Why treat obesity?
The entity of diabesity

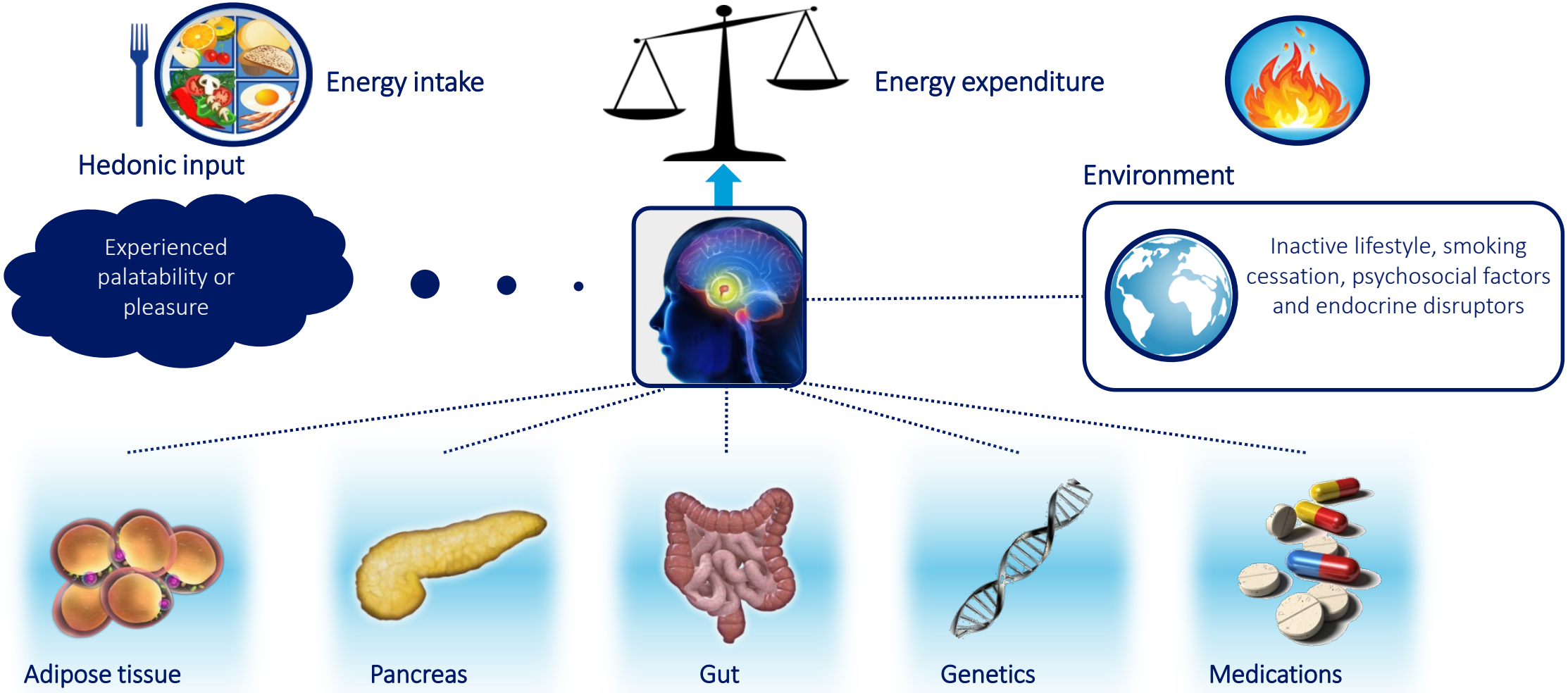
Dr. Ann Verhaegen
UZA
ZNA Jan Palfijn

Conflict of interest disclosures

Ann Verhaegen is a member of the Advisory Board and/or Speakers Bureau of:

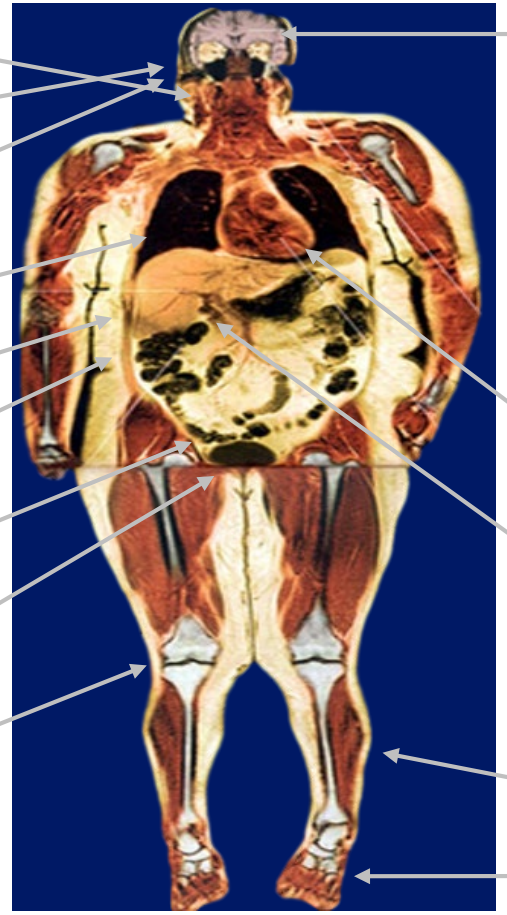
- Amgen
- AstraZeneca
- Boehringer Ingelheim
- Eli Lilly & Co
- Janssen-Cilag / J & J
- Merck Sharp & Dohme
- Novo Nordisk
- Sanofi

