to be called adult onset but was renamed in part because so many kids Hillary's age were getting it. As doctors have repeatedly warned, the world is experiencing a diabetes epidemic. In the U.S. alone, some 18 million suffer from one form or another, with 1.3 million new cases diagnosed last year—up from 878,000 in 1997. And although Type 2 diabetes still tends to strike people in their fifth or sixth decade, more children are getting it, a fact of grave concern to health officials.

Photograph for TIME by Steve Lisa

Relative risk of developing T2D by BMI category

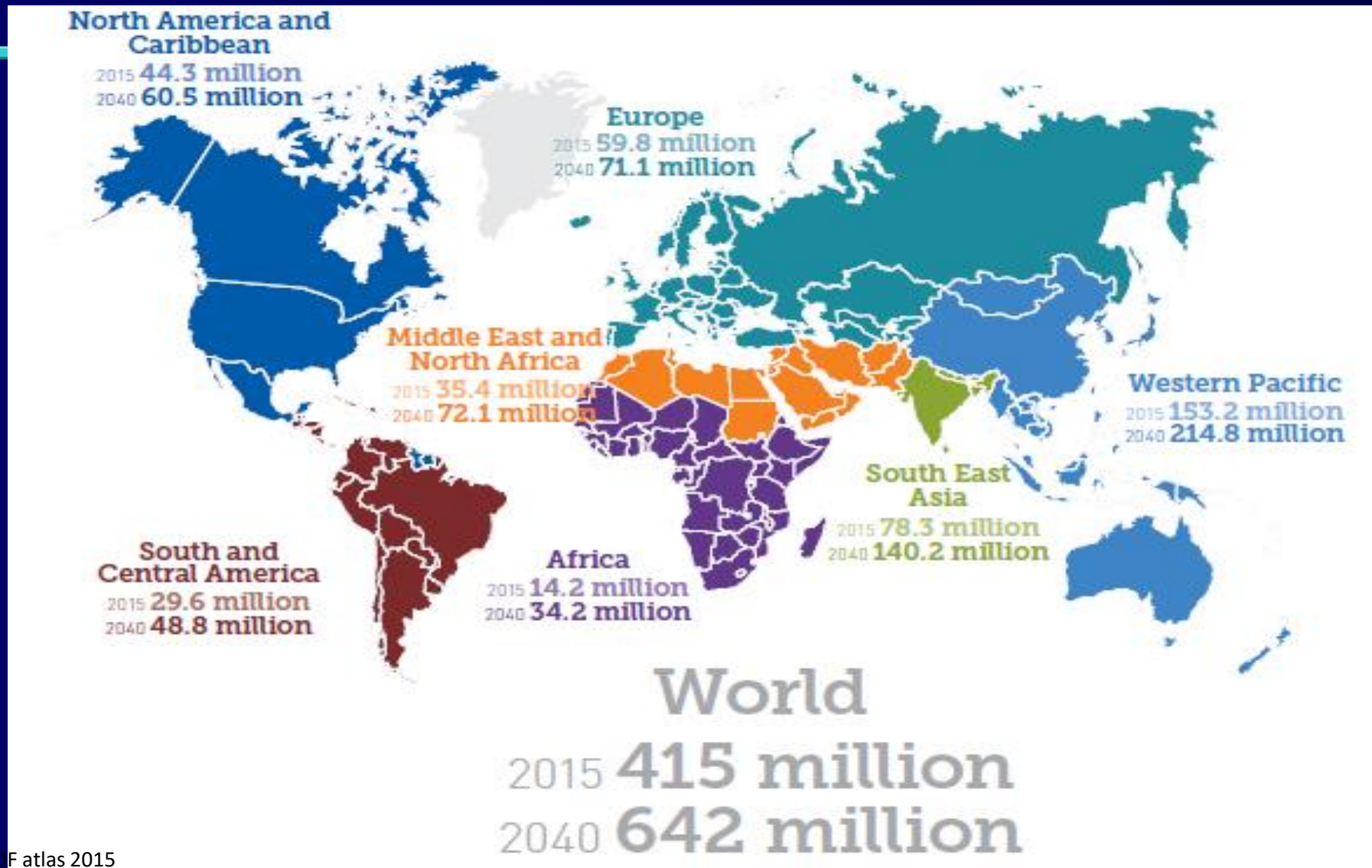


*Vs. BMI < 22 kg/m²; Data are for women only. n=114,281 female registered nurses aged 30–55 years
T2D, type 2 diabetes

Prevalence of diabetes



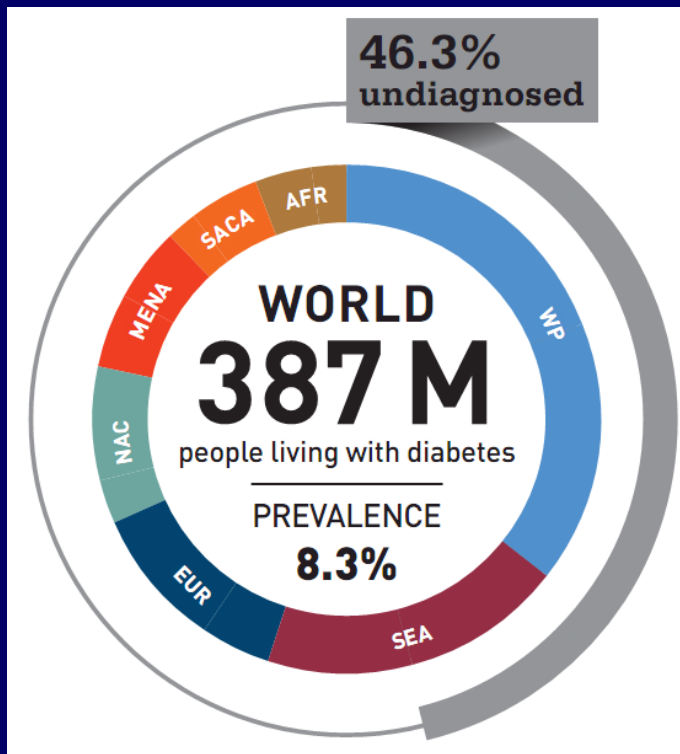
Estimated number of people with diabetes (ages 20-79 y)



Diabetes: een reusachtig en groeiend probleem

Elke 10 seconden ... 3 nieuwe diabetespatiënten

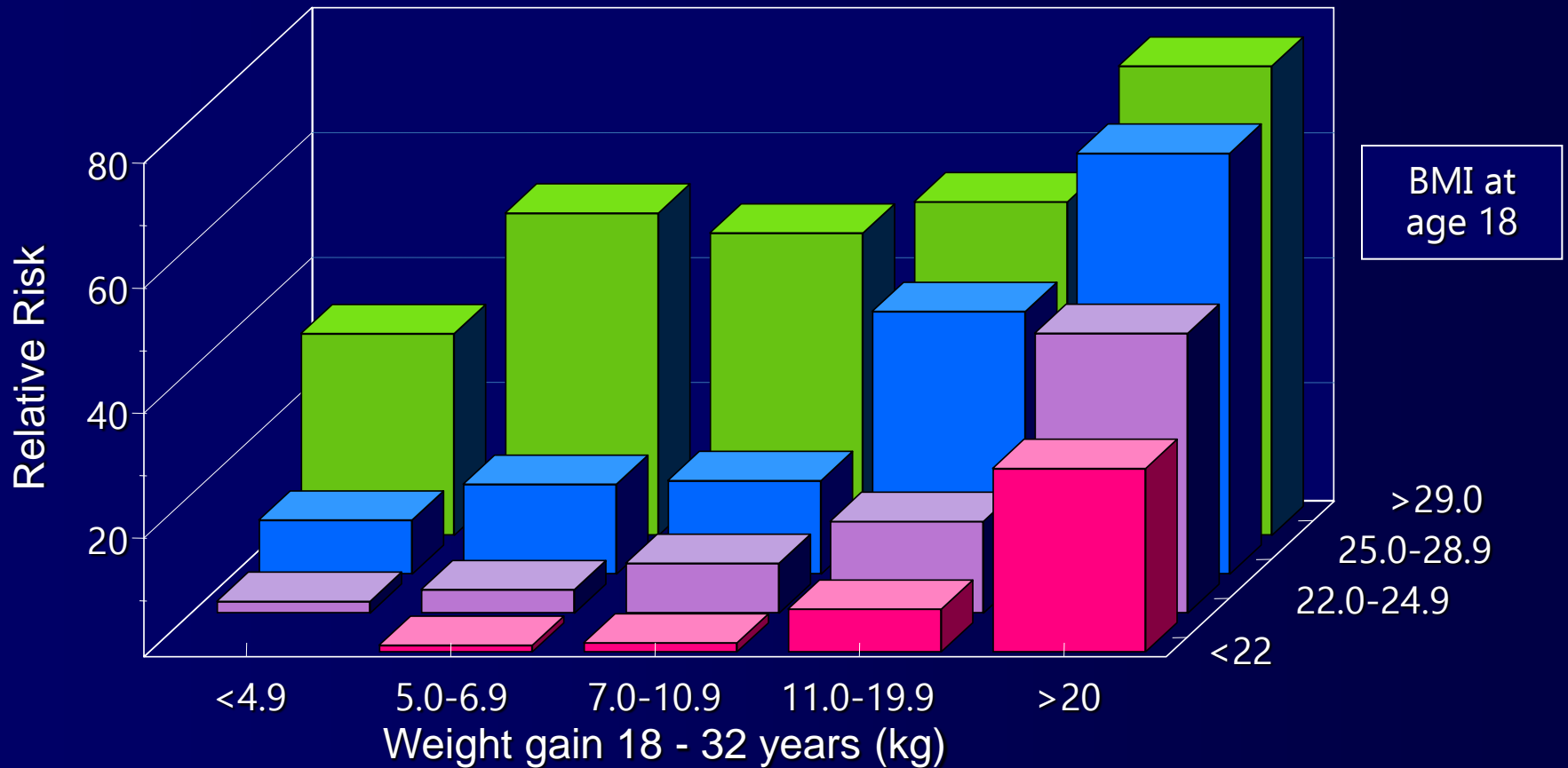
2014



2035



Relative risk for diabetes. Weight at age 18 and weight gain till 32 y.



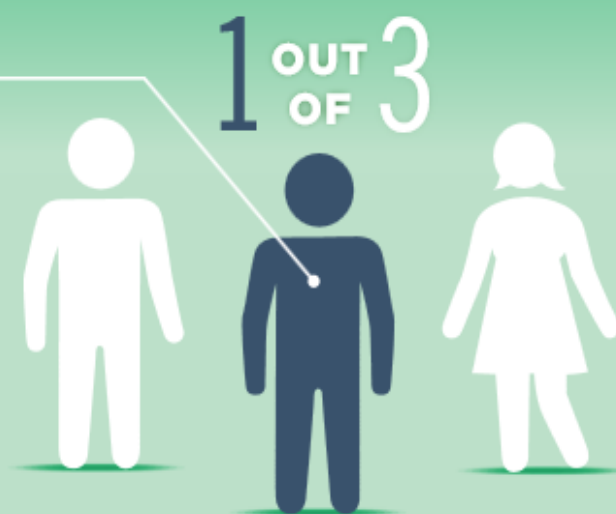
PREDIABETES

COULD IT
BE YOU?



86
MILLION

86 million American
adults—more than
1 out of 3—have
prediabetes

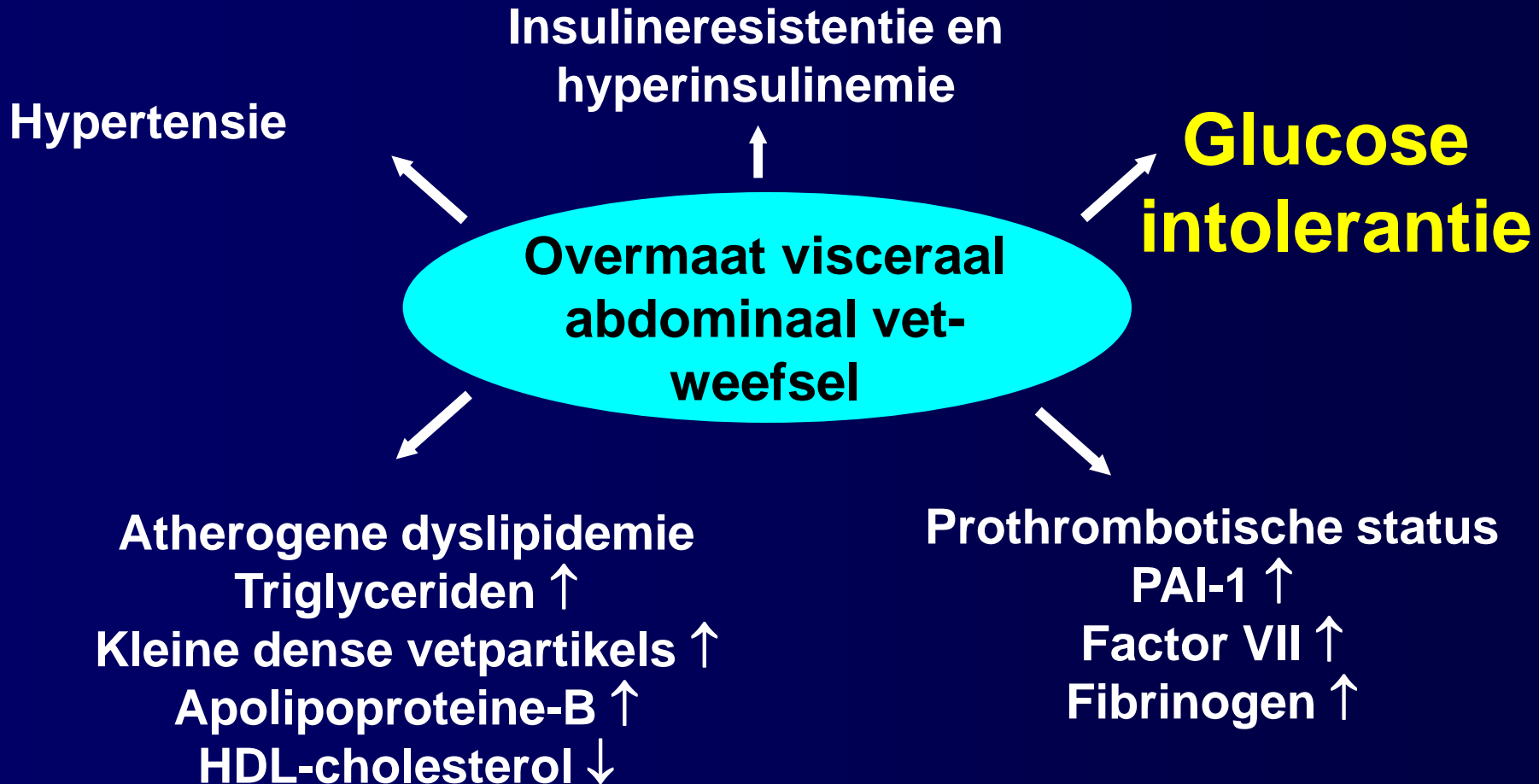


9 OUT OF 10 people with prediabetes
do not know they have it

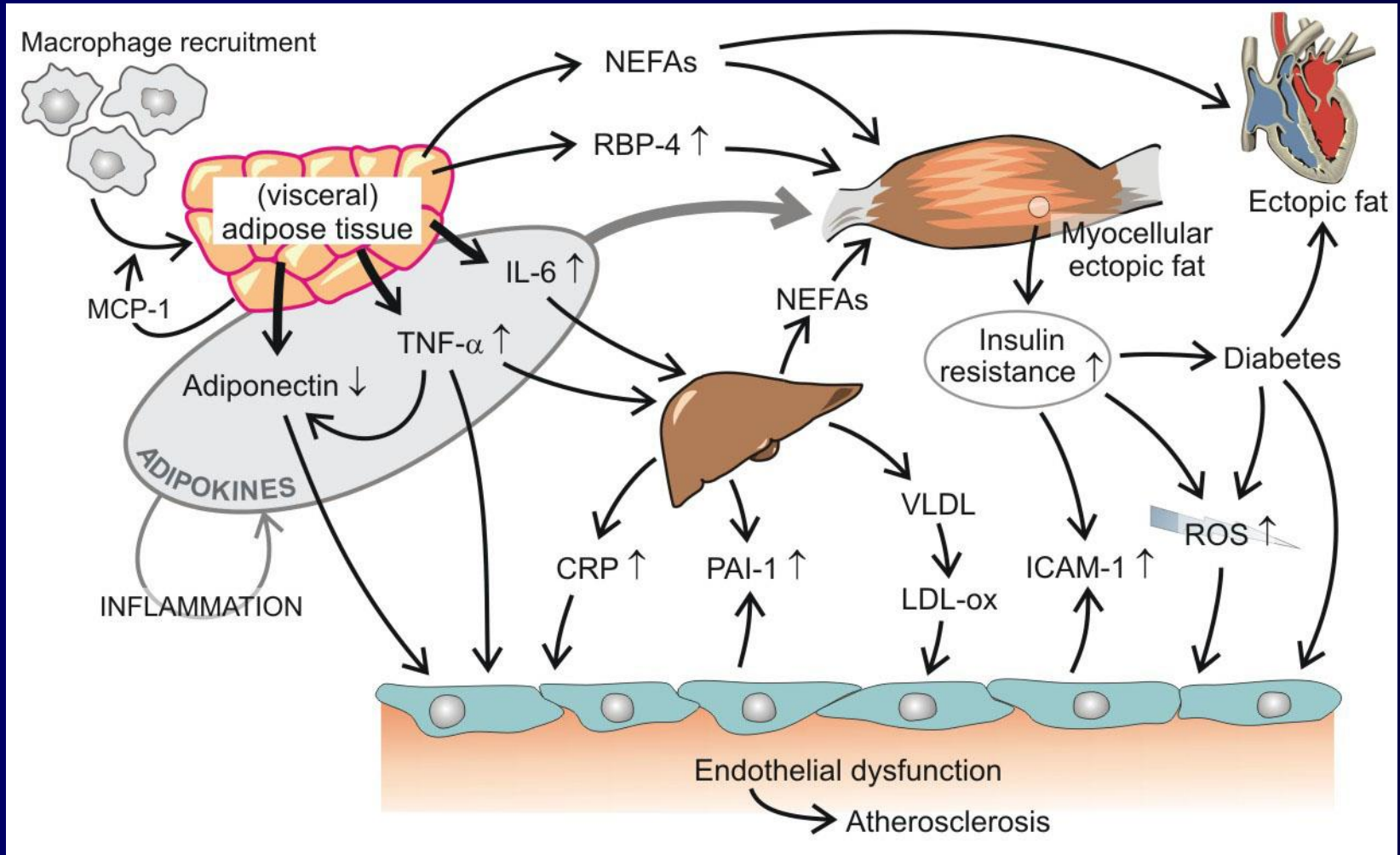
Ziekteproportie toe te schrijven aan obesitas

Type 2 diabetes	61%
Hypertension	17%
Coronary heart disease	17%
Gallbladder disease	30%
Osteoarthritis	24%
Breast cancer	11%
Endometrial cancer	34%
Colon cancer	11%