Obesity is a complex and multifactorial disease



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

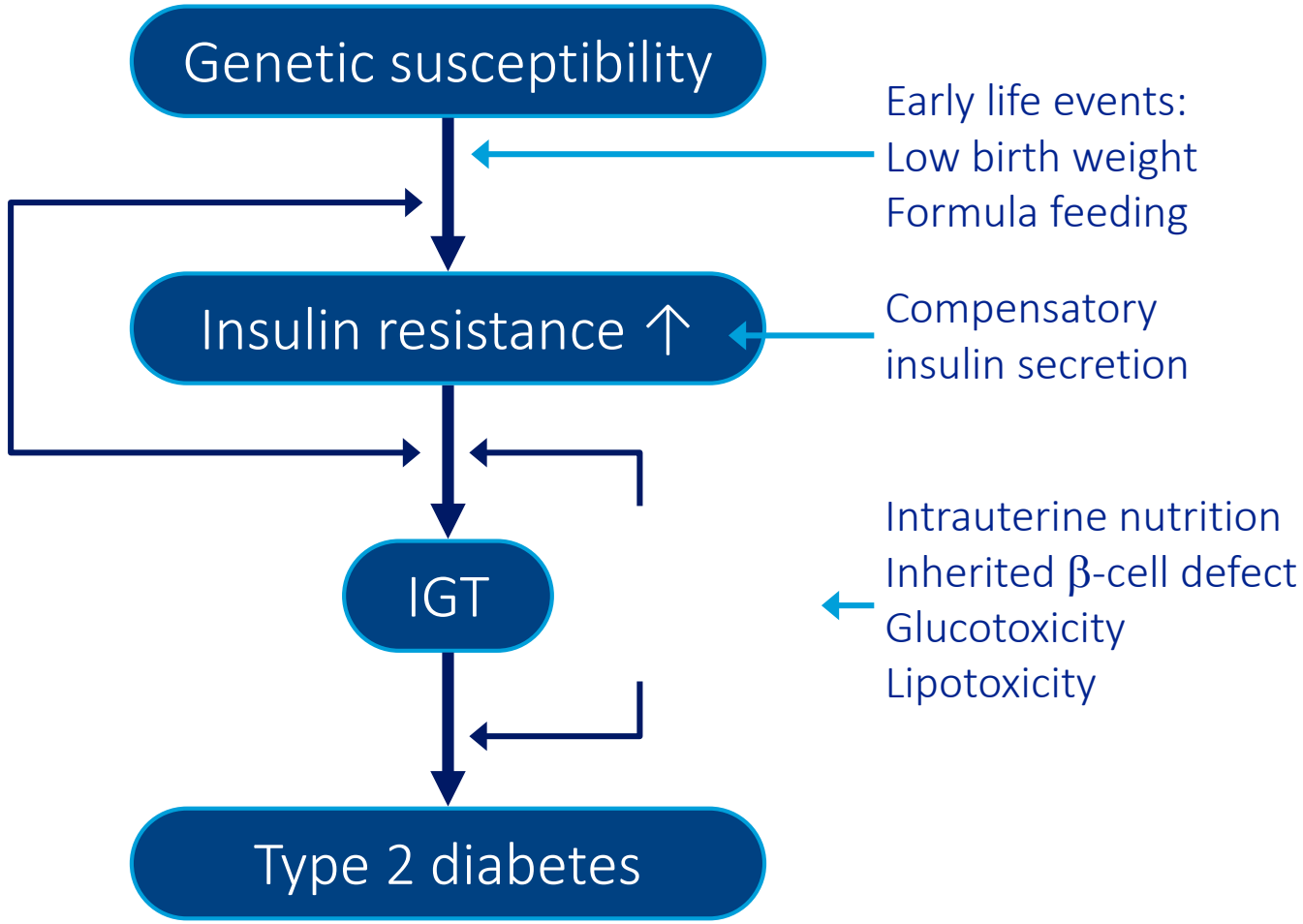
Obesity is associated with multiple complications



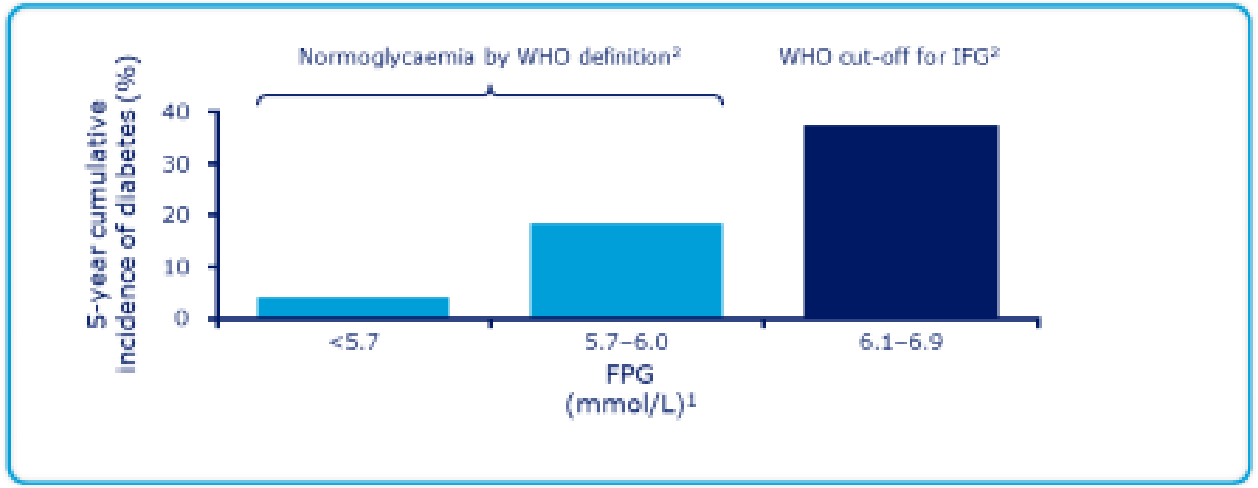
- Sleep apnoea
- Depression
- Anxiety
- Asthma
- NAFLD
- Gallstones
- Infertility
- Incontinence
- Arthrosis
- Physical functioning
- Stroke
- CVD and risk factors
  - Stroke
  - Dyslipidaemia
  - Hypertension
  - Coronary artery disease
  - Congestive heart failure
  - Pulmonary embolism
- Type 2 diabetes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

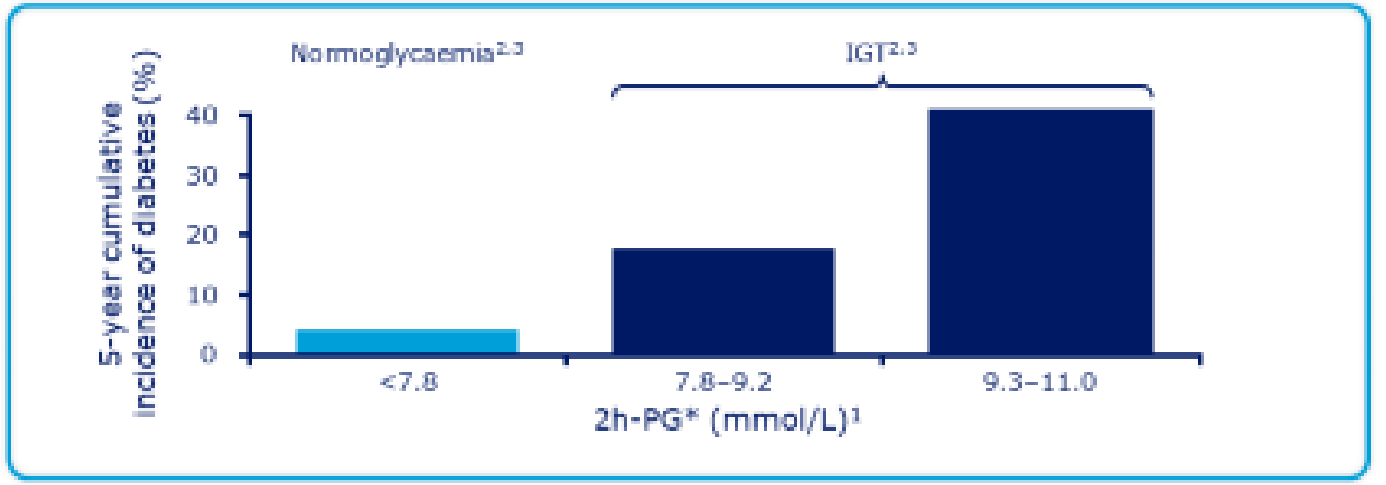
Adapted from Sharma AM. *Obes Rev*. 2010;11:808-9; Guh *et al. BMC Public Health* 2009;9:88; Luppino *et al. Arch Gen Psychiatry* 2010;67:220–9; Simon *et al. Arch Gen Psychiatry* 2006;63:824–30; Church *et al. Gastroenterology* 2006;130:2023–30; Li *et al. Prev Med* 2010;51:18–23; Hosler. *Prev Chronic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

Natural history of type 2 diabetes



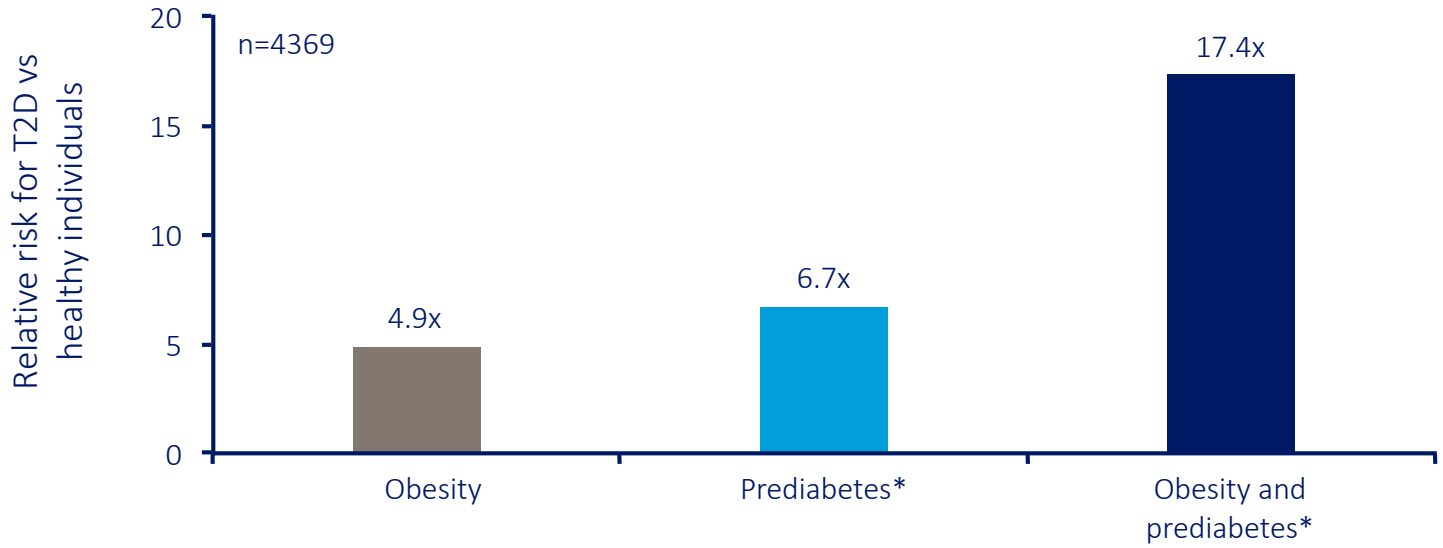
Impaired fasting glucose and glucose intolerance lead to an increased risk for T2DM





Gabir *et al*. *Diabetes Care* 2000;23:1108–12;