Viscerale obesitas en het insulineresistentie syndroom

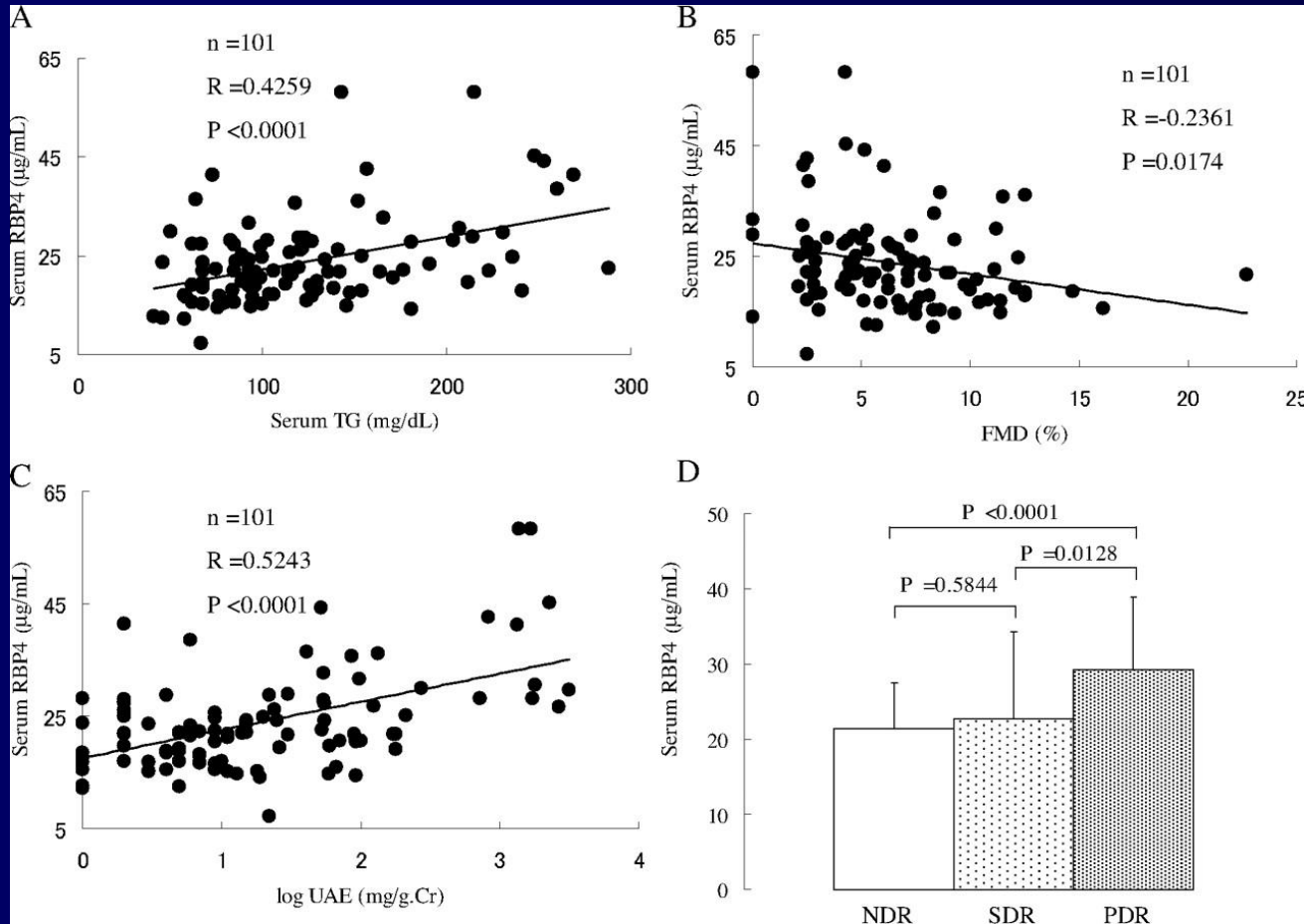


Involvement of adipose tissue, liver and muscle in **diabetes** and CV disease

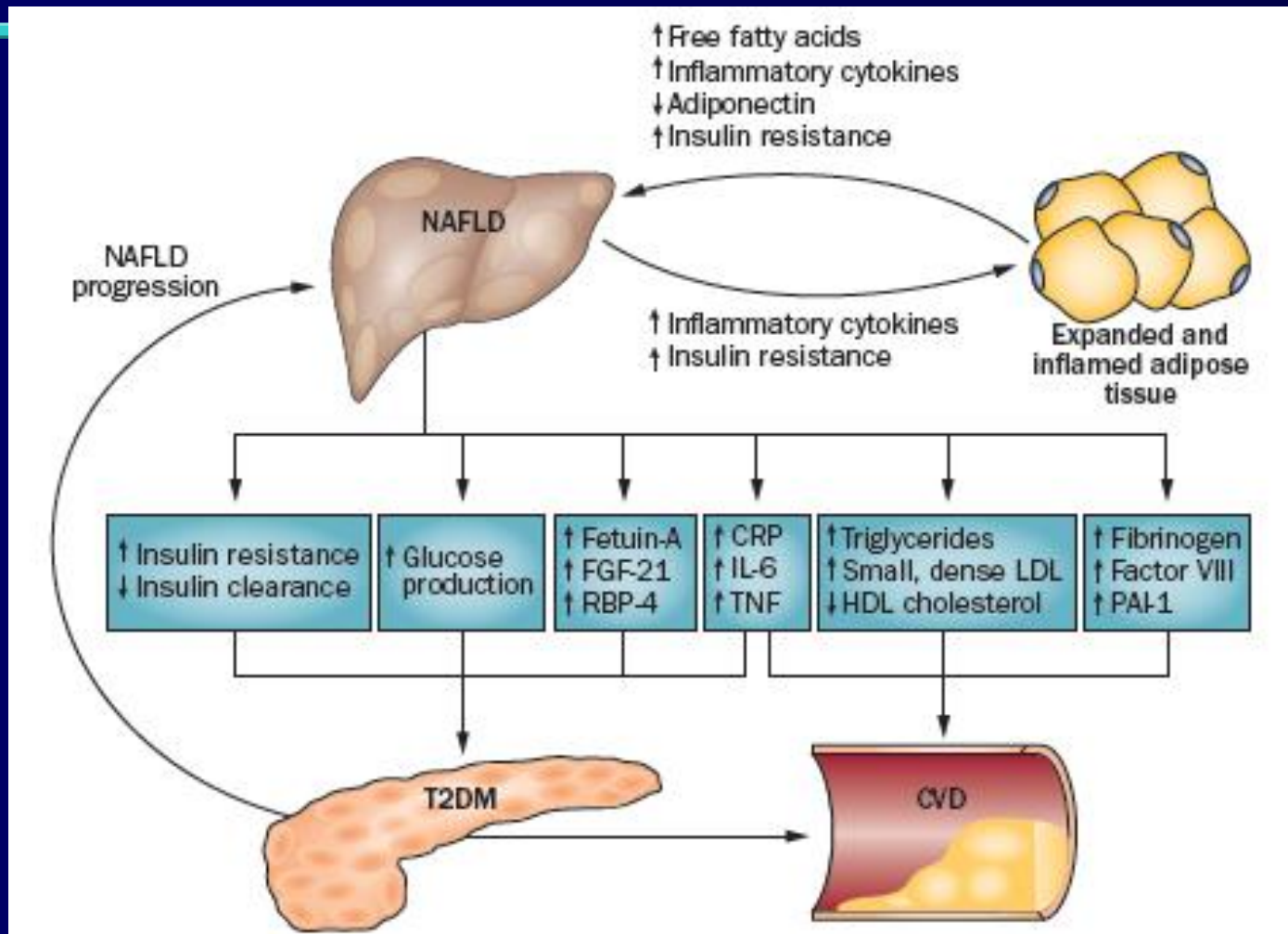


Adapted from L. Van Gaal et al, Nature, 2006

RBP4 concentration and biological risk factors in obesity & type 2 diabetic patients



From NASH to diabetes and CVD



A genetic variant PNPLA3 is involved in NAFLD/NASH

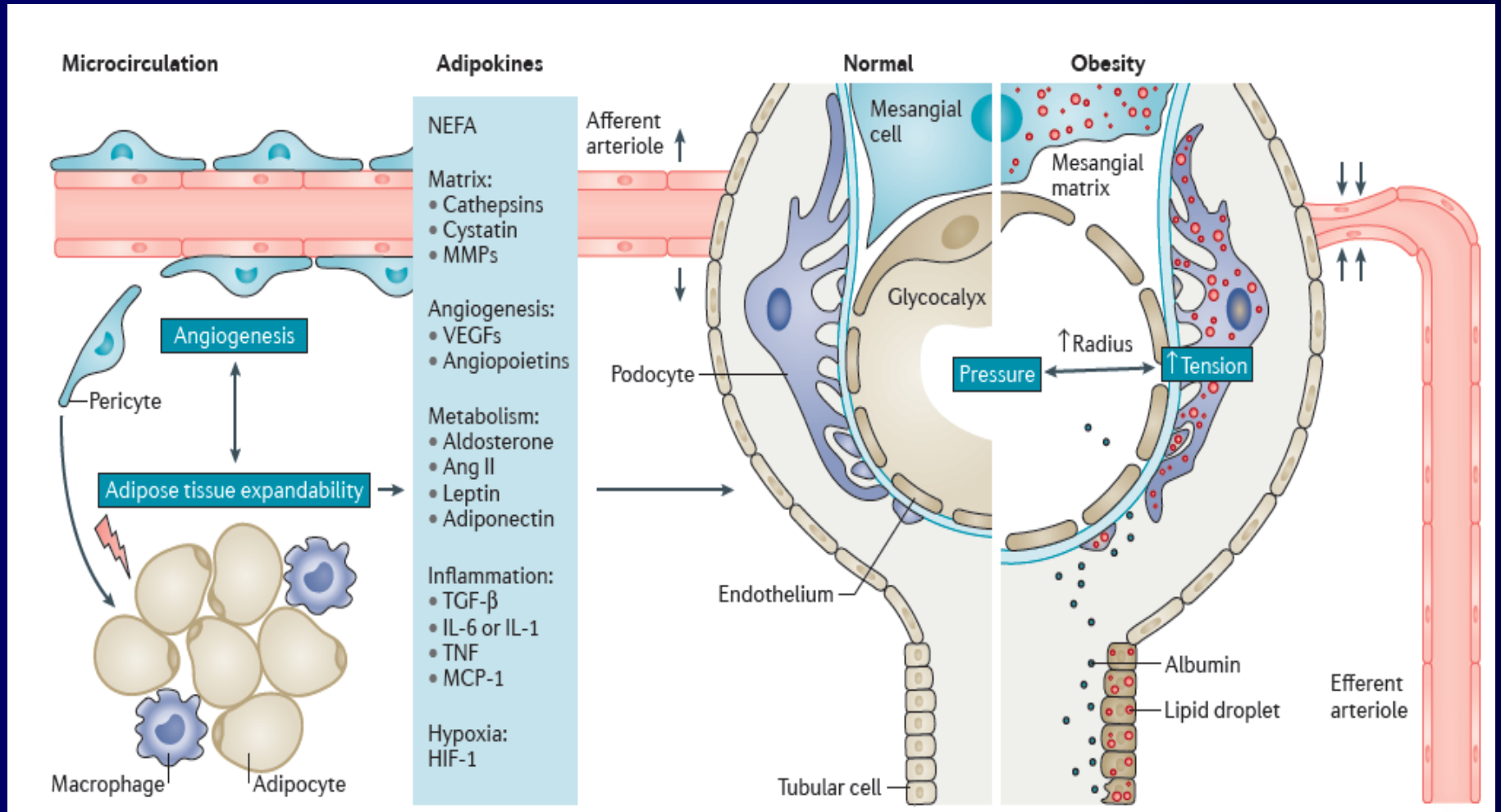
Original Article
EPIDEMIOLOGY

Obesity

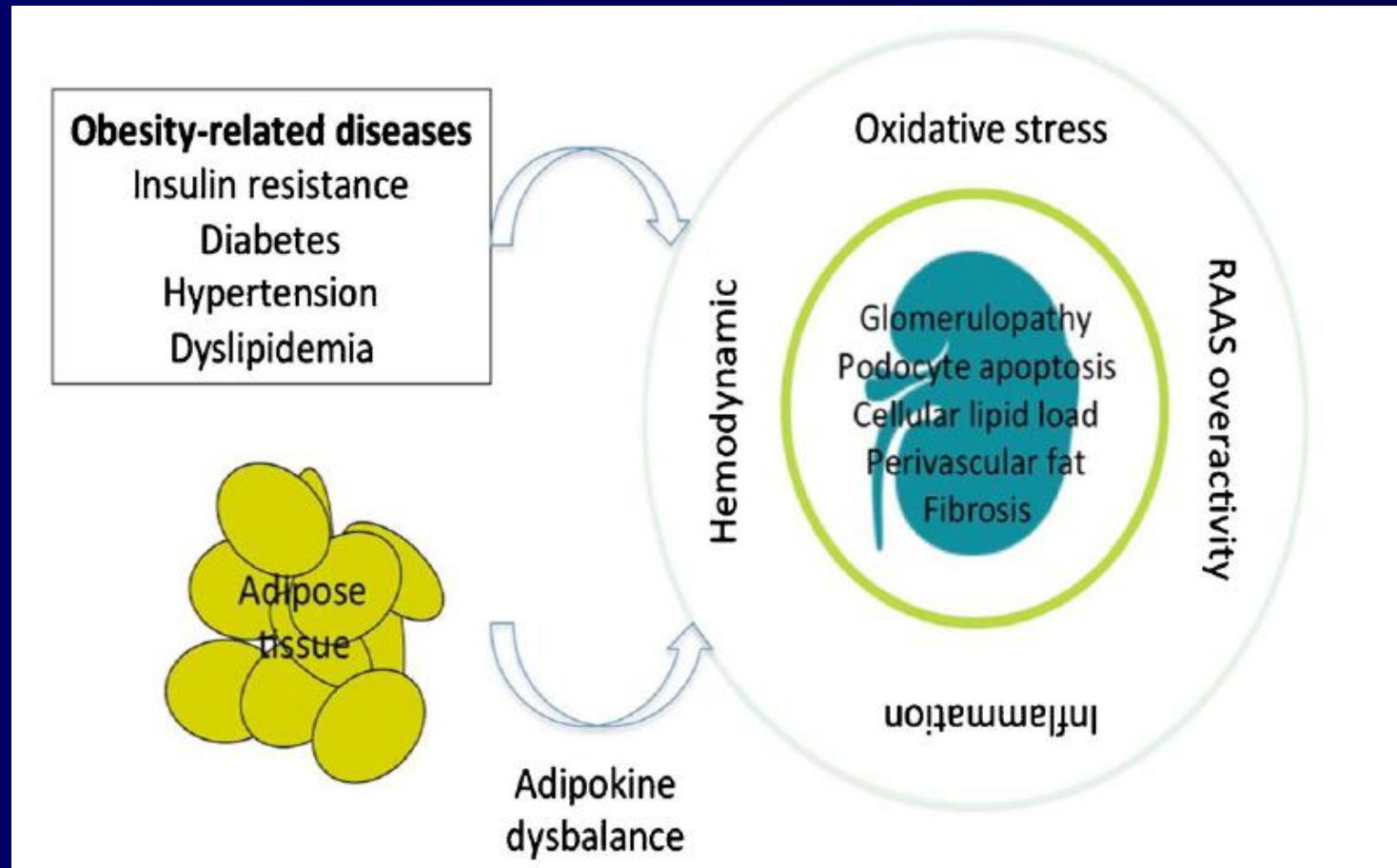
A Gene Variant of *PNPLA3*, But Not of *APOC3*, is Associated With Histological Parameters of NAFLD in an Obese Population

A. Verrijken¹, S. Beckers², S. Francque³, H. Hilden⁴, S. Caron^{5,6,7,8}, D. Zegers²,
M. Ruppert⁹, G. Hubens⁹, E. Van Marck¹⁰, P. Michielsen³, B. Staels^{5,6,7,8},
M.-R. Taskinen⁴, W. Van Hul² and L. Van Gaal¹

Potential role of adipokines in the origin of obesity related glomerulopathy



Mechanisms of renal damage in Obesity



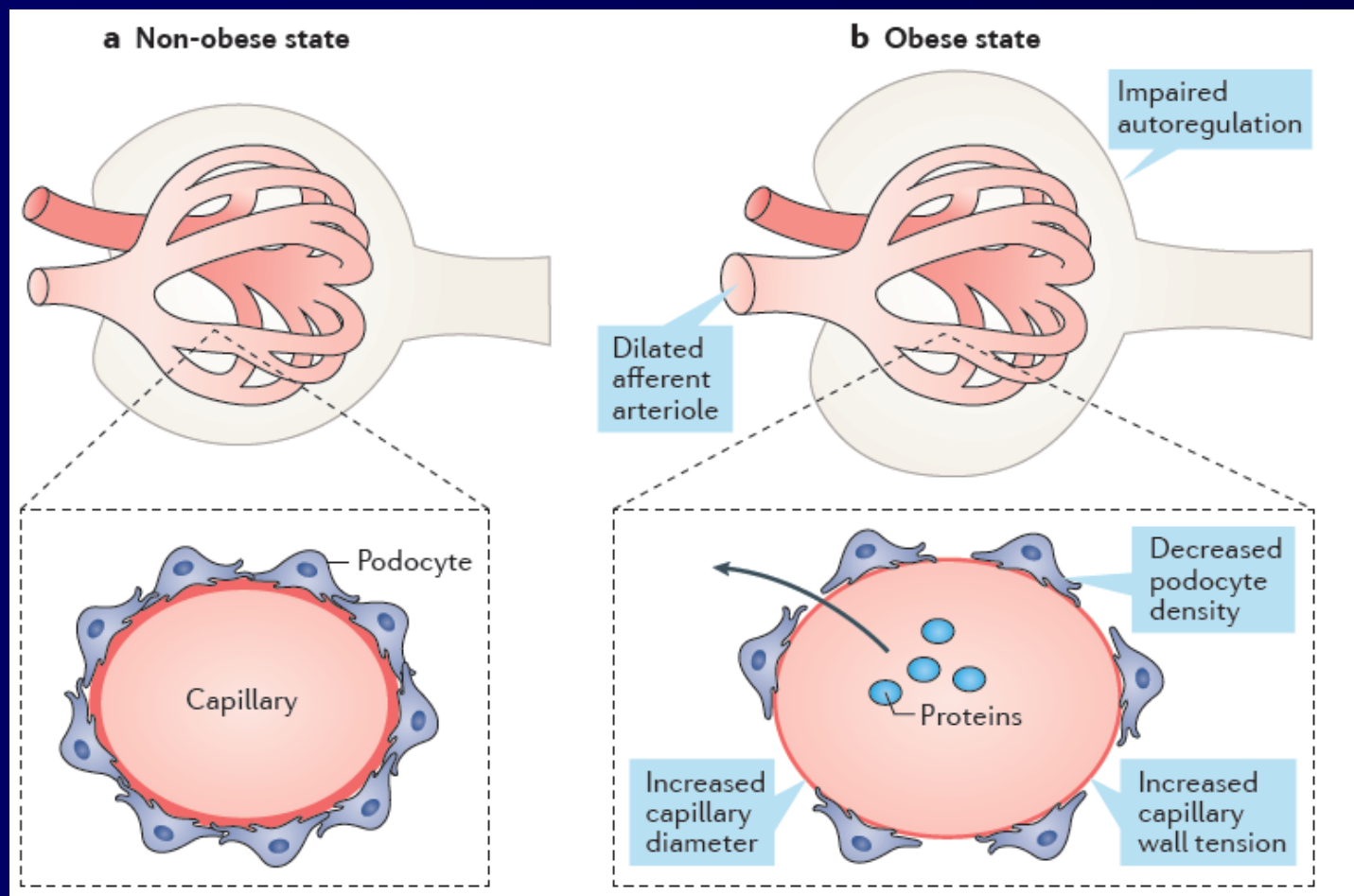
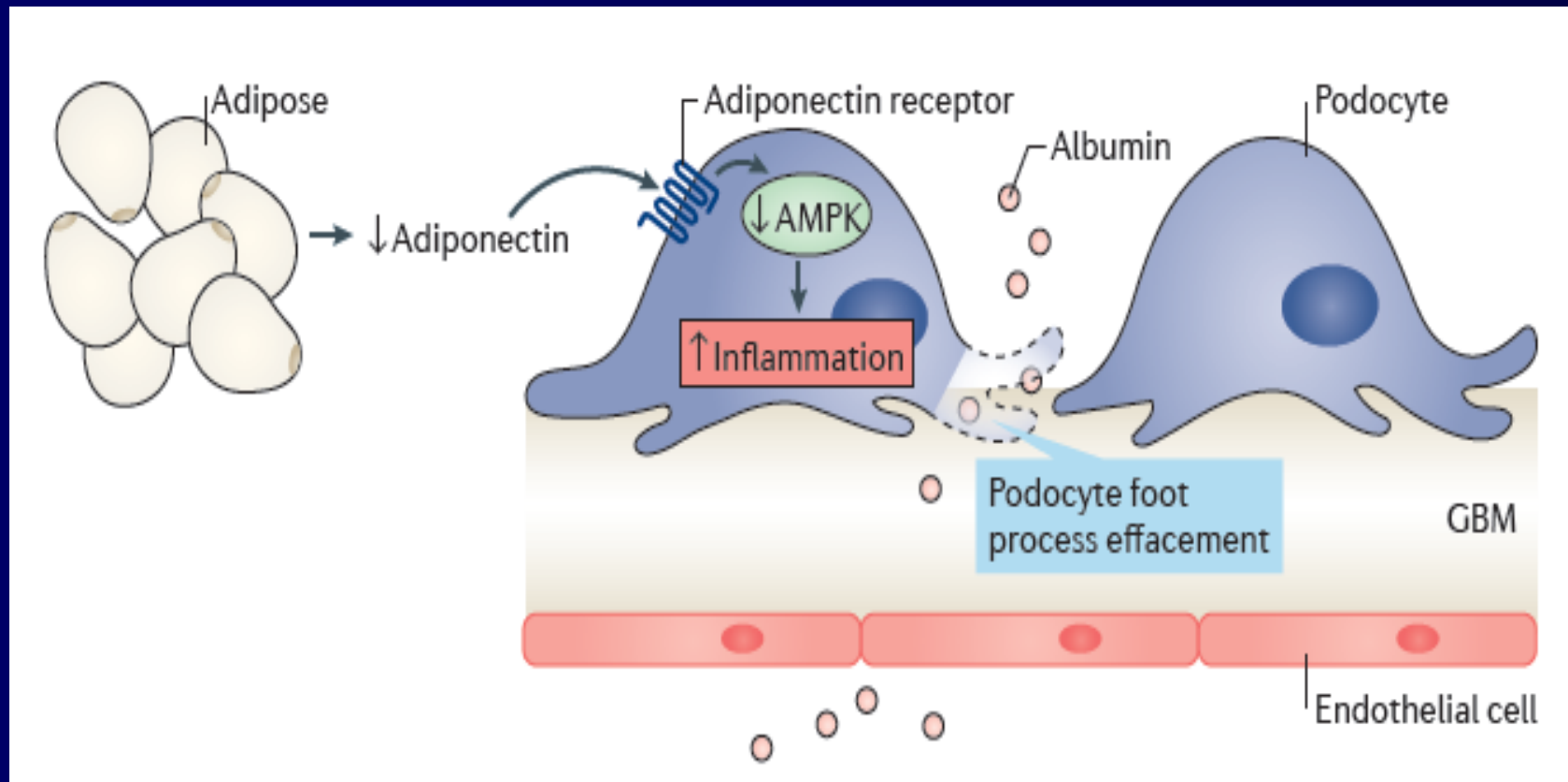


Figure 1 | **Mechanisms of kidney injury in the setting of obesity.**

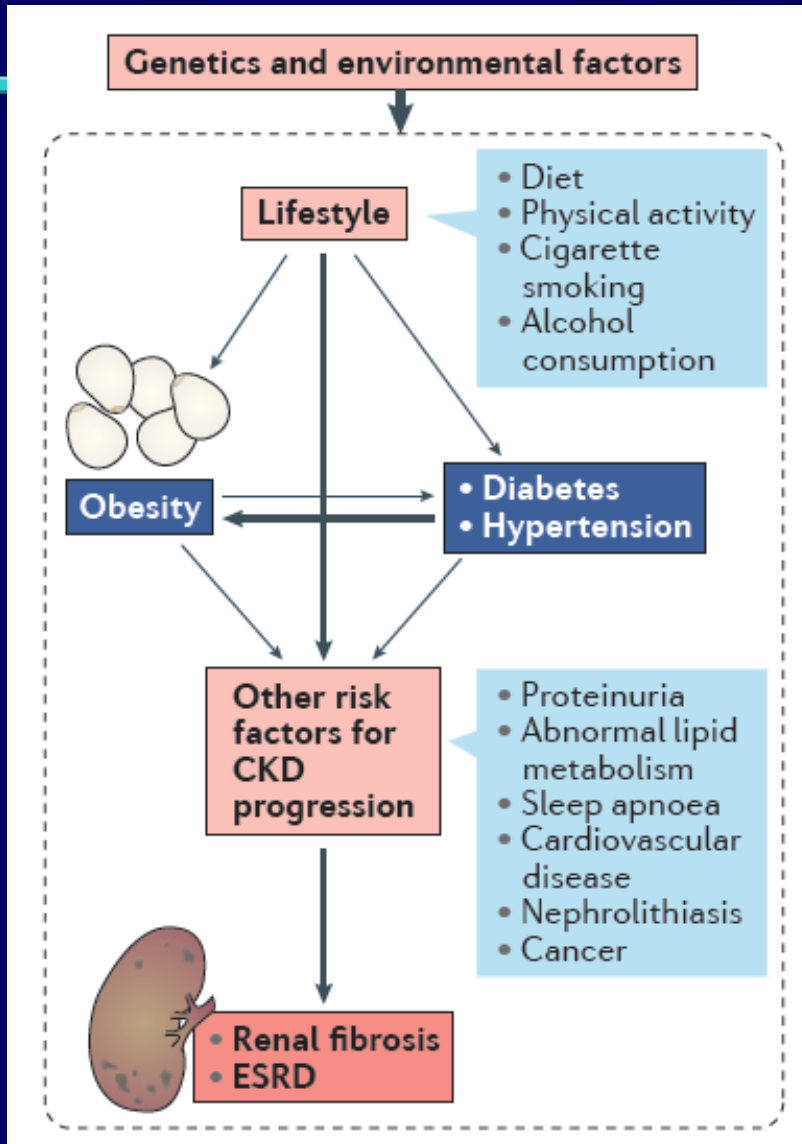
Effects of adiponectin on kidney podocyte function