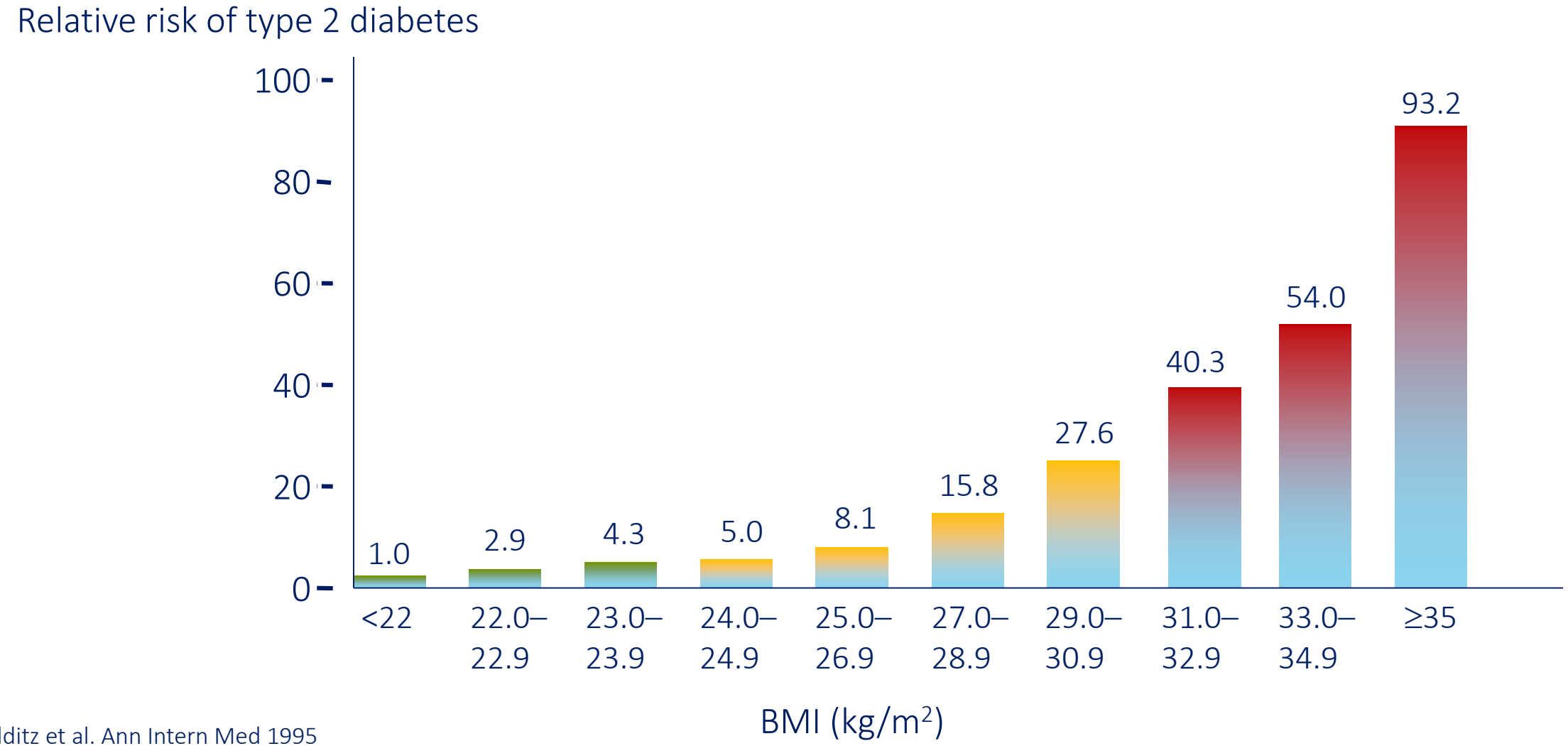
Individuals with obesity and prediabetes are at 17 times greater risk of type 2 diabetes



*Prediabetes defined as fasting plasma glucose of 110 mg/dL (6.1 mmol/L) and 2-h plasma glucose less than 140 mg/dL (7.8 mmol/L); impaired glucose regulation: fasting plasma glucose concentration 110–126 mg/dL (6.1–6.99 mmol/L) and/or 2-h plasma glucose concentration 140–200 mg/dL (7.8–11.09 mmol/L). RR, relative risk; T2D, type 2 diabetes

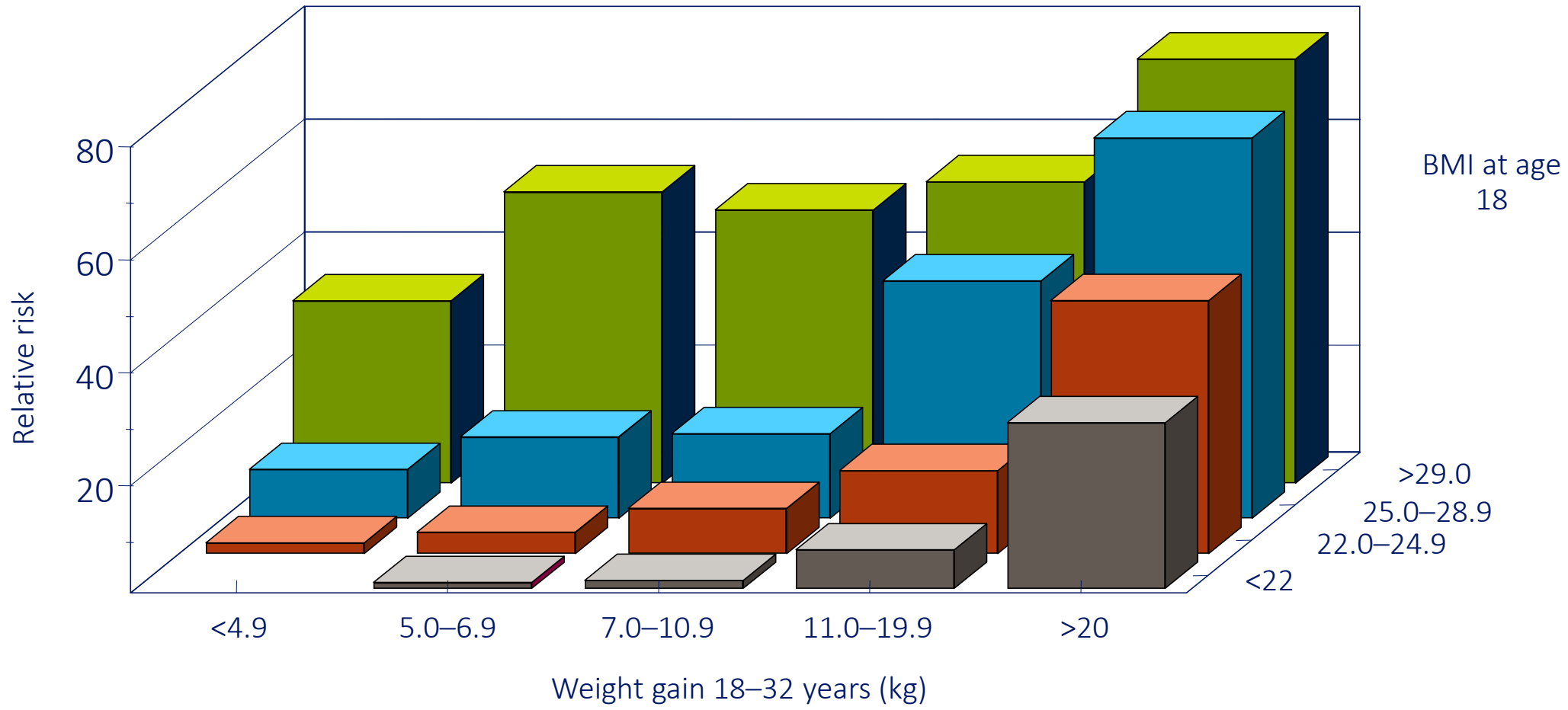
Hu *et al*. *Arch Intern Med* 2004;164:892–6

Excess weight is a risk factor for type 2 diabetes (Nurses Health Study)



Colditz et al. Ann Intern Med 1995

Relative risk for diabetes: weight at age 18 and weight gain till 32 years



BMI, body mass index

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

Environmental and lifestyle factors in obesity and diabetes

Sedentary behaviours increase risk of obesity

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

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

Hu FB et al. *JAMA* 2003;289:1785–91

Pollutants and risk of diabetes, metabolic syndrome and obesity

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

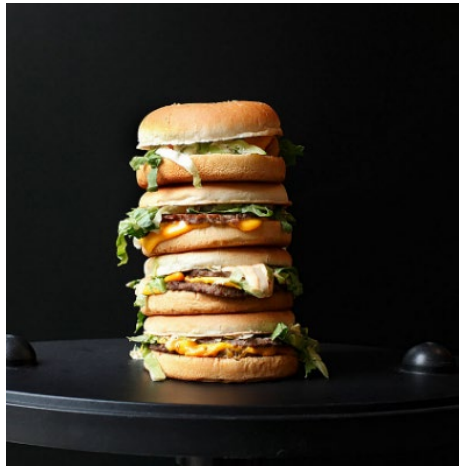
JI-SUN LIM, MD, PHD[1]
DUK-HEE LEE, MD, PHD[1]
DAVID R. JACOBS, JR., PHD[2,3]

Diabetologia (2011) 54:1273–1290
DOI 10.1007/s00125-011-2109-5

REVIEW

Environmental pollutants and type 2 diabetes: a review of mechanisms that can disrupt beta cell function

T. L. M. Hectors · C. Vanparys · K. van der Ven · G. A. Martens · P. G. Jorens · L. F. Van Gaal · A. Covaci · W. De Coen · R. Blust



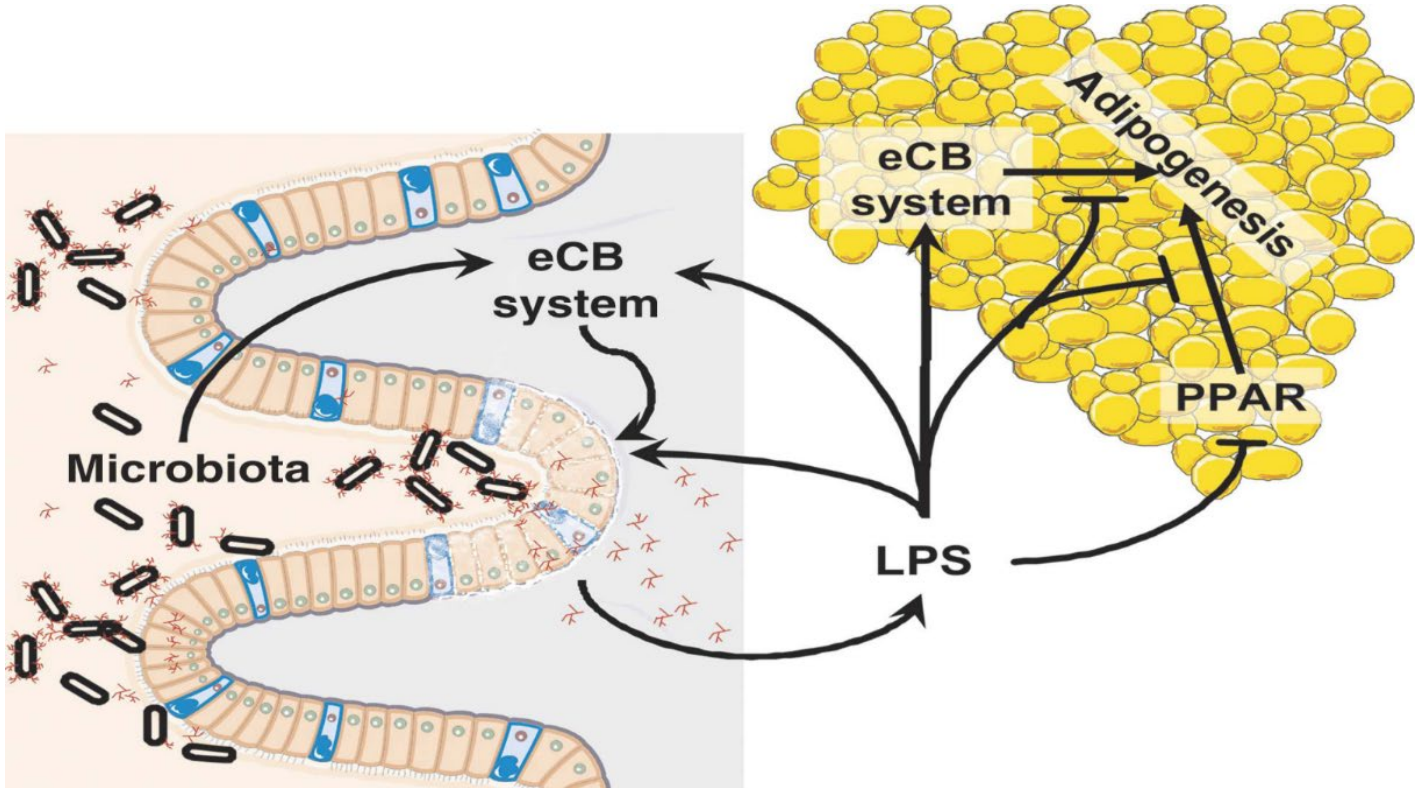
Lim JS et al. *Diabetes Care* 2008;31:1802–7; Hectors TL et al. *Diabetologia* 2011;54:1273–90