Association of Non-alcoholic Fatty Liver Disease with Chronic Kidney Disease: A Systematic Review and Meta-analysis



Giovanni Musso^{1*}, Roberto Gambino², James H. Tabibian³, Mattias Ekstedt⁴, Stergios Kechagias⁵, Masahide Hamaguchi⁶, Rolf Hultcrantz⁷, Hannes Hagström⁷, Seung Kew Yoon⁸, Phunchai Charatcharoenwitthaya⁹, Jacob George¹⁰, Francisco Barrera¹⁰, Svanhildur Hafliðadóttir¹¹, Einar Stefan Björnsson¹¹, Matthew J. Armstrong¹², Laurence J. Hopkins¹², Xin Gao¹³, Sven Francque¹⁴, An Verrijken¹⁵, Yusuf Yilmaz¹⁶, Keith D. Lindor³, Michael Charlton³, Robin Haring¹⁷, Markus M. Lerch¹⁸, Rainer Rettig¹⁹, Henry Völzke²⁰, Seungho Ryu²¹, Guolin Li²², Linda L. Wong²³, Mariana Machado²⁴, Helena Cortez-Pinto²⁴, Kohichiroh Yasui²⁵, Maurizio Cassader²



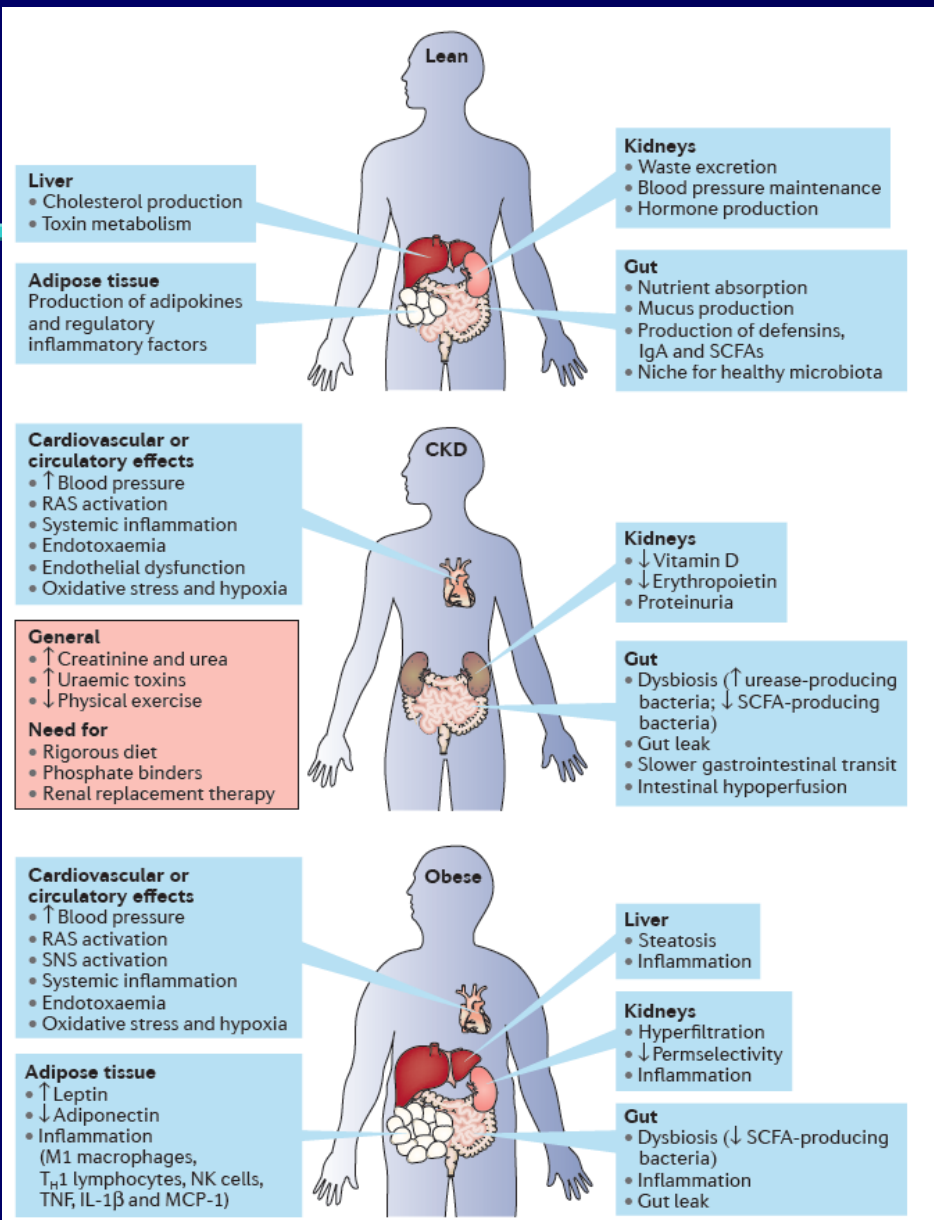
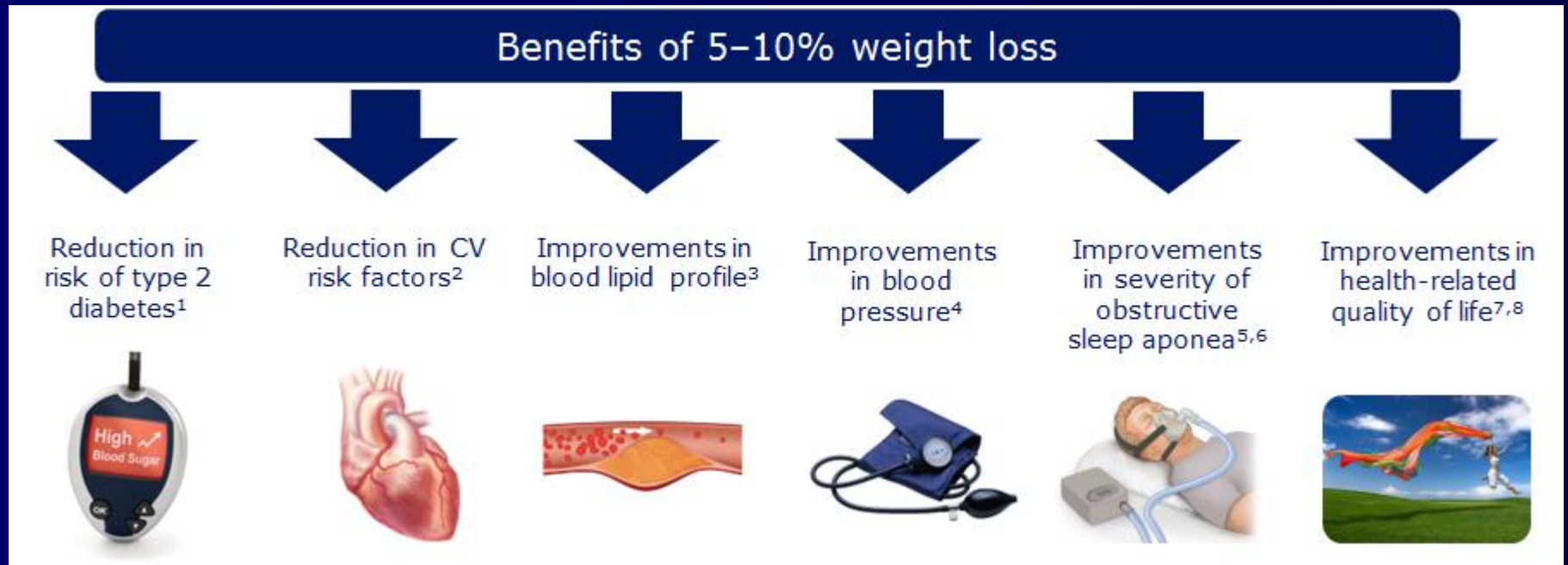


Figure 3 | The fat-intestine-kidney axis.

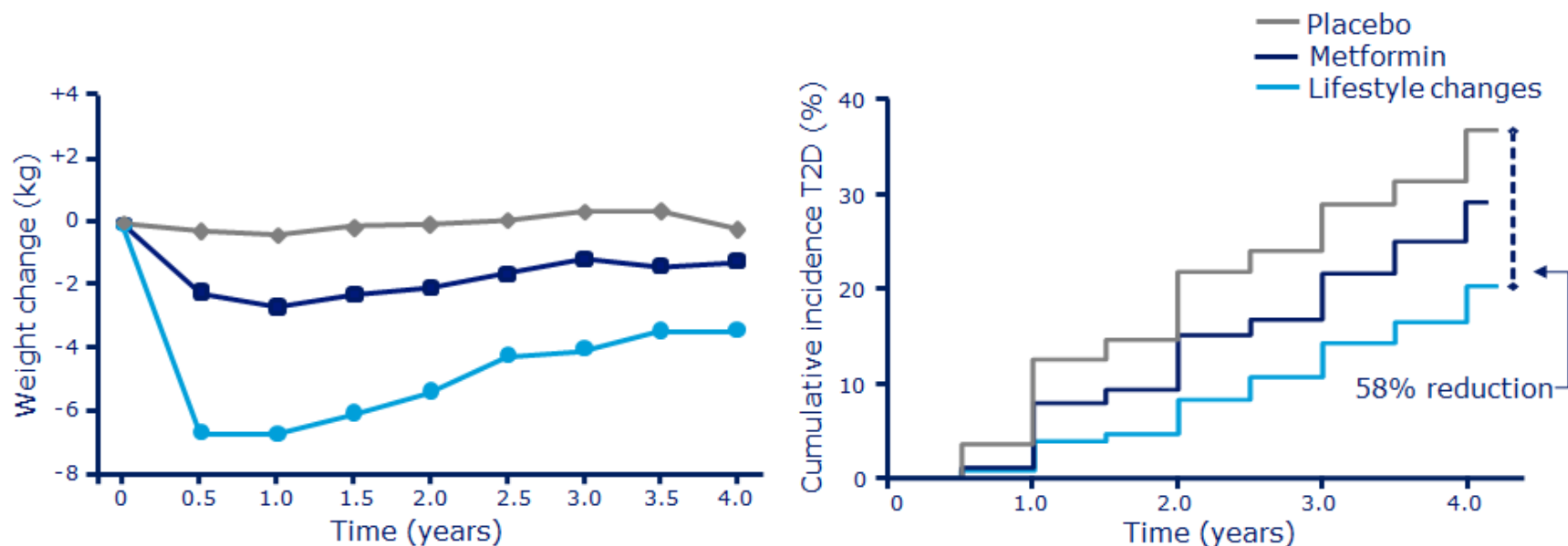
Weight loss improves obesity-related comorbidities



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

2. Reviewed in Van Gaal et al, *Int J Obesity*, 1996

In obese patients with prediabetes, weight loss reduces the risk of type 2 diabetes

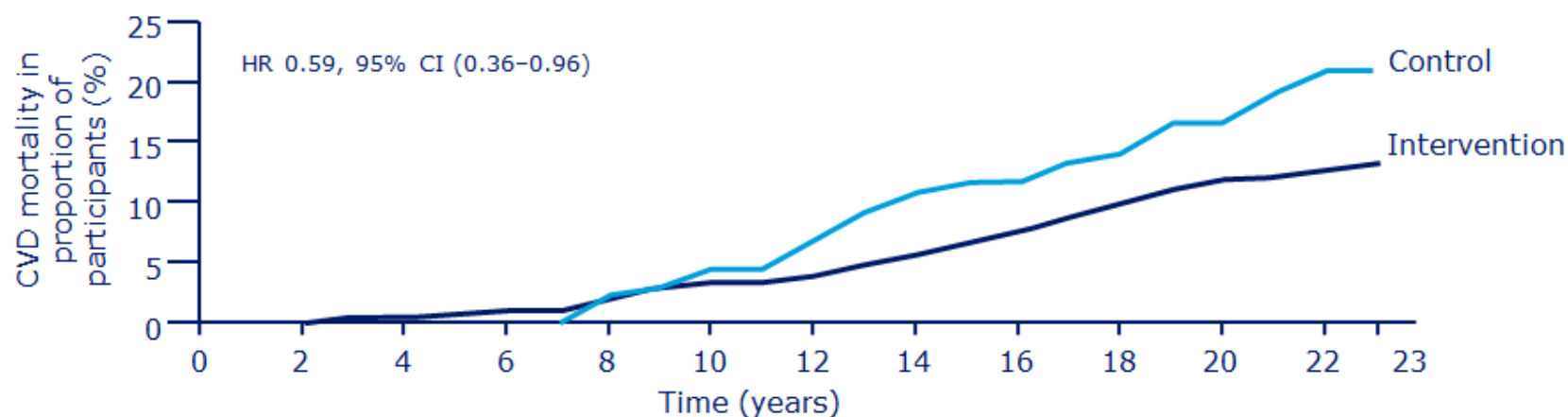


n=3234 men and women with prediabetes*; mean BMI=34

*Fasting plasma glucose 95–135 mg/dL (5.3–6.9 mmol/L) or ≤ 125 mg/dL in patients from American Indian clinics; plasma glucose 2 h after an oral glucose tolerance test 140–199 mg/dL (7.8–11.0 mmol/L); T2D, type 2 diabetes

Knowler et al. *N Engl J Med* 2002;346:393–403

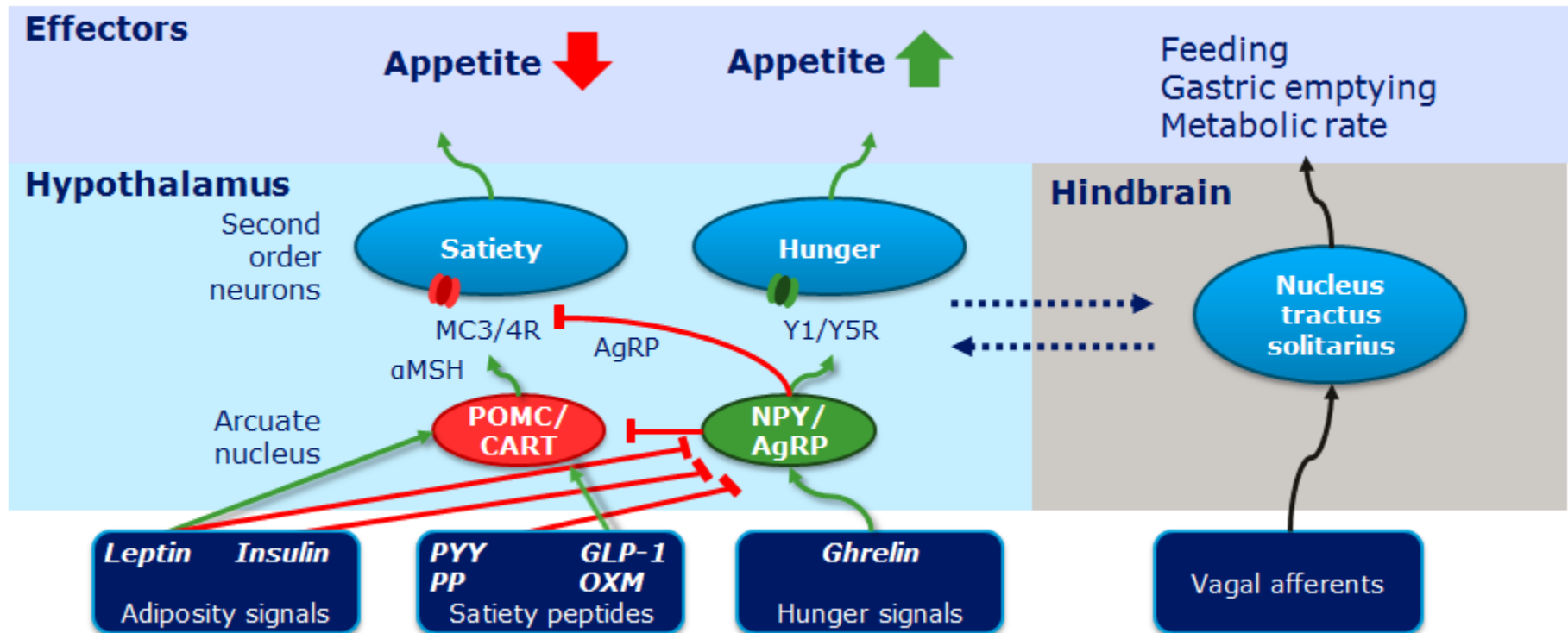
Weight loss in patients with prediabetes reduces long-term incidence of cardiovascular mortality



Cumulative death incidence (%; 95% CI)	Intervention (n=430)	Control (n=138)	Hazard ratio (95% CI)	P-value
All-cause mortality	28.1% (23.9–32.4)	38.4% (30.0–46.5)	0.71 (0.51–0.99)	0.049
Cardiovascular disease mortality	11.9% (8.8–15.0)	19.6% (12.9–26.3)	0.59 (0.36–0.96)	0.033
Diabetes incidence	72.6% (68.4–76.8)	89.9% (84.9–94.9)	0.55 (0.40–0.76)	0.001

Data are n(%) unless stated otherwise. HR, hazard ratios adjusted by clinic

Peripheral signals modulate appetite and energy expenditure via hypothalamic neurons



AgRP, Agouti-related protein; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; α-MSH, α-melanocyte stimulating hormone; GLP-1R, glucagon-like peptide-1 receptor; OXM, oxyntomodulin

Adapted from Badman & Flier. *Science* 2005;307:1909–14; Seo *et al. Endocr J* 2008;55:867–74

The challenges with WEIGHT control

Complex pathophysiology

Targets (expectations) difficult to achieve

Current (pharma) therapies are associated with
side effects

Co-morbid challenges: blood pressure & CVD

Other challenges: patient adherence & cost

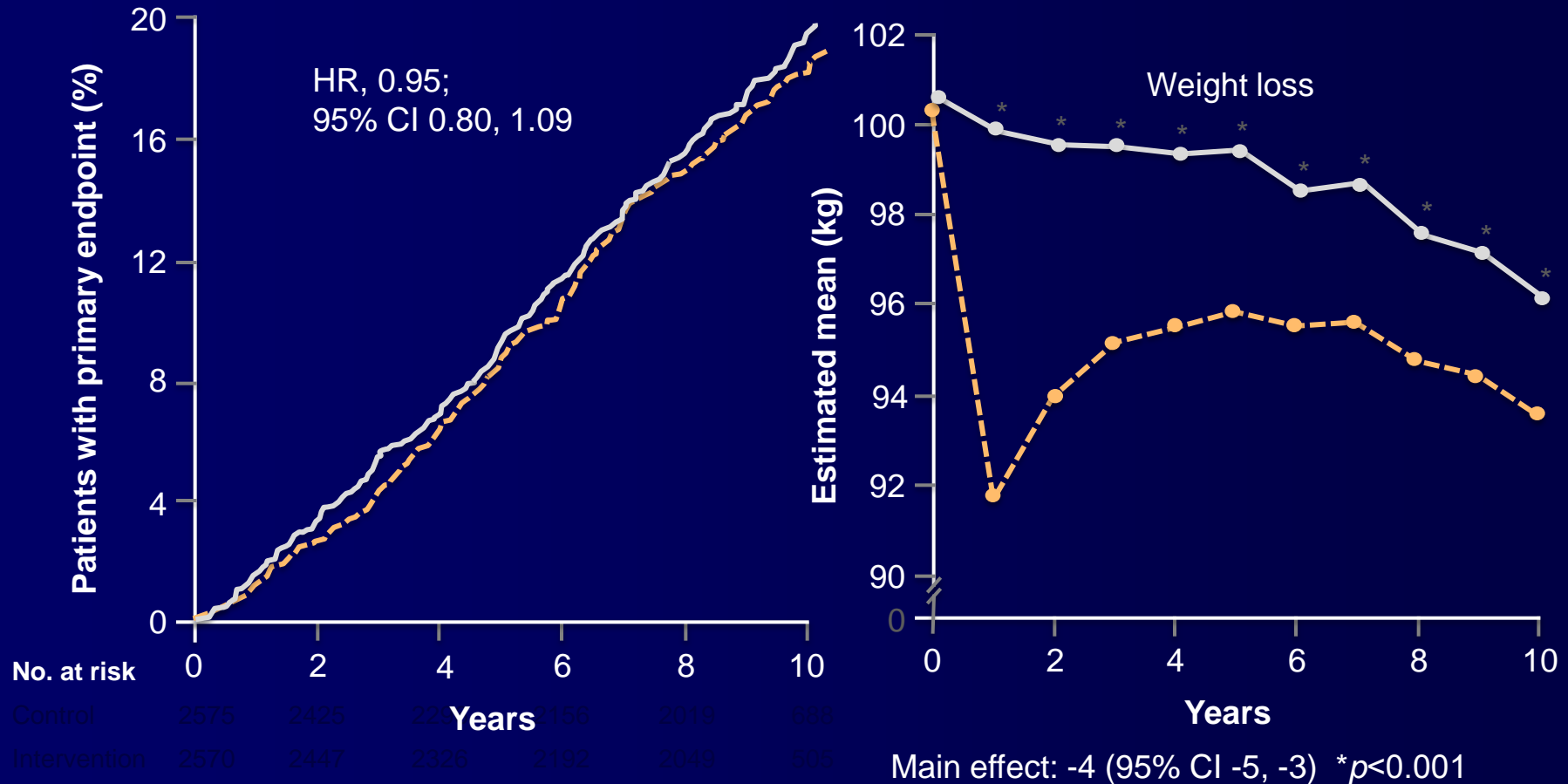
Results from the Look AHEAD Study

- **8.6 % weight loss of initial weight in more than 2500 overweight or obese patients with type 2 diabetes**
- **Comprehensive lifestyle intervention**
- **38 % of individuals in lifestyle intervention had weight loss > 10 % of initial weight**

Intensive lifestyle intervention, focused on weight loss, did not improve CV risk in

T2D

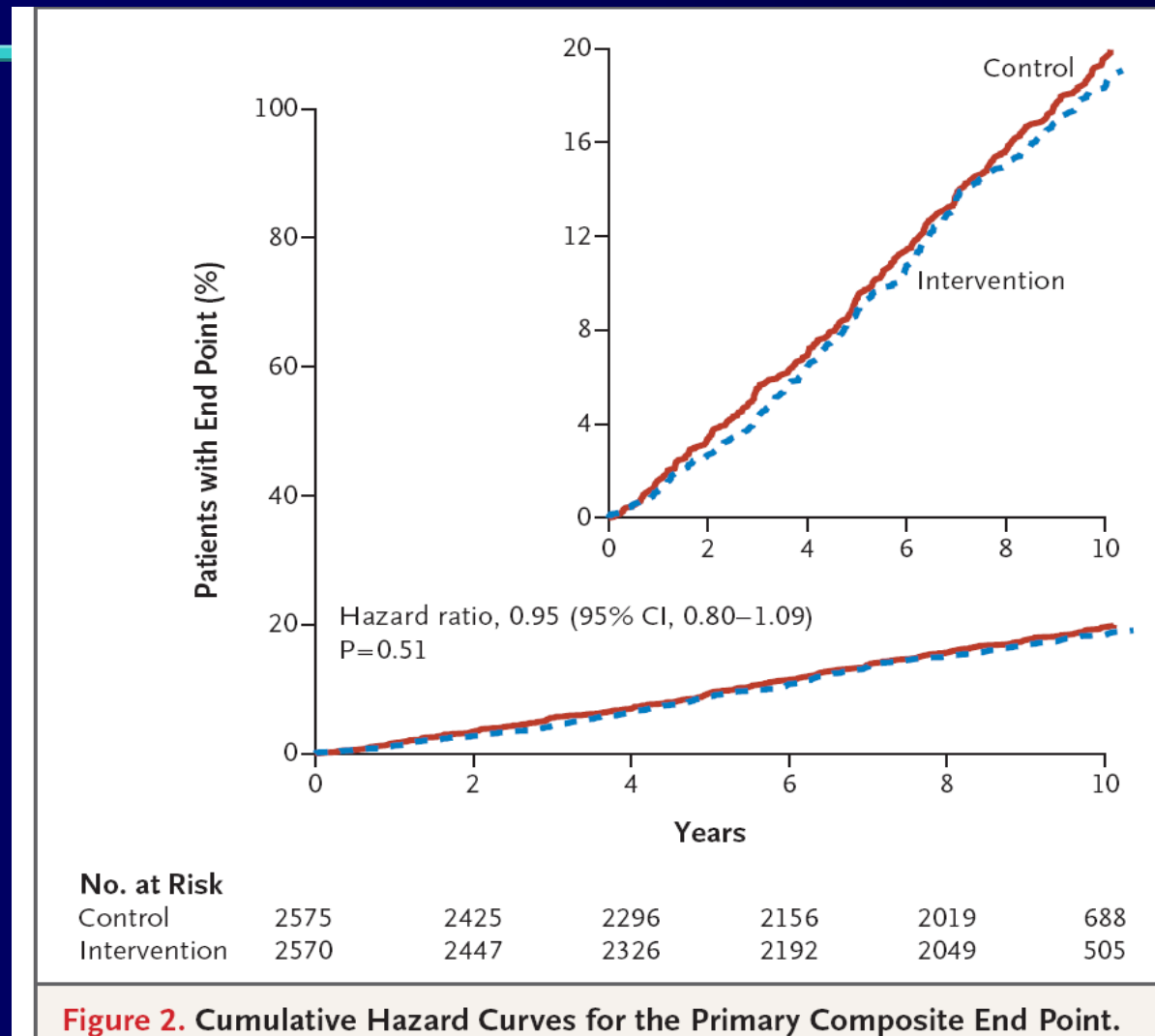
--- Intervention — Control



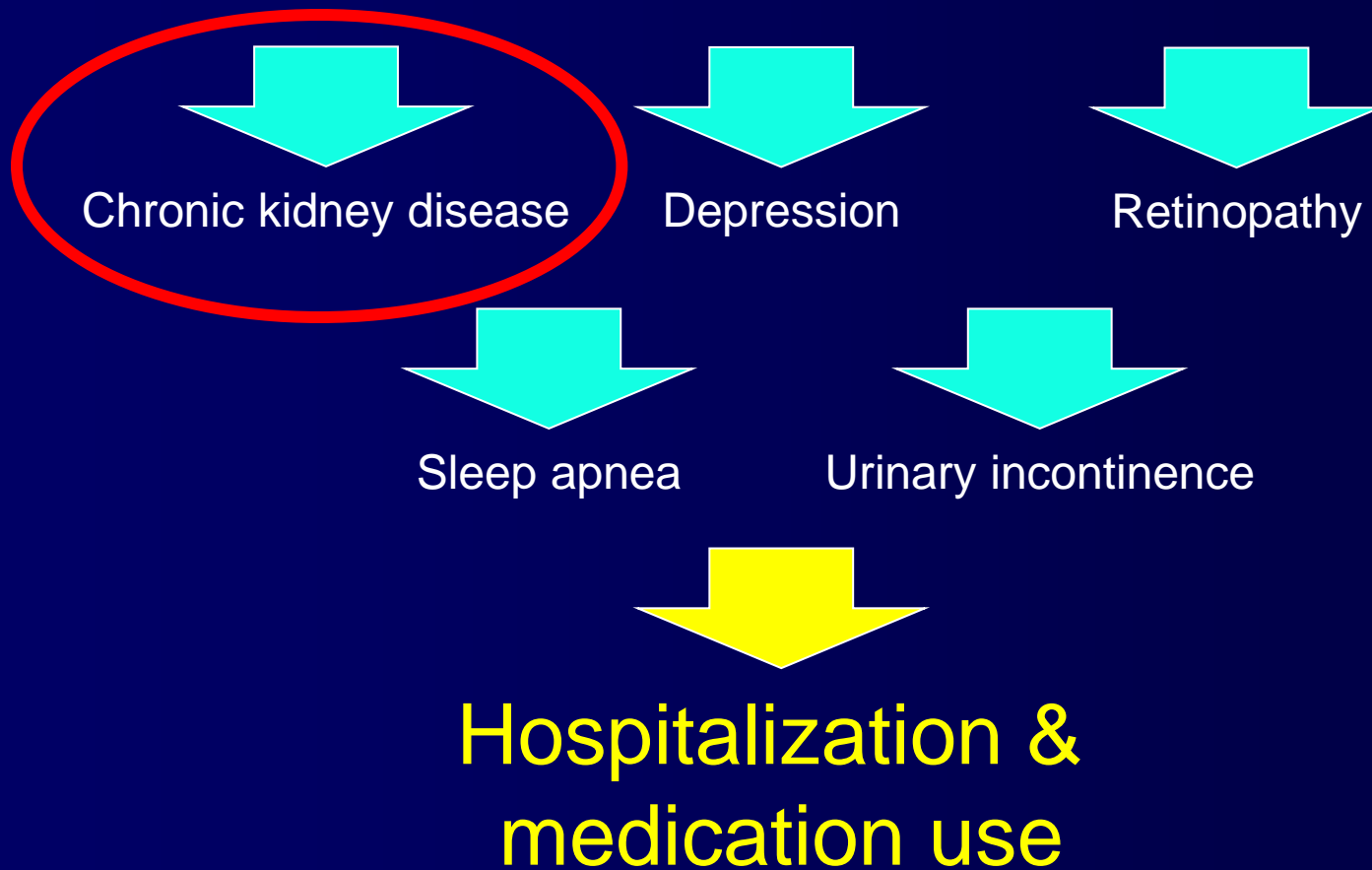
Endpoint: Composite of CV death, non-fatal MI, non-fatal stroke and hospitalisation for angina

Look AHEAD Research Group. *N Engl J Med* 2013;369:145

Look AHEAD: NO cardiovascular benefit



Although no significant improvement in CV outcomes, other benefits were observed



Look AHEAD : Association between the magnitude of weight loss and incidence of CV disease in T2D patients

	Intensive lifestyle intervention weight-change categories (percentage weight loss in first year)							Intensive lifestyle intervention fitness-change categories (change in metabolic equivalents in first year)						
	Overall control group (reference)	Gain or stable (<2% loss)	Small loss (≥2-<5%)	Medium loss (≥5-<10%)	Large loss (≥10%)	Hazard ratio per SD weight change	p value	Overall control group (reference)	Loss or stable (<0.5 loss)	Small gain (≥0.5-<1.0)	Medium gain (≥1.0-<2.0)	Large gain (≥2.0)	Hazard ratio per SD fitness change	p value
Primary outcome														
Events per person-years	351/20 891	58/3087	69/3766	114/6446	120/8266	--	--	303/19 025	148/8025	53/3081	64/4743	59/4190	--	--
Crude rate per 100 person-years	1.68	1.88	1.88	1.77	1.45	--	--	1.59	1.84	1.72	1.35	1.41	--	--
Unadjusted hazard ratio (95% CI)	1.00	1.14 (0.86-1.51)	1.09 (0.85-1.42)	1.06 (0.86-1.31)	0.84 (0.68-1.04)	0.88 (0.69-0.98)	0.02	1.00	1.18 (0.97-1.43)	1.06 (0.79-1.42)	0.84 (0.64-1.10)	0.87 (0.66-1.15)	0.90 (0.80-1.01)	0.08
Adjusted hazard ratio* (95% CI)	1.00	1.29 (0.96-1.72)	1.04 (0.80-1.36)	1.15 (0.92-1.43)	0.80 (0.65-0.99) p=0.039†	0.75 (0.57-0.95)	0.006	1.00	1.19 (0.97-1.46)	1.06 (0.78-1.43)	0.85 (0.64-1.13)	0.90 (0.68-1.21)	0.91 (0.80-1.03)	0.15
Secondary outcome														
Events per person-years	503/20 436	82/3009	108/3643	151/6335	173/8136	--	--	433/18 657	211/7844	78/3041	92/4663	86/4111	--	--
Crude rate per 100 person-years	2.46	2.72	2.96	2.38	2.13	--	--	2.32	2.69	2.57	1.97	2.09	--	--
Unadjusted hazard ratio (95% CI)	1.00	1.14 (0.90-1.44)	1.22 (0.99-1.50)	0.97 (0.81-1.17)	0.85 (0.72-1.02)	0.86 (0.78-0.94)	0.0007	1.00	1.18 (1.00-1.39) p=0.048†	1.09 (0.86-1.39)	0.85 (0.68-1.06)	0.90 (0.71-1.13)	0.91 (0.83-1.01)	0.07
Adjusted hazard ratio* (95% CI)	1.00	1.28 (1.01-1.64) p=0.045†	1.19 (0.96-1.47)	1.02 (0.84-1.23)	0.79 (0.66-0.95) p=0.011†	0.82 (0.74-0.90)	<0.0001	1.00	1.17 (0.99-1.39)	1.08 (0.84-1.38)	0.83 (0.66-1.05)	0.93 (0.73-1.18)	0.92 (0.83-1.02)	0.12
Data are for primary and secondary outcomes associated with percentage weight loss and fitness changes over the first year. *Adjusted for sex, age, baseline weight (from weight-change models), baseline fitness (from fitness-change models), history of cardiovascular disease, insulin use, diabetes duration, smoking status, LDL cholesterol, systolic blood pressure, and diastolic blood pressure. †p value refers to pairwise comparison with overall control group.														
Table 3: Comparison of control group (reference) with intensive weight-loss intervention weight-loss and fitness-change categories														

The Look AHEAD Research Group –
Lancet Diabetes Endocrinol 2016;4:913-21

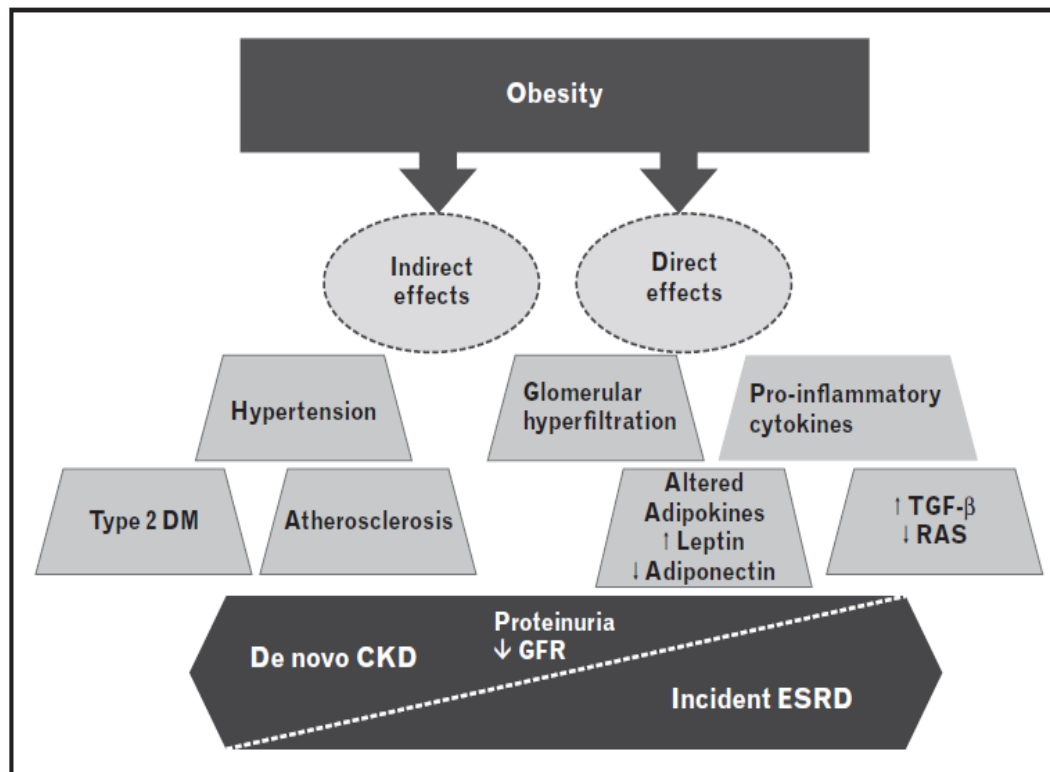
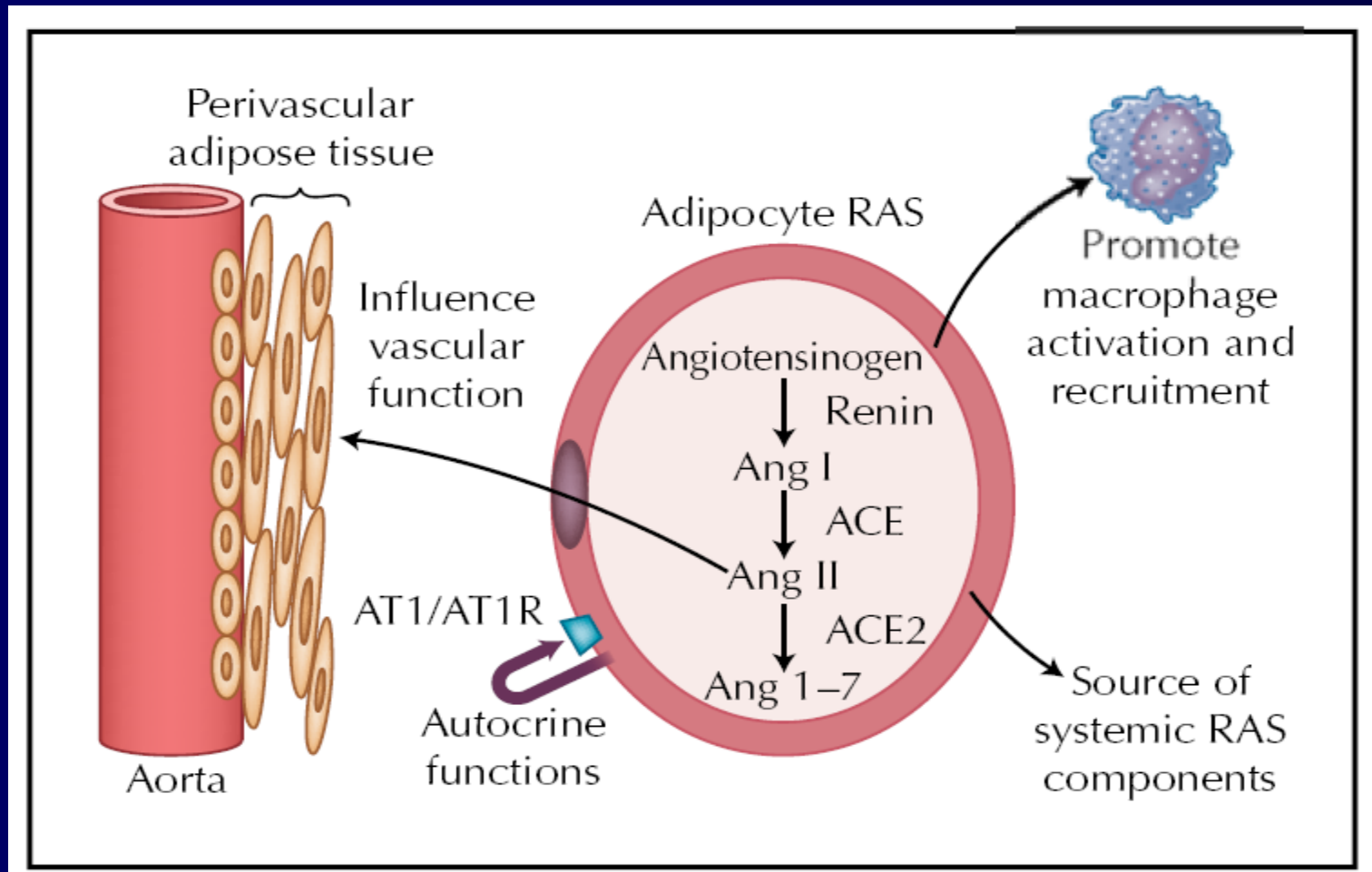
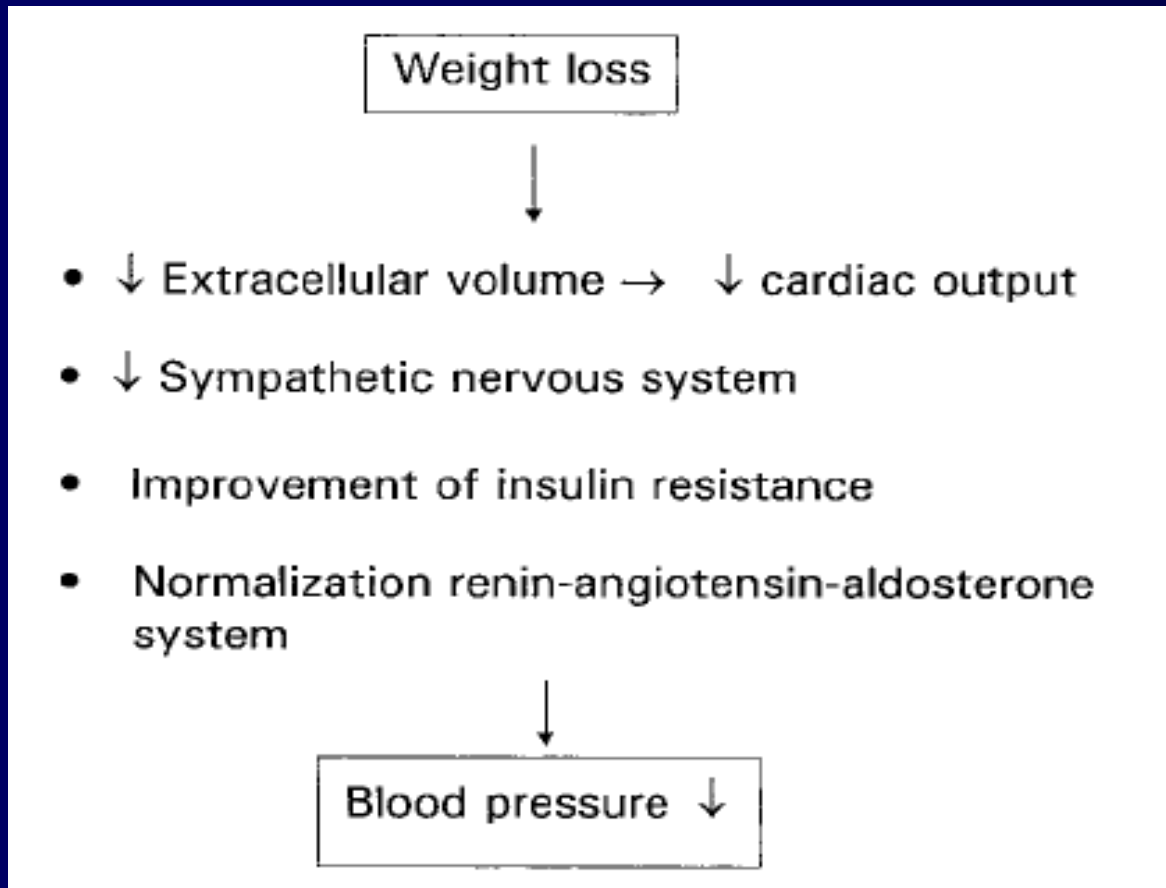


FIGURE 1. Potential pathways by which obesity leads to the development of chronic kidney disease. CKD, chronic kidney disease; DM, diabetes mellitus; ESRD, end-stage renal disease; GFR, glomerular filtration rate; RAS, renin–angiotensin–aldosterone system; TGF- β , transforming growth factor beta.