ARTICLE

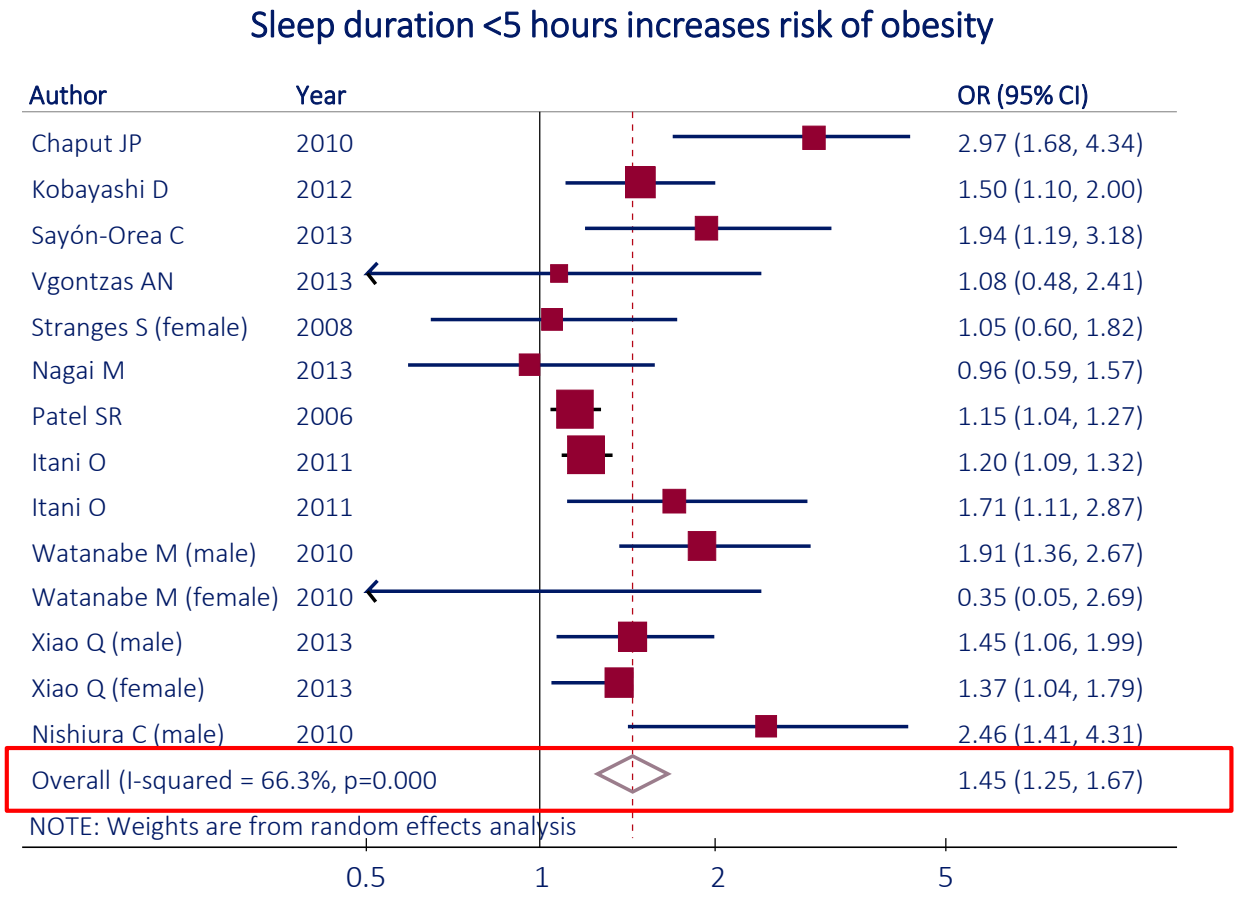
doi:10.1038/nature13793

Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Jotham Suez[1], Tal Korem[2]*, David Zeevi[2]*, Gili Zilberman-Schapira[1]*, Christoph A. Thaiss[1], Ori Maza[1], David Israeli[3], Niv Zmora[4,5,6], Shlomit Gilad[7], Adina Weinberger[2], Yael Kuperman[8], Alon Harmelin[8], Ilana Kolodkin-Gal[9], Hagit Shapiro[1], Zamir Halpern[5,6], Eran Segal[2] & Eran Elinav[1]