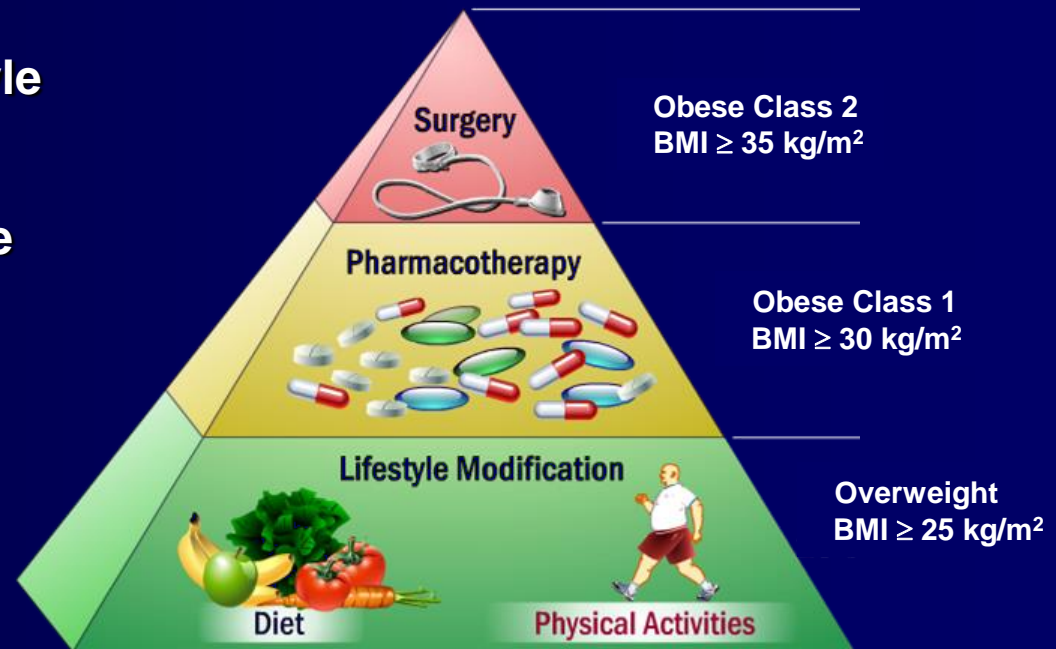


Weight loss and hypertension

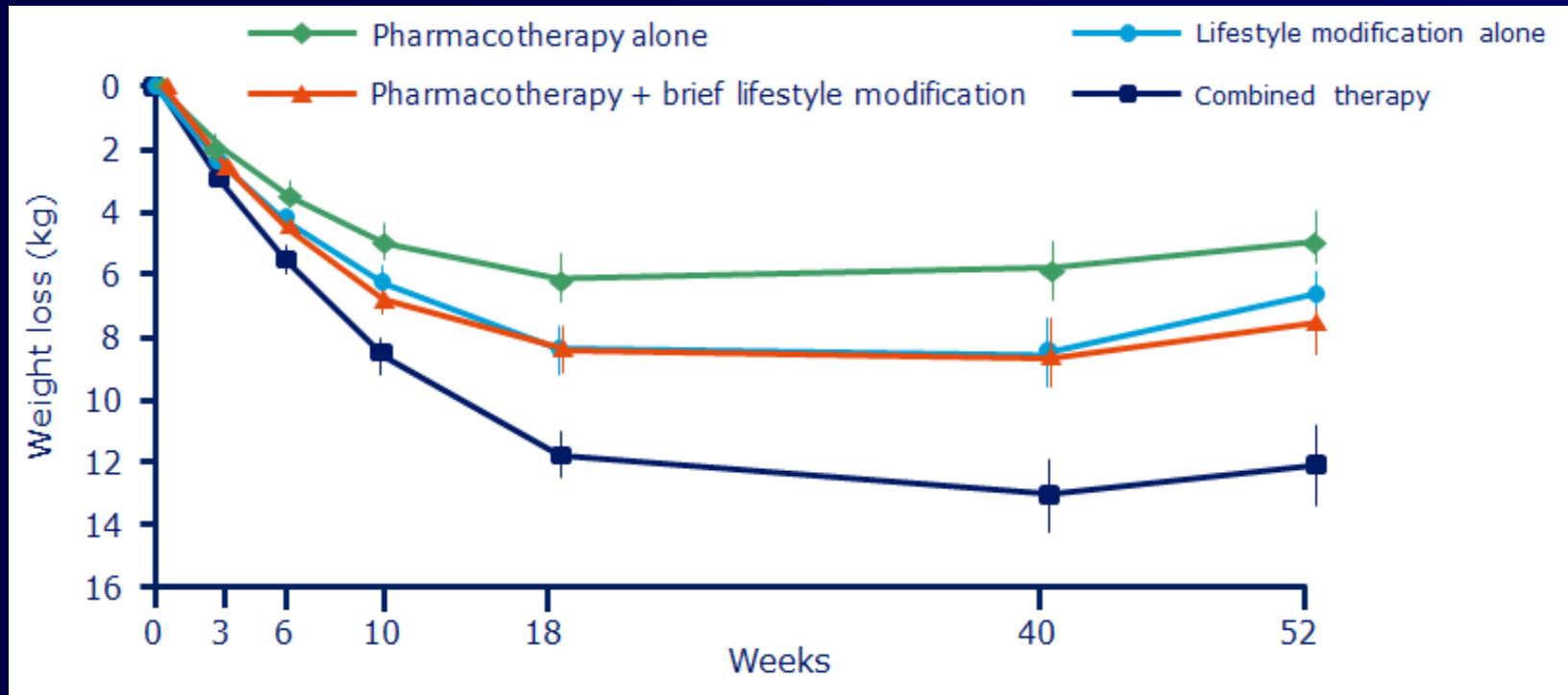


Pharmacotherapy helps with adherence to a lifestyle change

1. Increase the number of patients responding to lifestyle modification
2. Increase the magnitude of the response
3. Increase the duration of the response



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



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 lifestyle counselling sessions

Overview

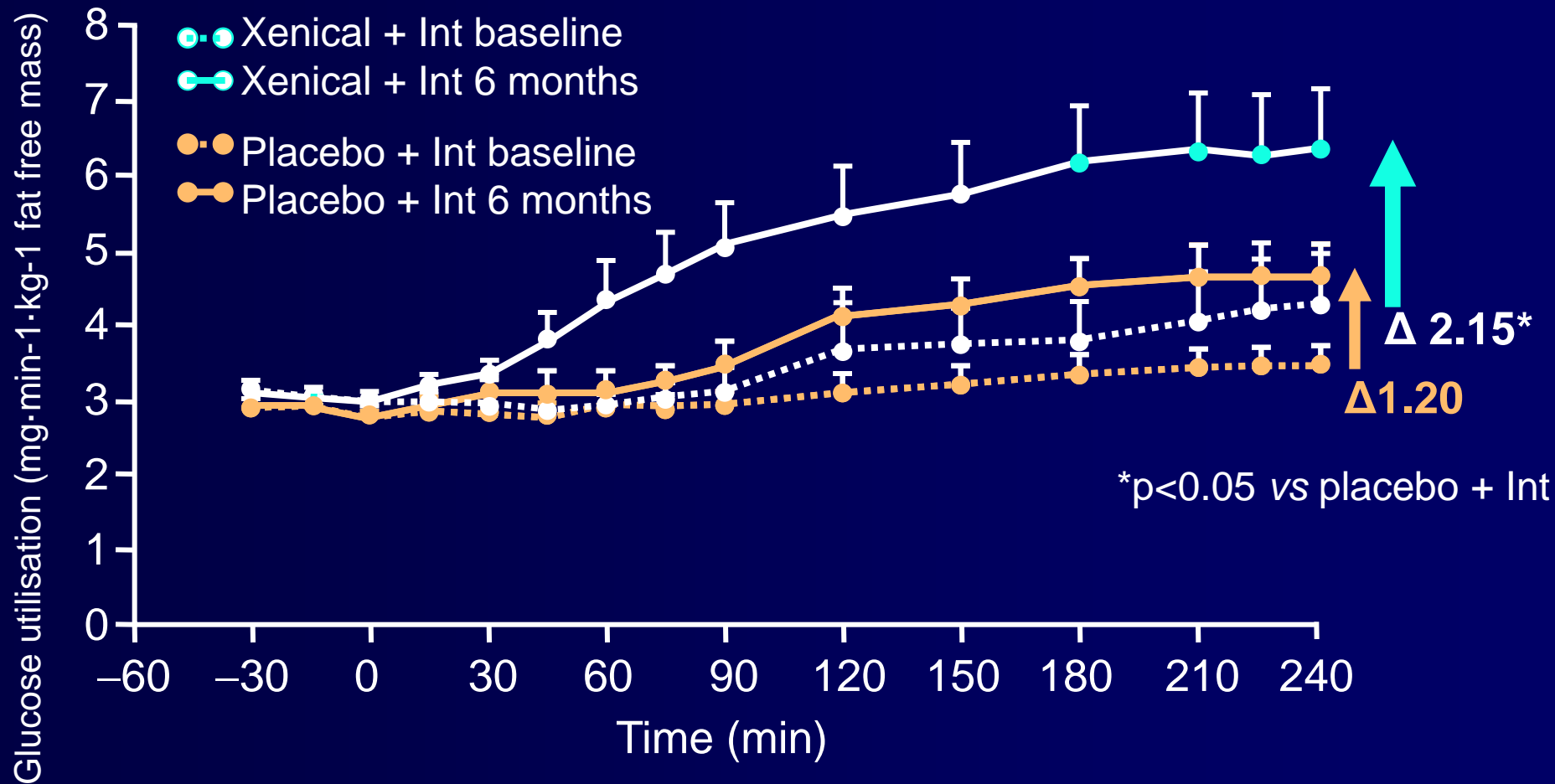
- ▶ Review of anti-obesity medications approved in Europe
 - ▶ **orlistat** (XENDOS trial)¹
 - ▶ **naltrexone / bupropion** (COR trial programme)²
 - ▶ **liraglutide 3.0 mg** (SCALE Obesity and Prediabetes study)³
- ▶ Anti-obesity medications outside Europe
- ▶ How to achieve weight maintenance ?
- ▶ Future options: more than a dream ?

1. Torgerson JS et al. Diabetes Care 2004; 27: 155–61

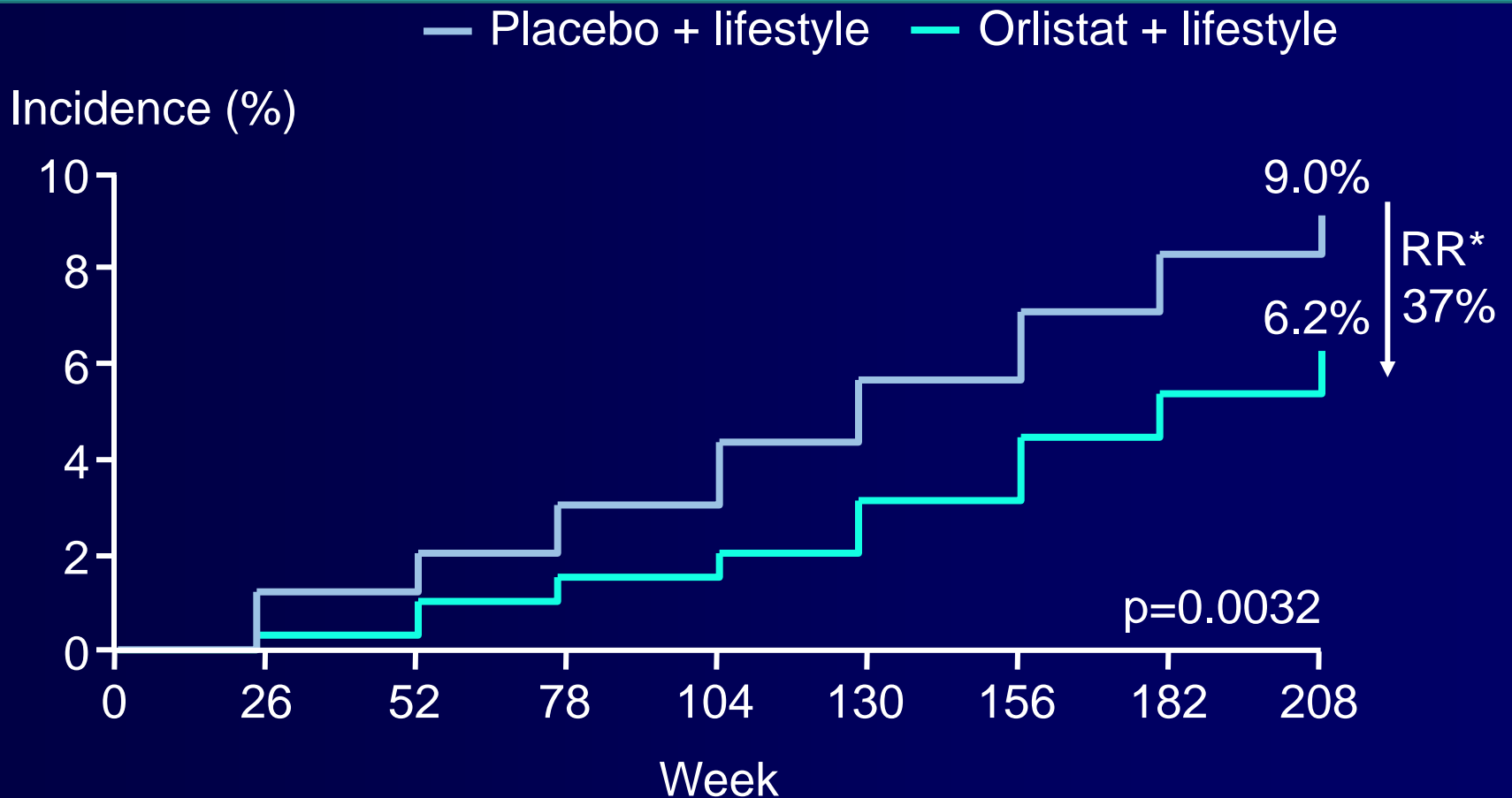
2. Greenway FL et al. Lancet 2010; 376: 595-605

3. le Roux CW et al. Obesity Week, 2–6 November 2015, Los Angeles, CA, USA (T-P-LB-3843)

Improvement in glucose utilisation with orlistat compared with placebo at 6 months

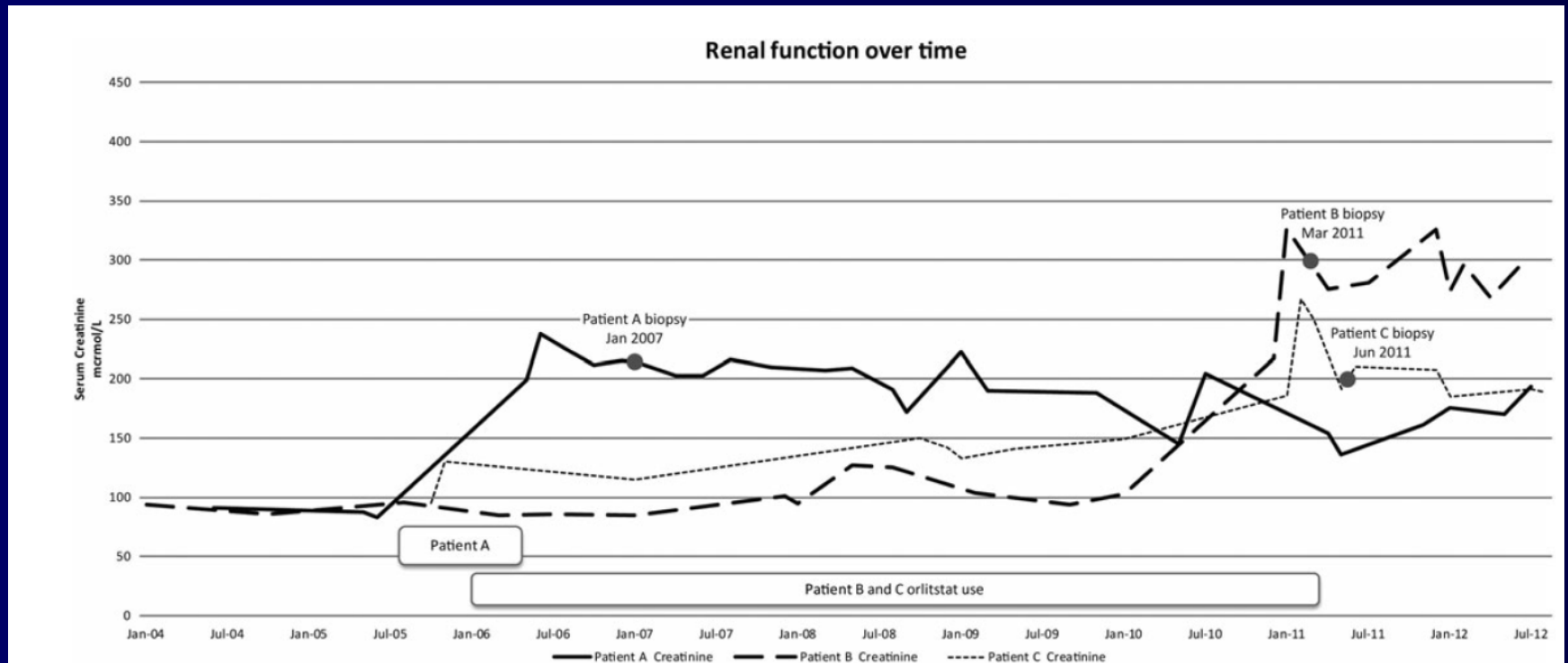


Cumulative incidence of type 2 diabetes All patients in Xendos prevention study

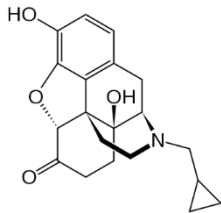


**Reduction in risk of progressing to type 2 diabetes versus placebo + lifestyle*

Potential nephrotoxic effect of orlistat

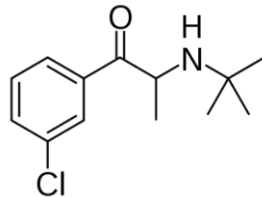


Naltrexone + Bupropion



Systematic IUPAC name

17-(cyclopropylmethyl)-4,5 α -epoxy-3,14-dihydroxymorphinan-6-one

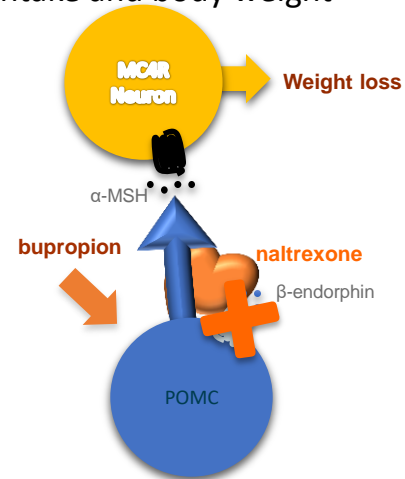


Systematic IUPAC name

(\pm)-2-(*tert*-Butylamino)-1-(3-chlorophenyl)propan-1-one

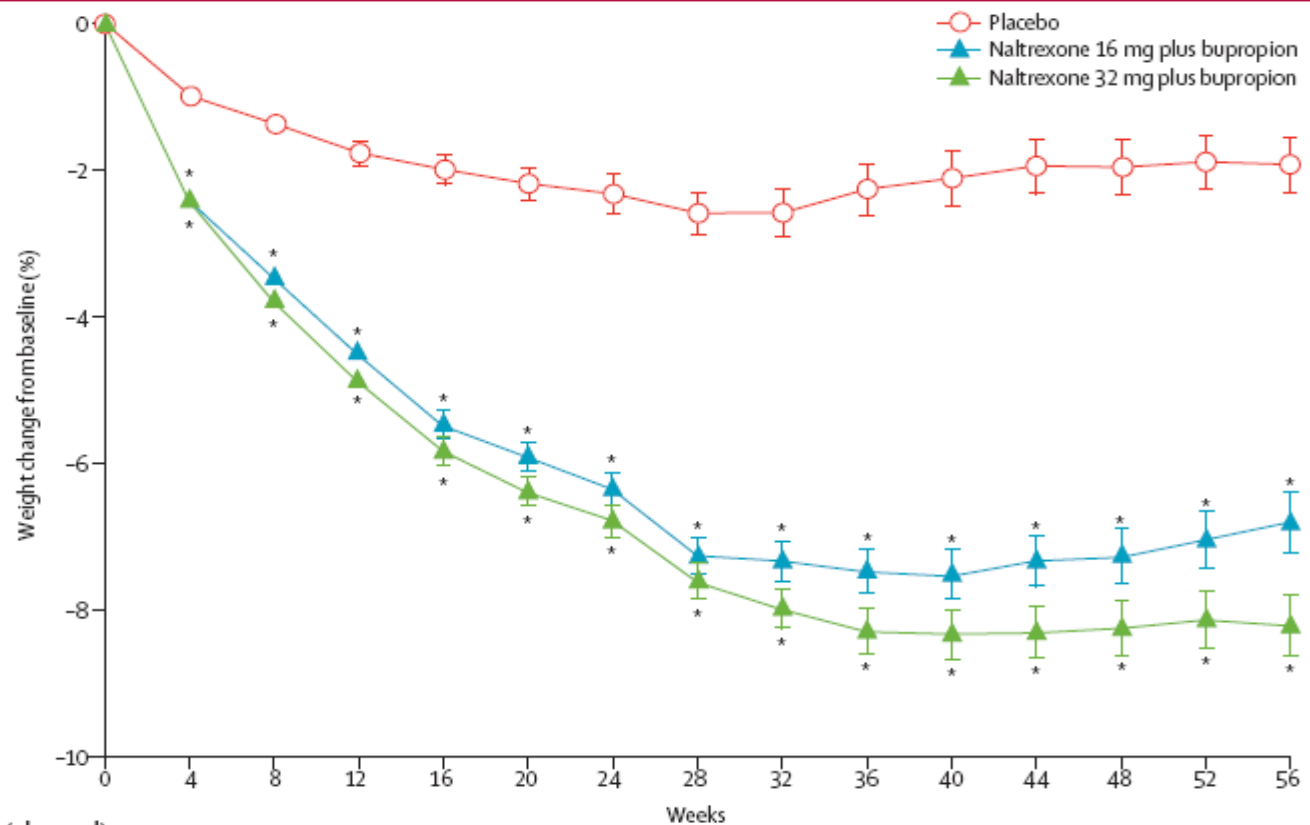
• Preclinical/clinical evidence for drug synergy:

- synergistic increase in POMC activity
- Synergistic decrease in food intake and body weight



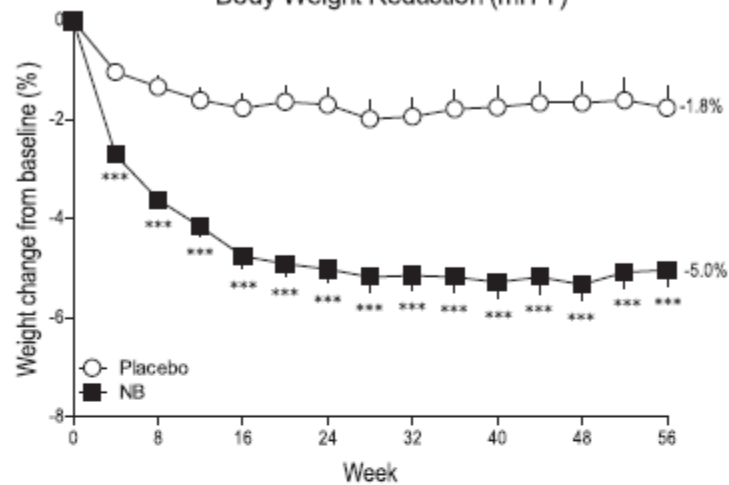
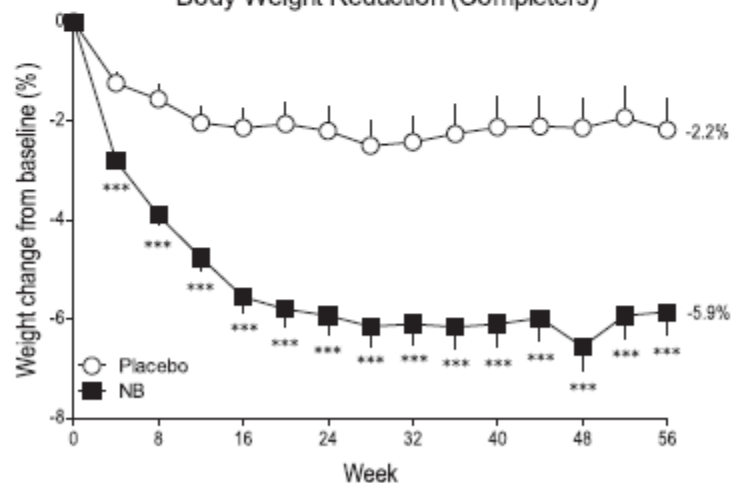
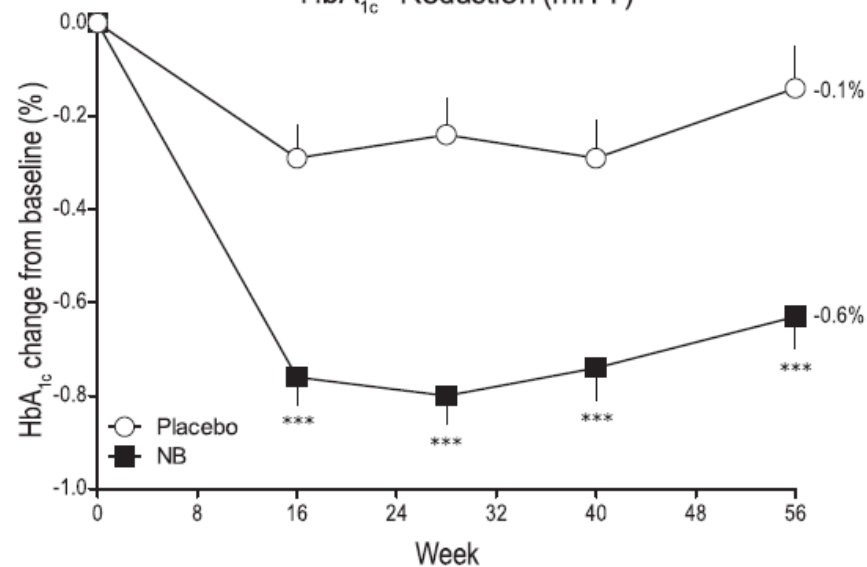
DA, dopamine; NE, norepinephrine; POMC, proopiomelanocortin; MSH, melanocyte-stimulating hormone; MC4R, melanocortin-4 receptor.

Weight loss by naltrexone / bupropion

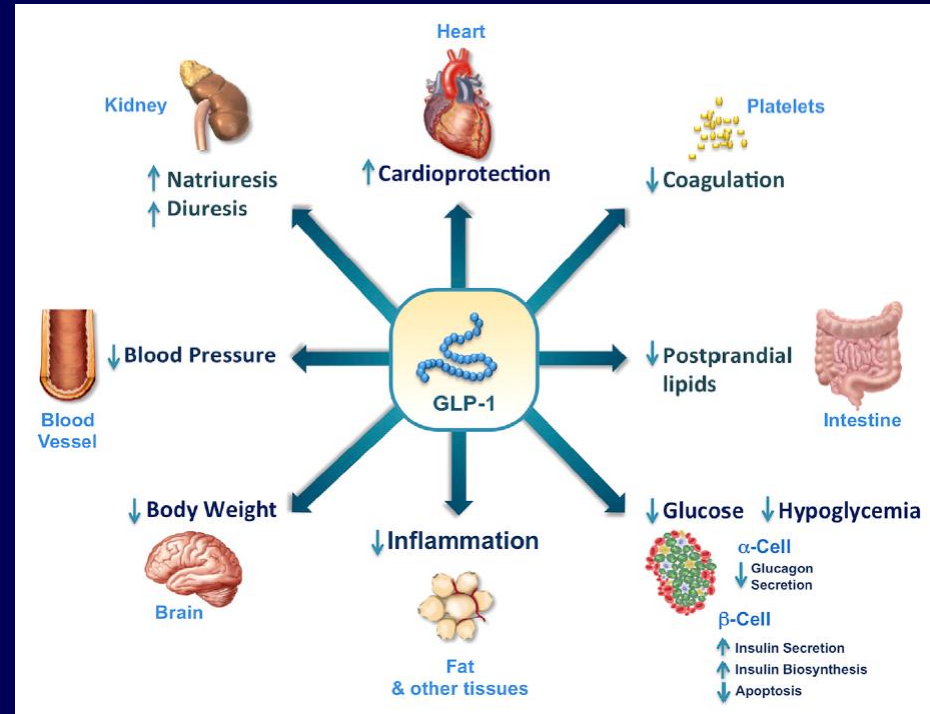
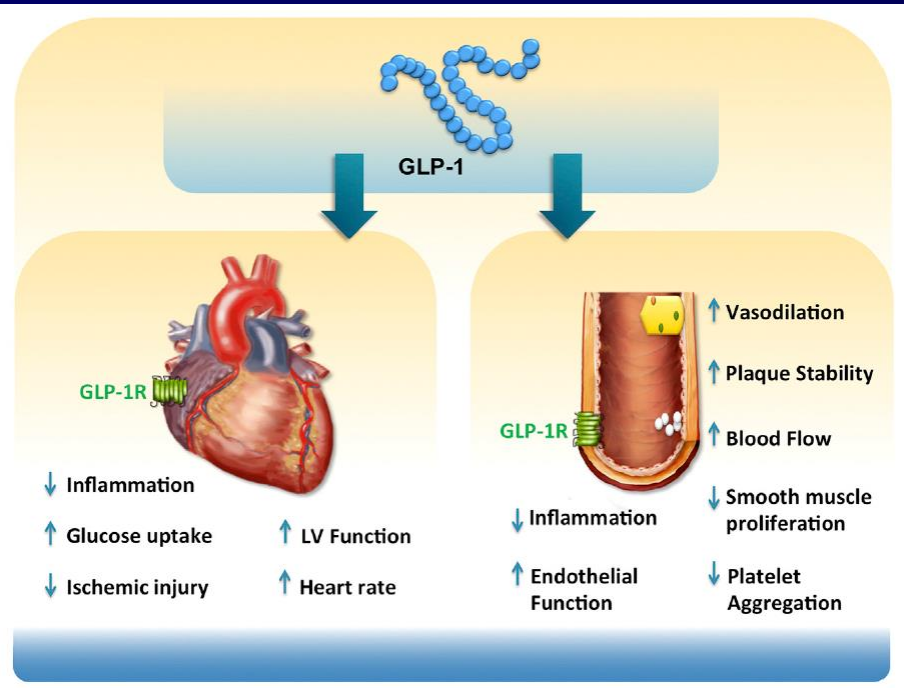


Number of participants by visit (observed)

Placebo	507	463	420	394	365	353	327	318	308	302	296	291	289	277
Naltrexone 16 mg plus bupropion	467	410	373	351	346	341	311	311	302	297	300	284	283	273
Naltrexone 32 mg plus bupropion	467	411	391	372	365	361	343	327	321	316	311	305	298	284

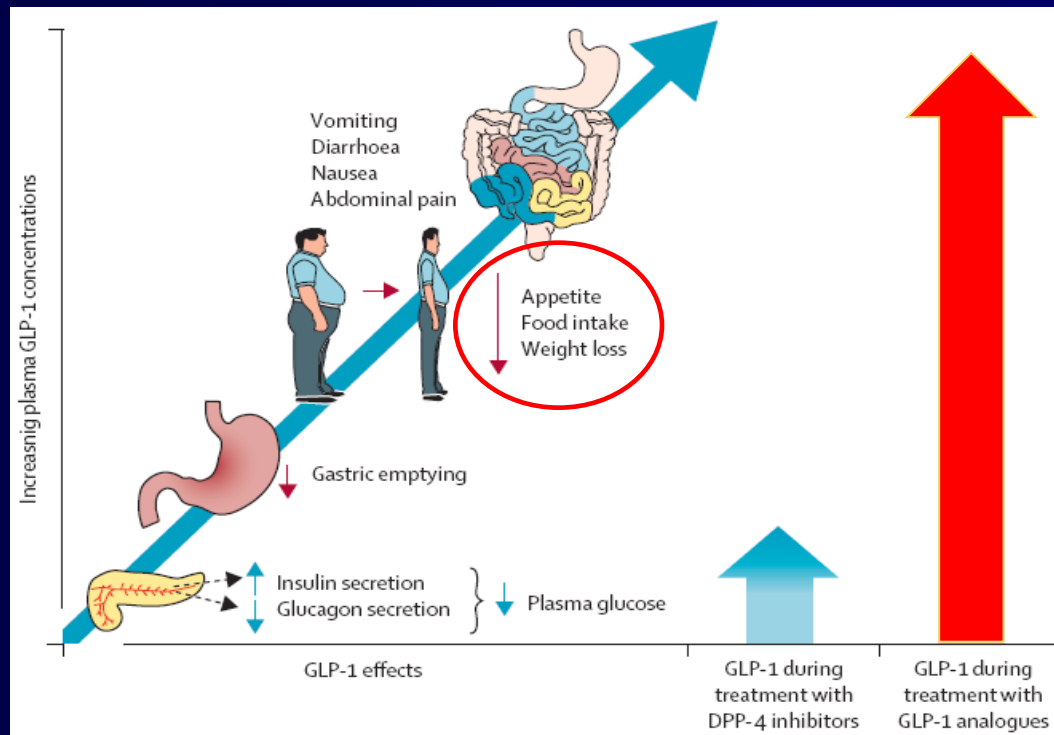
A**Body Weight Reduction (mITT)****B****Body Weight Reduction (Completers)****C****HbA_{1c} Reduction (mITT)**

Effects of GLP-1

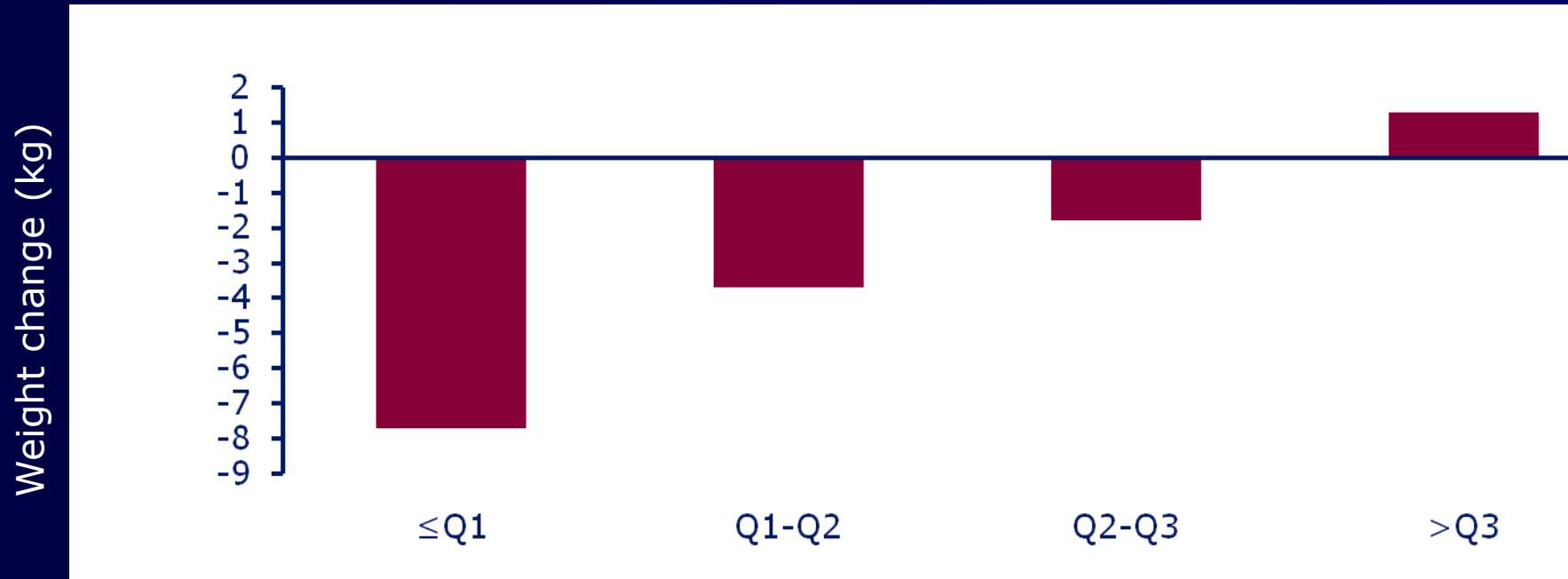


Drucker DJ, *Cell Metabolism* 2016; Epub ahead of print. DOI: <http://dx.doi.org/10.1016/j.cmet.2016.06.009>

Therapeutic implications with incretin-mediated therapies

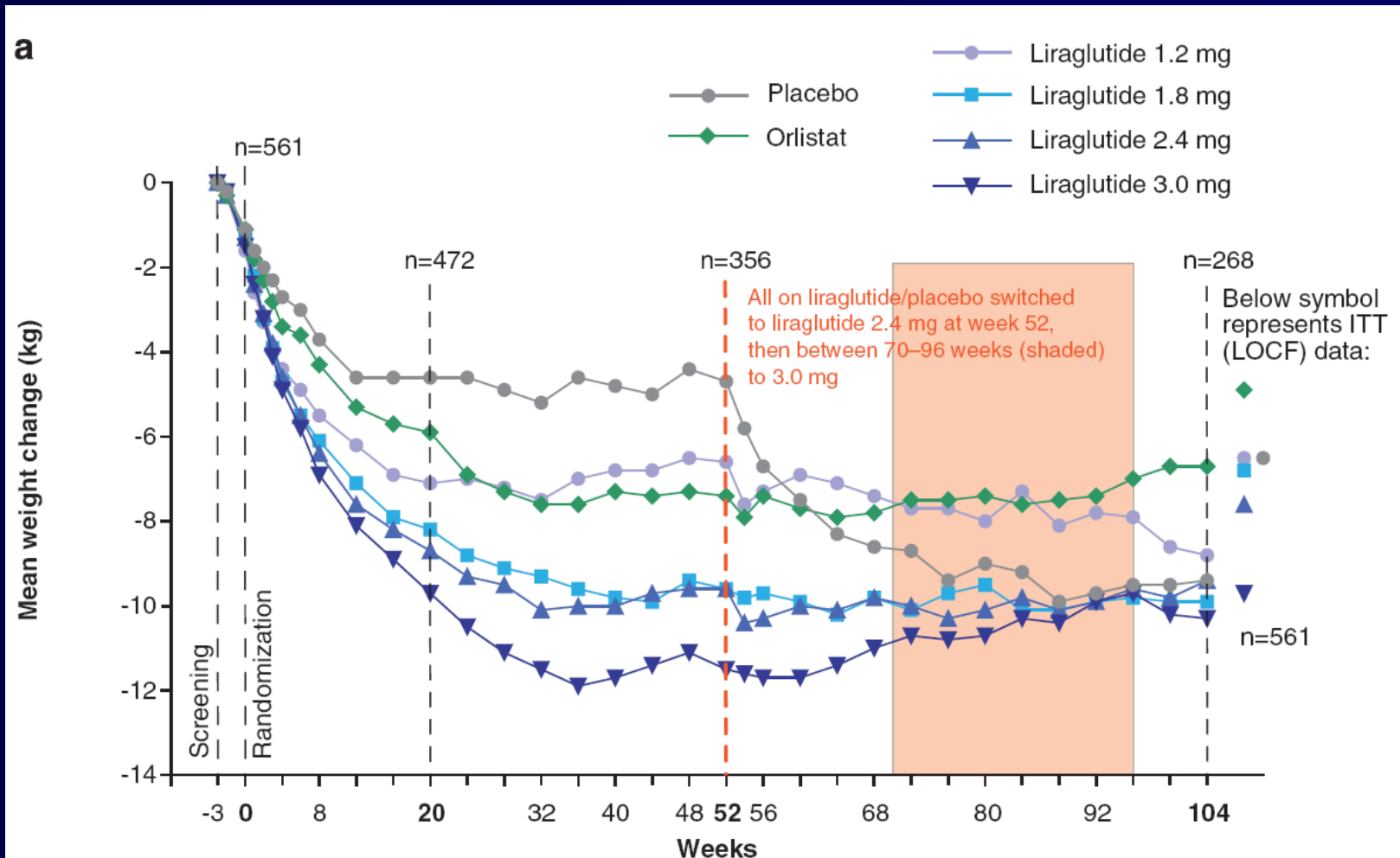


A quarter of patients lose an average of 7.7 kg with liraglutide



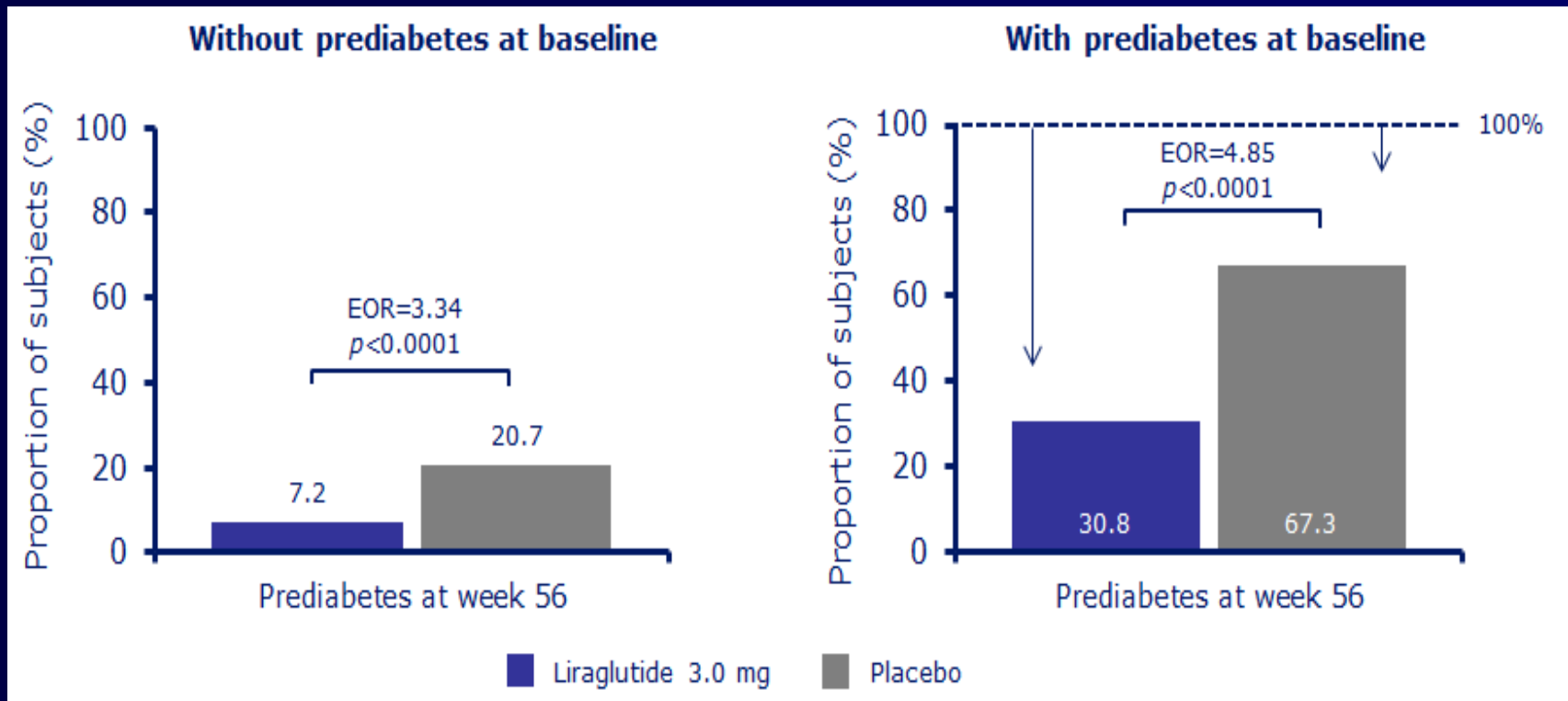
■ Liraglutide 1.8 mg + met + SU

Extension study with GLP-1 agonist in non-diabetic obese individuals



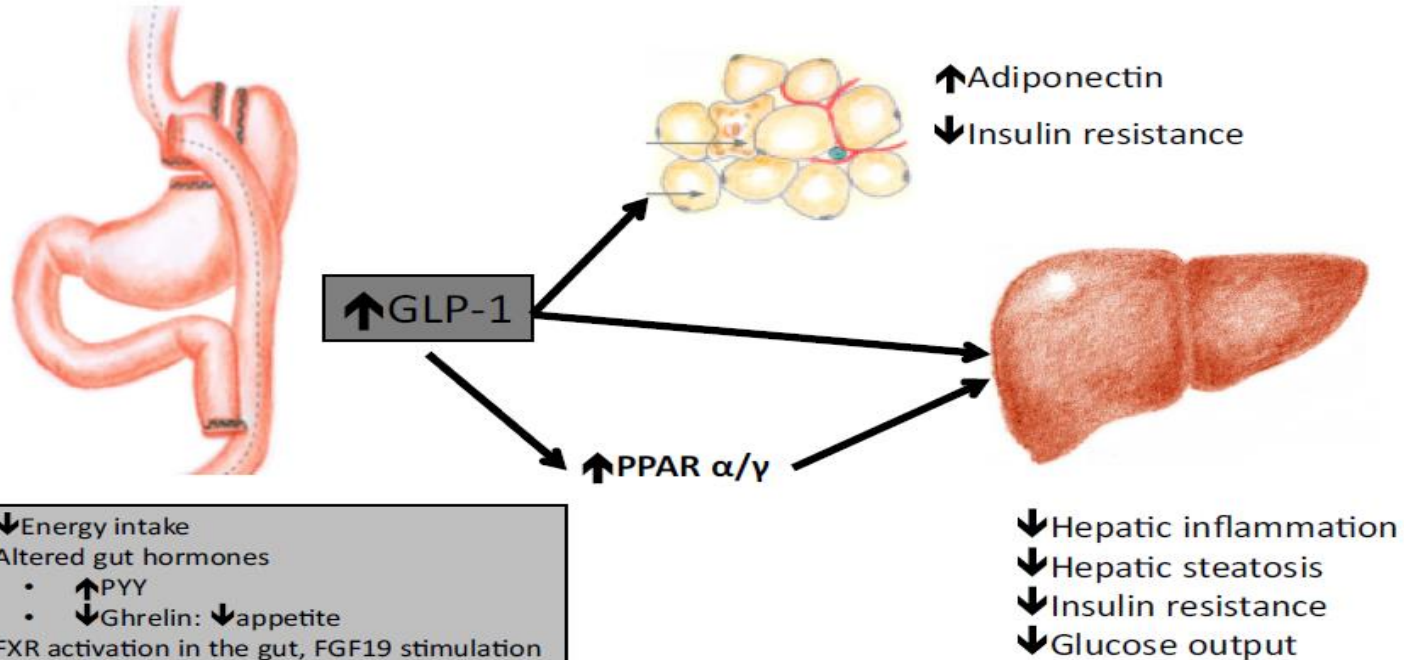
Prevalence of prediabetes after 56 weeks