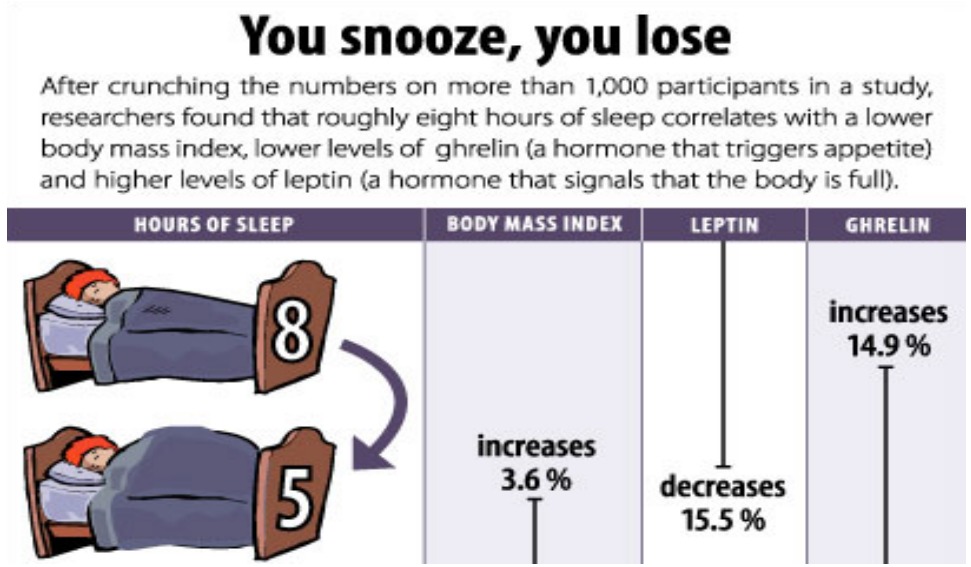
Sleep restriction and risk of obesity



European Journal of Endocrinology (2008) **159** S59–S66 ISSN 0804-4643

Sleep and the epidemic of obesity in children and adults

Eve Van Cauter[1] and Kristen L Knutson[2]
Departments of [1]Medicine, MC1027 and [2]Health Studies, University of Chicago, 5841 S. Maryland Avenue Chicago, Illinois 60637, USA
(Correspondence should be addressed to E Van Cauter; Email: evcauter@medicine.bsd.uchicago.edu)