By screening prediabetes status



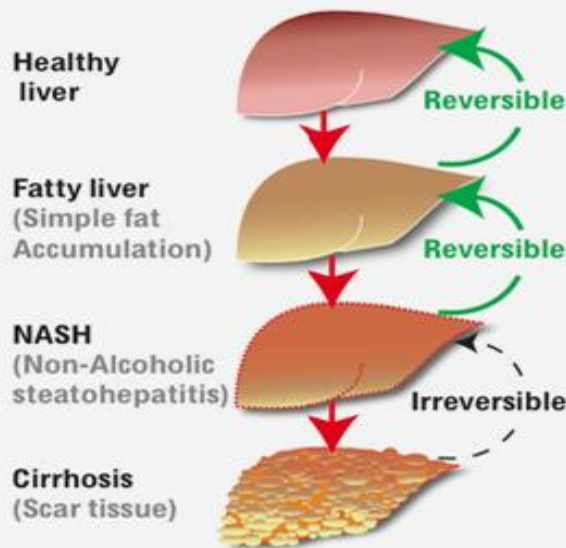
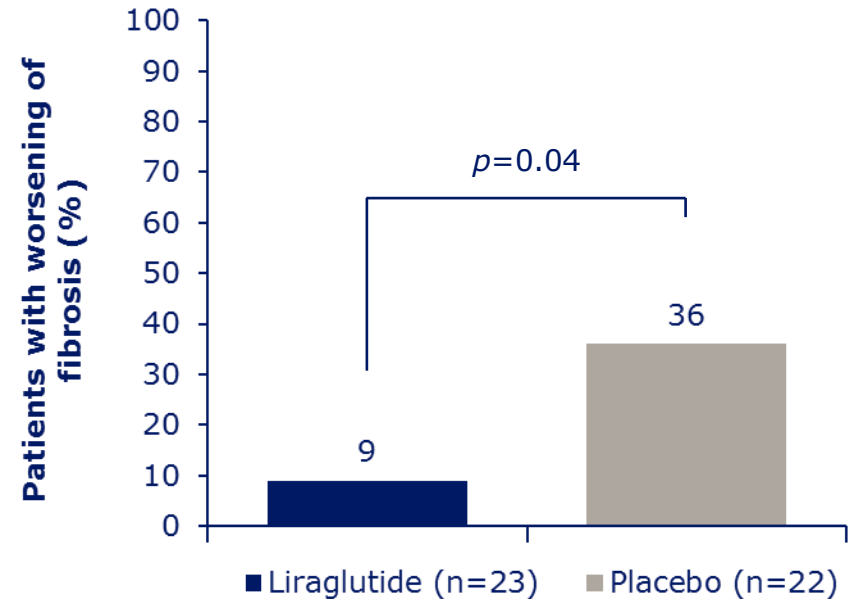
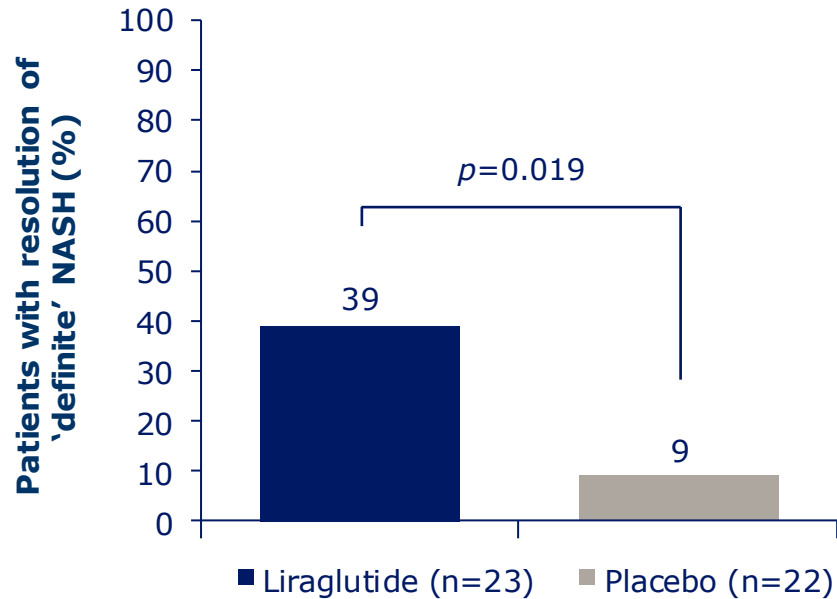
FAS LOCF. Graphs are observed proportions. Statistical analysis is logistic regression
EOR, estimated odds ratio; FAS, full analysis set; LOCF, last observation carried forward

Obesity, NASH and treatment options



GLP-1: glucagon-like peptide 1, EE: energy expenditure, PYY: Protein Y, FXR: farnesoid X receptor, FGF19: fibroblast growth factor-19, PPAR α/γ: peroxisome proliferator-activated receptor α/γ

LEAN in NASH: Change in liver histology by liraglutide



LEADER

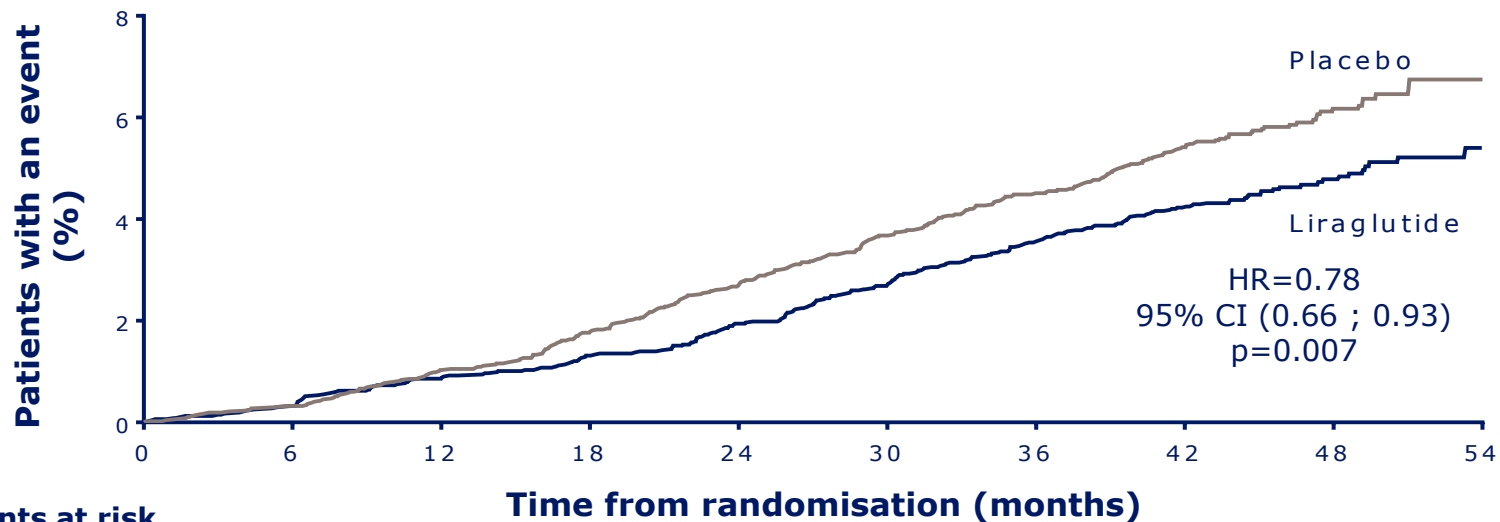
9,340 patients 32 countries 27,600,000+ data points
11,000+ people involved 5+ years 410 sites
25,000+ patient years of exposure
13,500+ monitor visits



LEADER[®]

Liraglutide Effect and Action in Diabetes:
Evaluation of cardiovascular outcome Results

CV death with liraglutide in obese patients with type 2 diabetes



Patients at risk

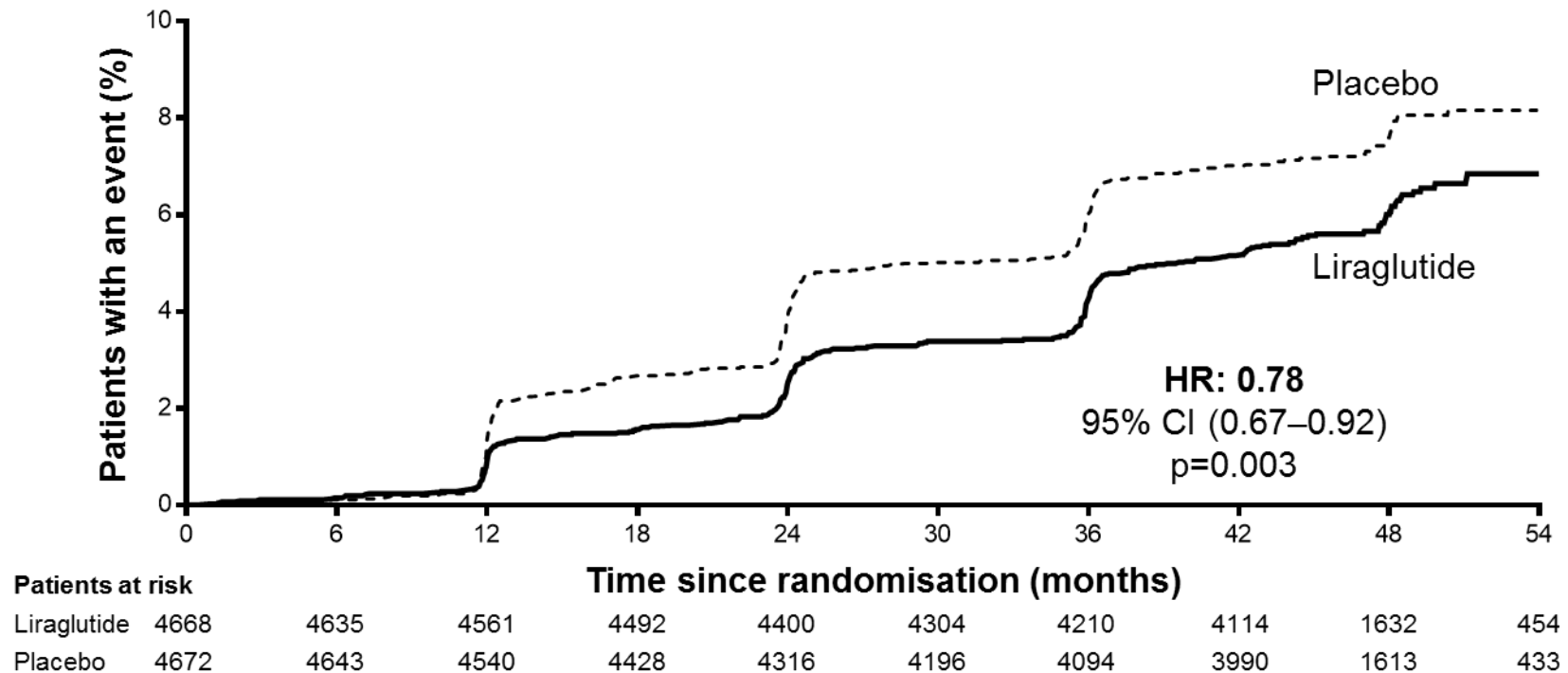
	0	6	12	18	24	30	36	42	48	54
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

The cumulative incidences were estimated with the use of the Kaplan-Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Time to first renal event

Macroalbuminuria, doubling of serumcreatinine,*
ESRD, renal death



*and eGFR ≤ 45 mL/min/1.73 m² per MDRD

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the HRs with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months.

CI: confidence interval; ESRD: end-stage renal disease; HR: hazard ratio

Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany

LEADER[®]

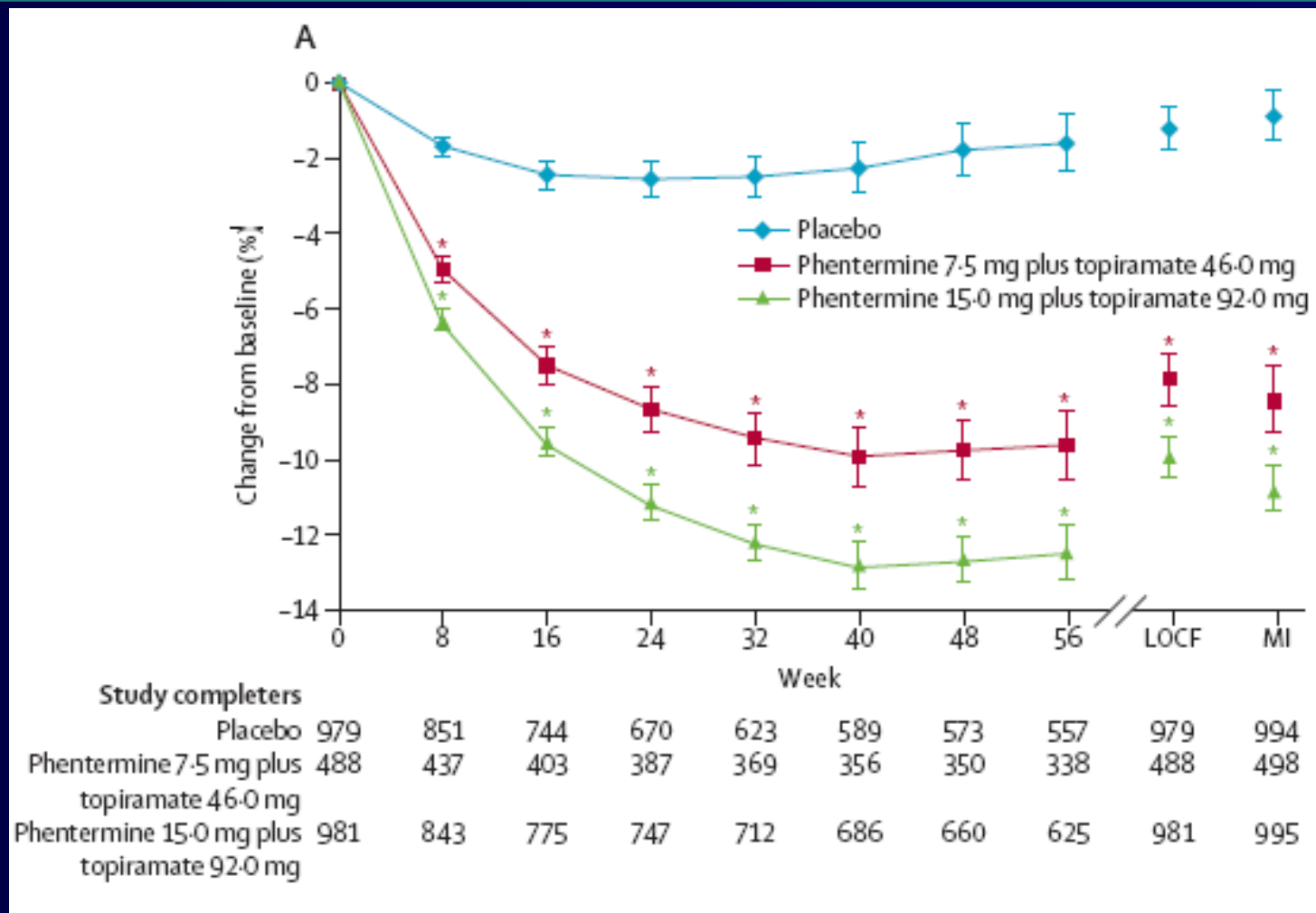
Liraglutide Effect and Action in Diabetes:
Evaluation of cardiovascular outcome Results

Overview

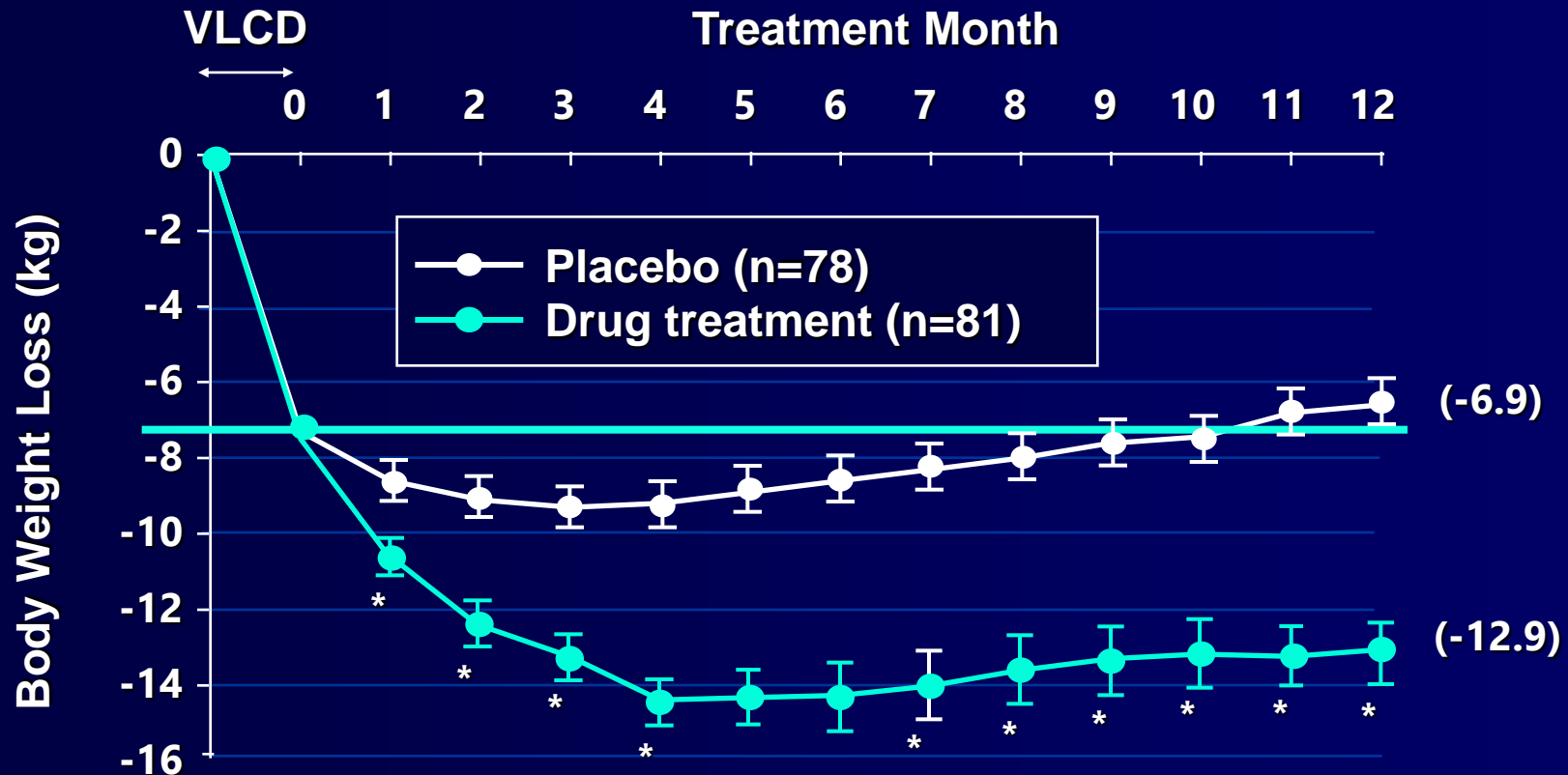
- ▶ Review of anti-obesity medications approved in Europe
 - ▶ orlistat (XENDOS trial)
 - ▶ naltrexone / bupropion (COR trial programme)
 - ▶ liraglutide 3.0 mg (SCALE Obesity and Prediabetes study)
- ▶ **Anti-obesity medications outside Europe**
- ▶ How to achieve weight maintenance ?
- ▶ Future options: more than a dream ?



Topiramate/phentermine combo approach

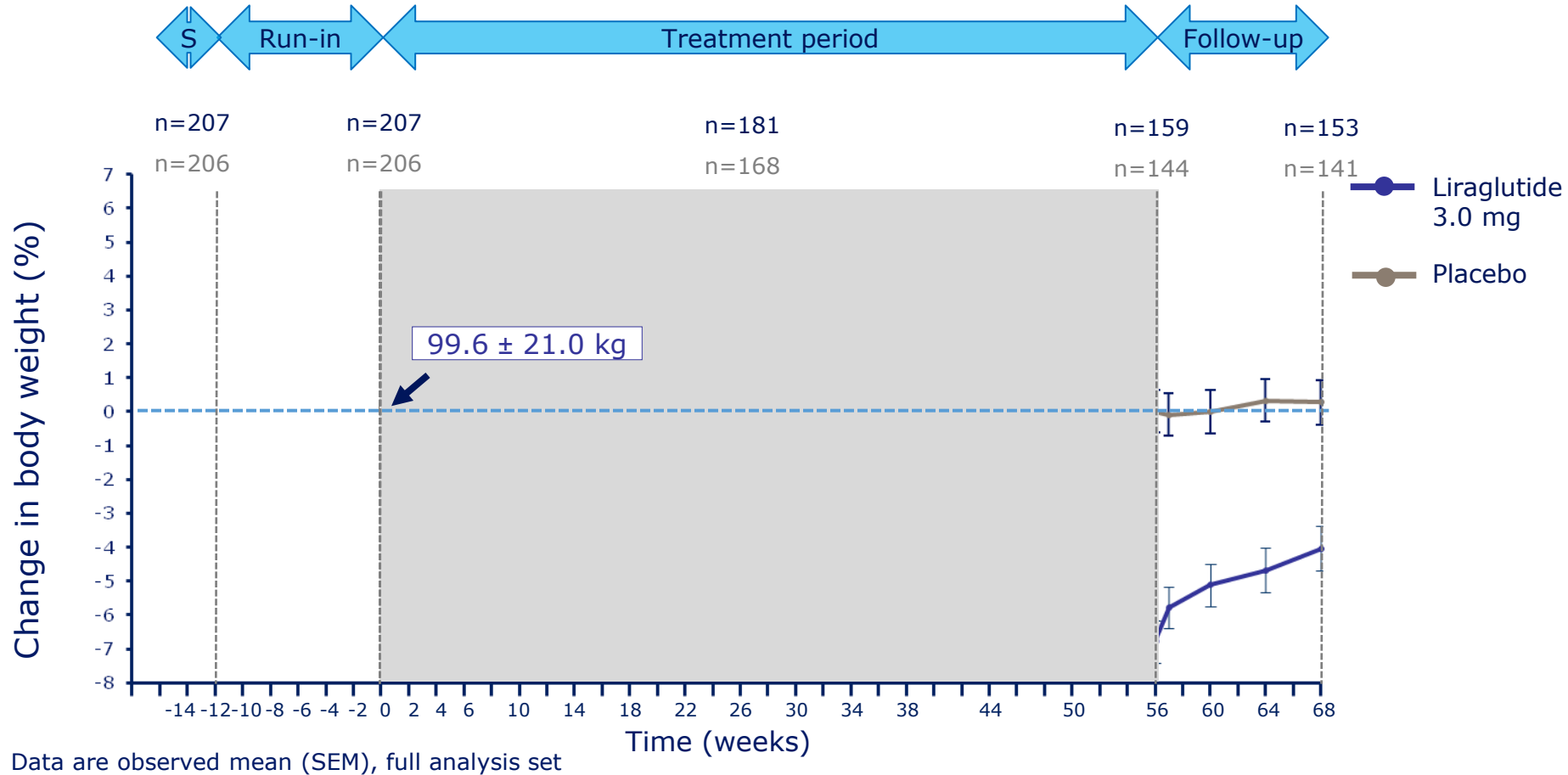


VLCD and pharmacotherapy



• $p < 0.001$, comparison vs placebo

Mean % change in body weight from run-in to week 68



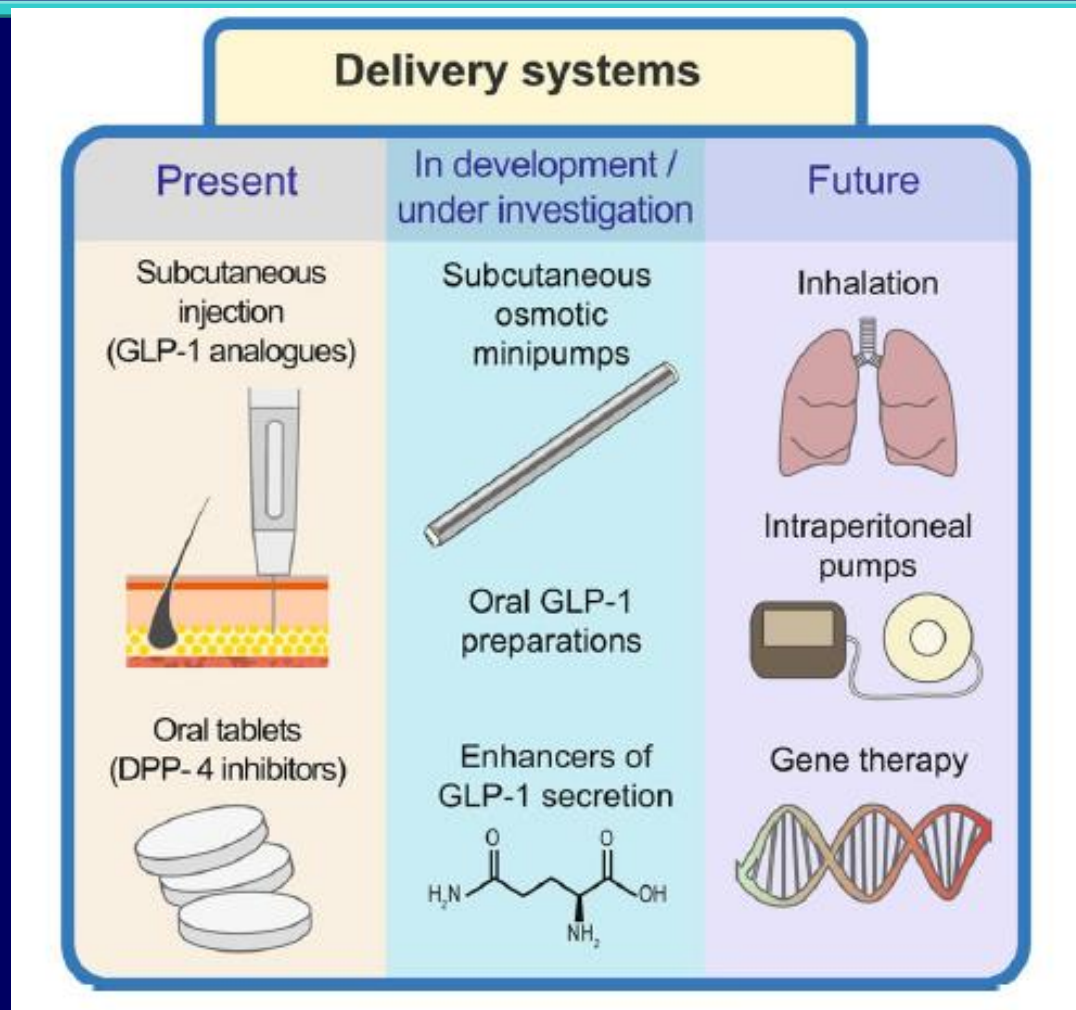
Why still a future for pharmacology ?

- ▶ Long-term success lifestyle intervention extremely disappointing
- ▶ Bariatric procedures appropriate and successful but contra-indications and not available for millions of obese individuals
- ▶ Potential benefits of modest weight reduction
- ▶ Difficult willingless agencies to consider pharma
- ▶ Many strategic and political +++ conflicts
- ▶ Due to specific MOA, weight independent metabolic benefits
- ▶ **Right** drug for **right** patient, given by **right** HCP

BMI and success after renal transplant ?

- ▶ **Renal transplant outcome** is best in BMI < 30 for...
- ▶ Mortality outcome and survival at 1, 2 and 3 years
- ▶ Graft survival
- ▶ Acute rejection
- ▶ **ESRD patients with BMI > 30** should lose weight prior to RT
- ▶ Bariatric surgery, if necessary

New approaches of delivery



In adult patients with diabetes not adequately controlled on mealtime insulin

Using SYMLIN



BJP

British Journal of
Pharmacology

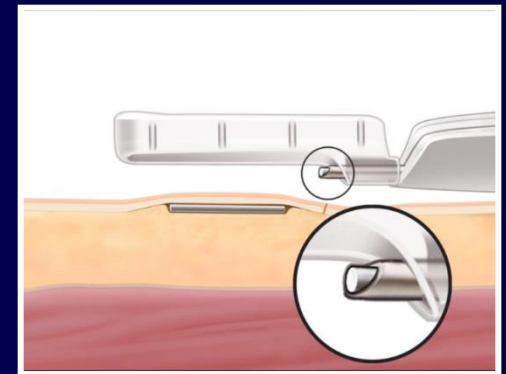
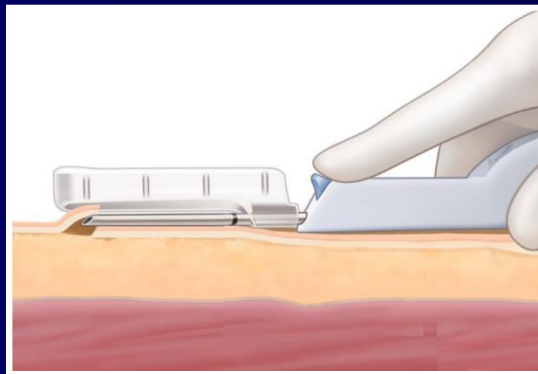
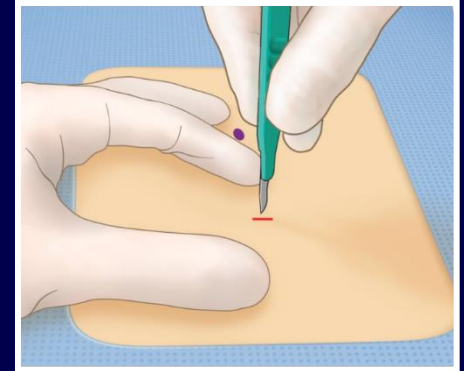
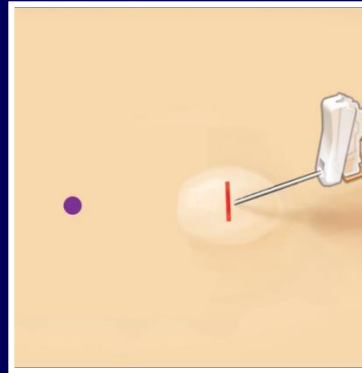
Themed Section: Secretin Family (Class B) G Protein-Coupled Receptors –
from Molecular to Clinical Perspectives

REVIEW

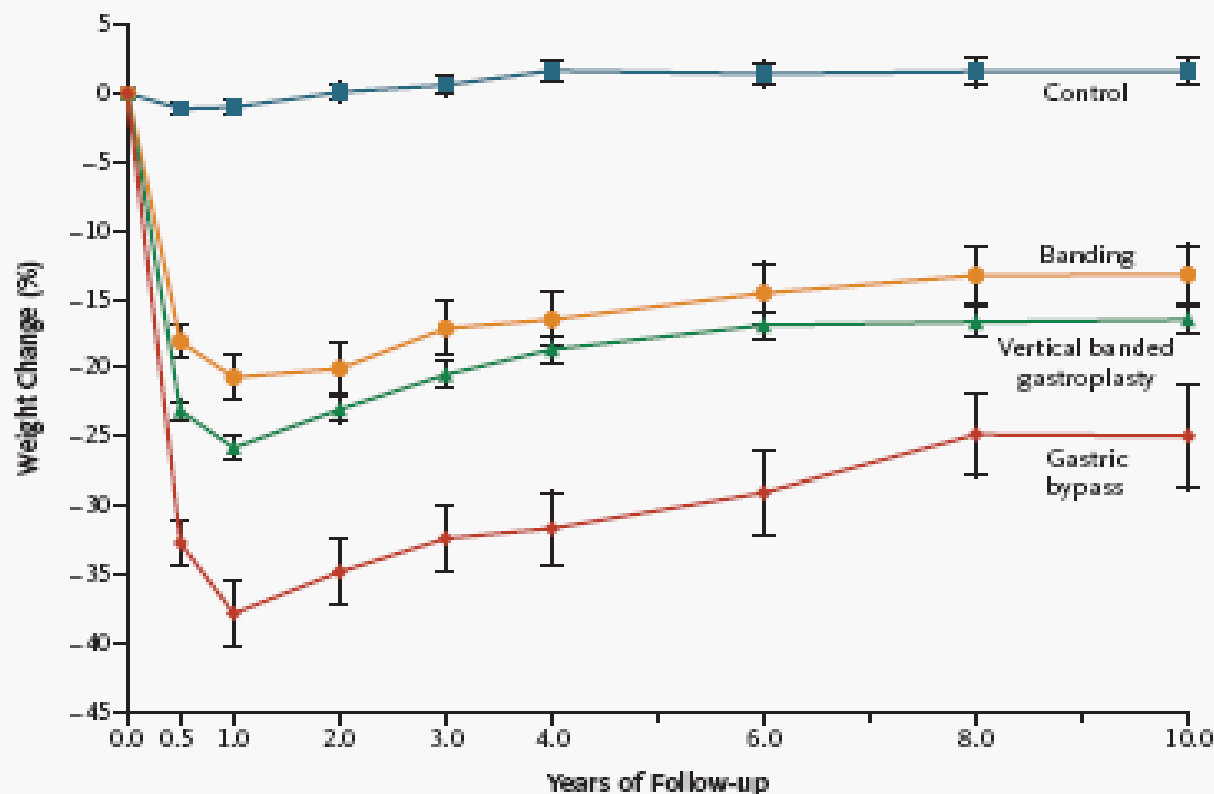
GLP-1R and amylin agonism in metabolic disease: complementary mechanisms and future opportunities

Jonathan D Roth, Mary R Erickson, Steve Chen and David G Parkes

Subcutaneous delivery of exenatide by ITCA 650



Does type of surgery impact maintenance ?



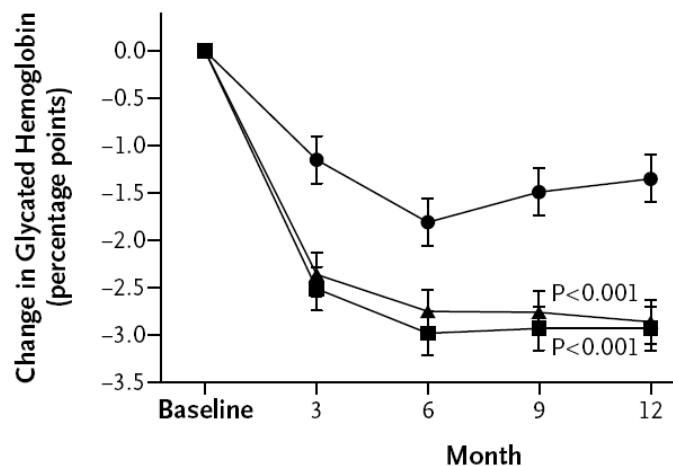
No. of Subjects

Control	627	585	594	587	577	563	542	535	627
Banding	156	150	154	153	149	150	147	144	156
Vertical banded gastroplasty	451	438	438	438	429	417	412	401	451
Gastric bypass	34	34	34	34	33	32	32	29	34

Does type of surgery impact maintenance ?

● Intensive medical therapy ■ Roux-en-Y gastric bypass ▲ Sleeve gastrectomy

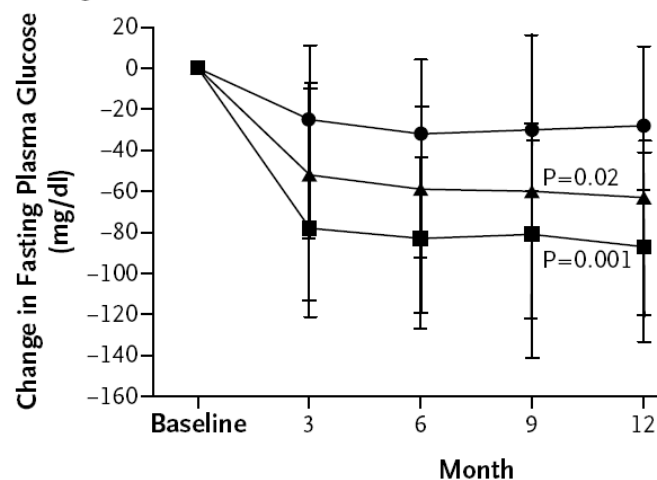
A Change in Glycated Hemoglobin



Value at Visit

Intensive medical therapy	8.9	7.7	7.1	7.4	7.5
Roux-en-Y gastric bypass	9.3	6.8	6.3	6.4	6.4
Sleeve gastrectomy	9.5	7.1	6.7	6.7	6.6

B Change in Fasting Plasma Glucose

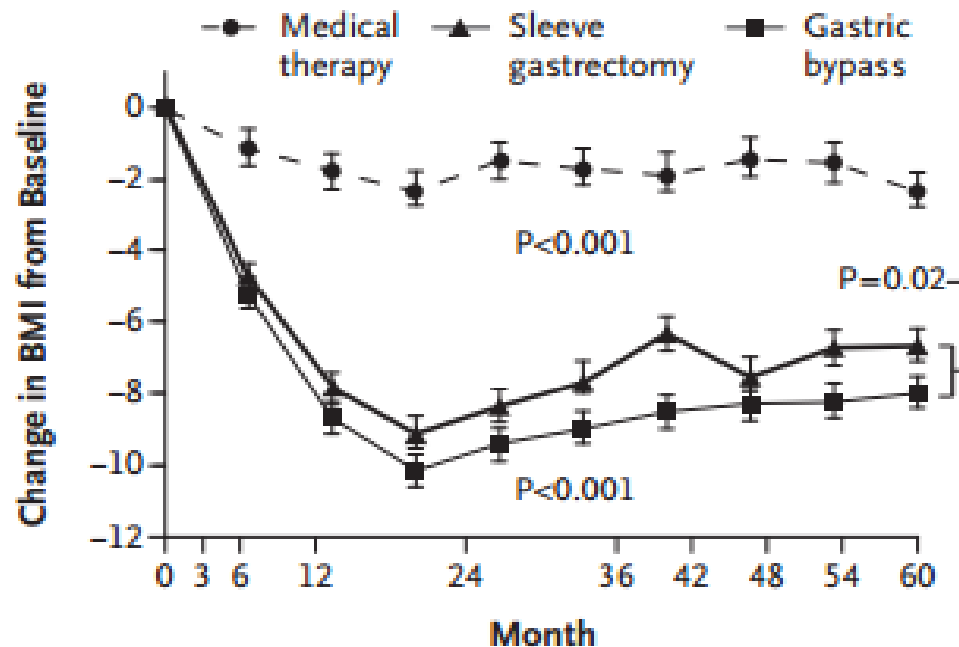


Value at Visit

Intensive medical therapy	155	122	113	120	120
Roux-en-Y gastric bypass	193	109	96	96	99
Sleeve gastrectomy	164	118	104	102	97

Bariatric surgery versus intensive medical therapy for diabetes – 5 year outcomes

C Body-Mass Index



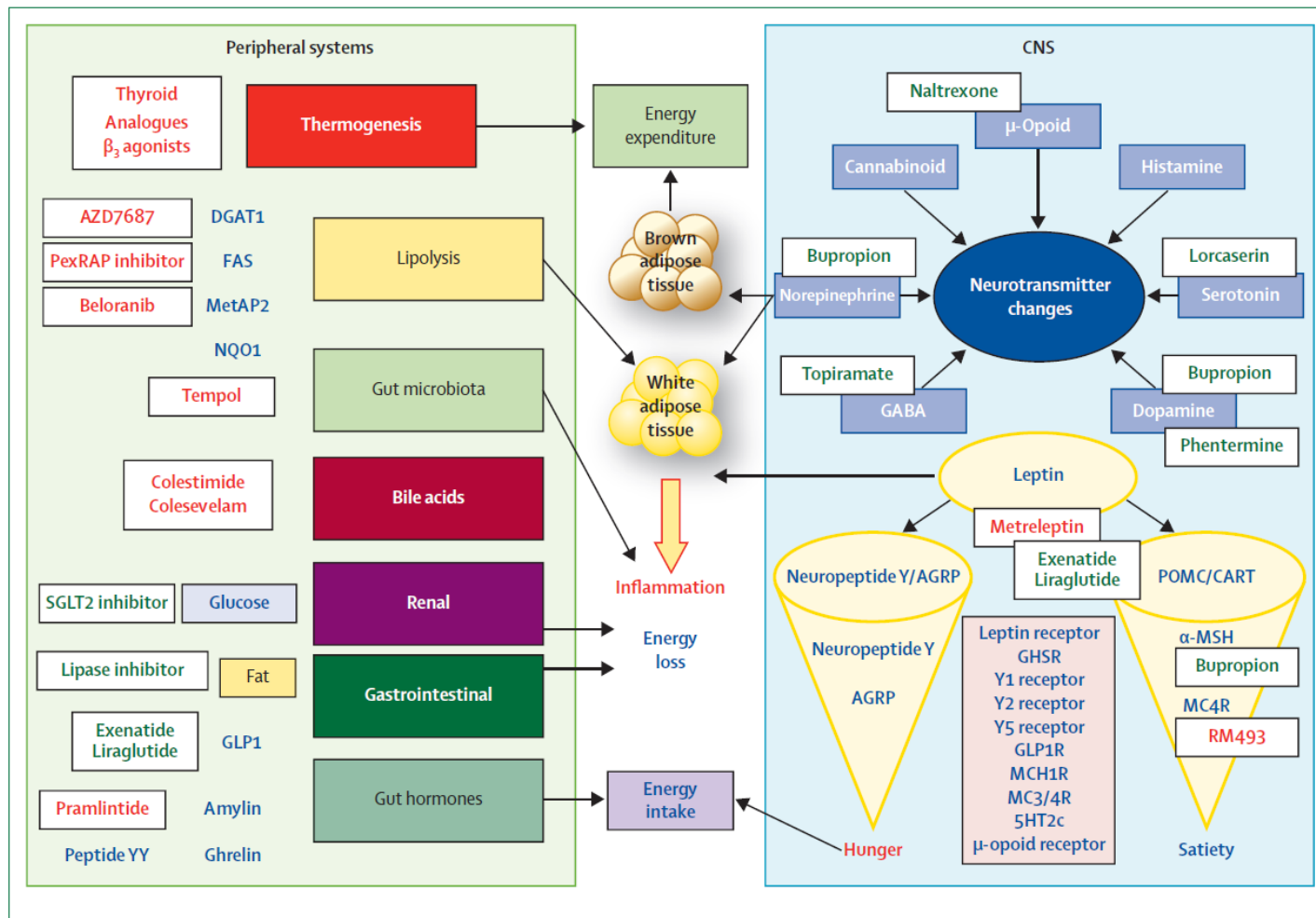
Mean Value at Visit

Medical therapy	36.4	34.1	35.0	34.8	35.1	34.0
Gastric bypass	37.0	26.9	27.4	28.2	28.6	28.9
Sleeve gastrectomy	36.0	26.9	27.7	28.1	28.2	29.3

ORIGINAL ARTICLE

Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 5-Year Outcomes

Philip R. Schauer, M.D., Deepak L. Bhatt, M.D., M.P.H., John P. Kirwan, Ph.D., Kathy Wolski, M.P.H., Ali Aminian, M.D., Stacy A. Brethauer, M.D., Sankar D. Navaneethan, M.D., M.P.H., Rishi P. Singh, M.D., Claire E. Pothier, M.P.H., Steven E. Nissen, M.D., and Sangeeta R. Kashyap, M.D., for the STAMPEDE Investigators*





How do they get fat ... ?
Are they addicted ?





Universiteit Antwerpen



Thank you !