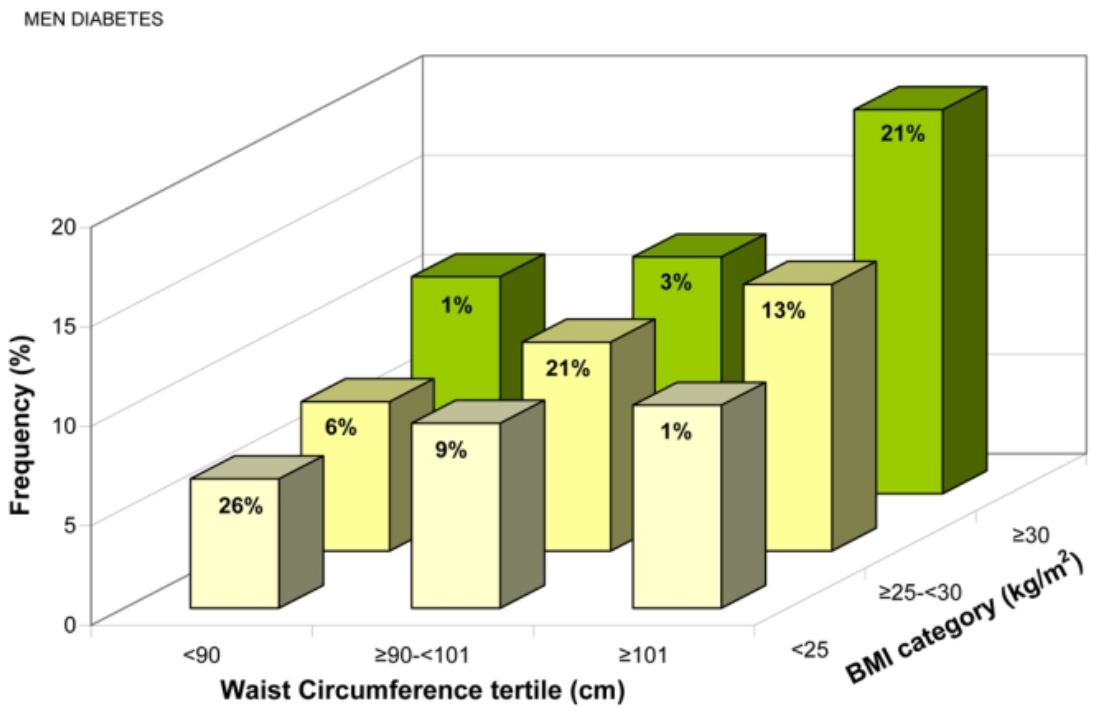


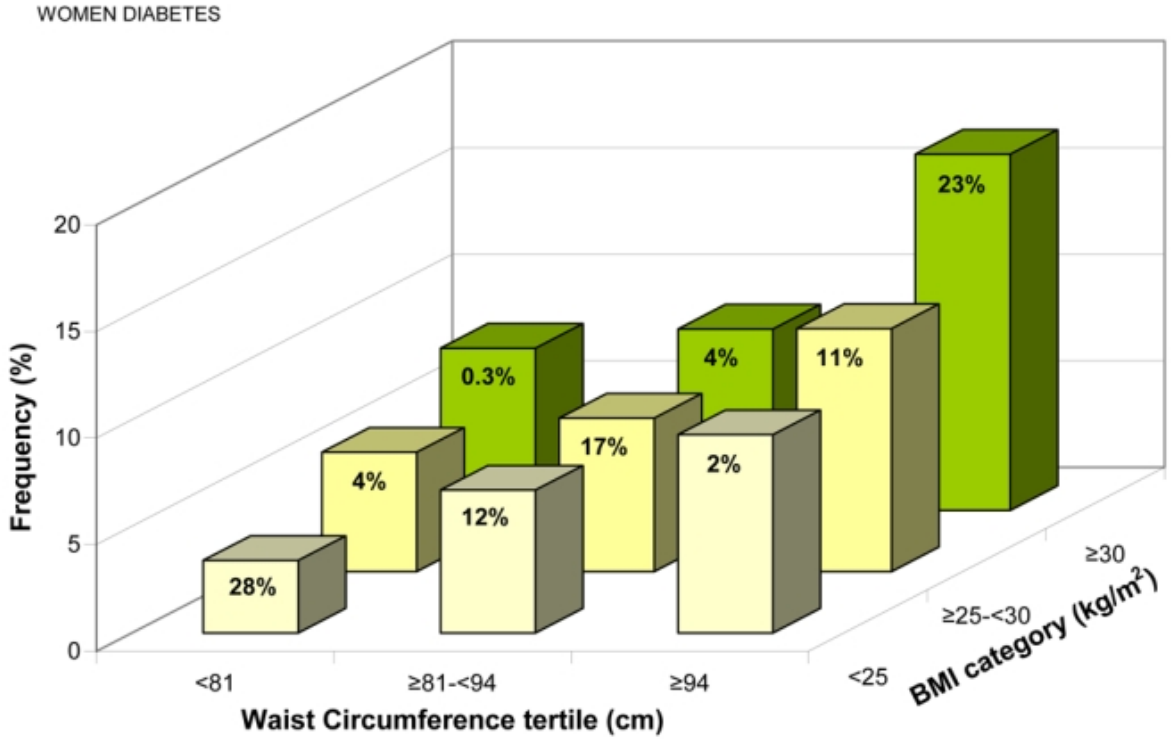
CI, confidence interval; OR, odds ratio

Wu Y et al. *Sleep Med* 2014;15:1456–62; Van Cauter E & Knutson KL. *Eur J Endocrinol* 2008;159 Suppl 1:S59–66

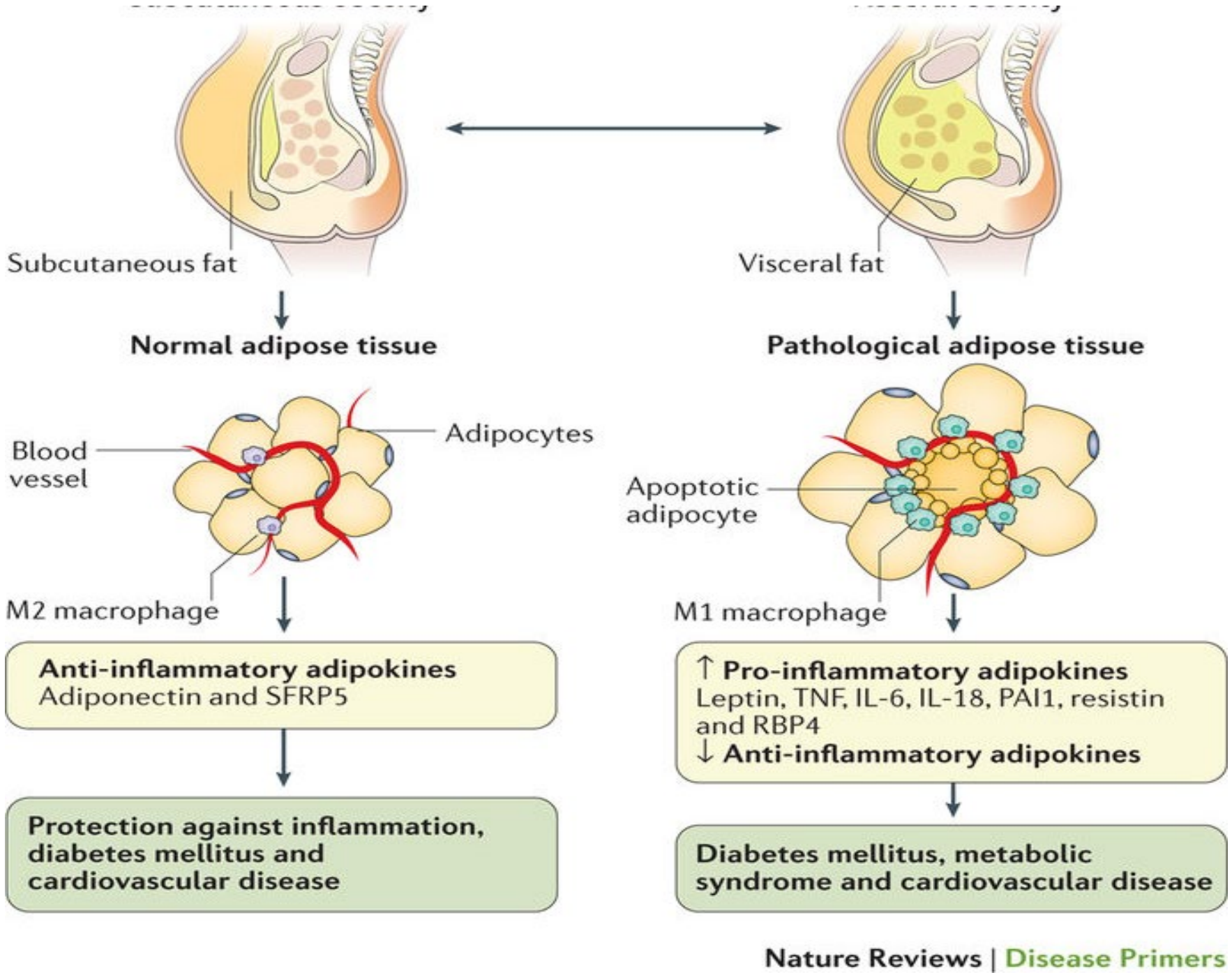
Mechanisms linking obesity to diabetes, CVD and NASH

Prevalence of diabetes according to waist & BMI (worldwide IDEA study)



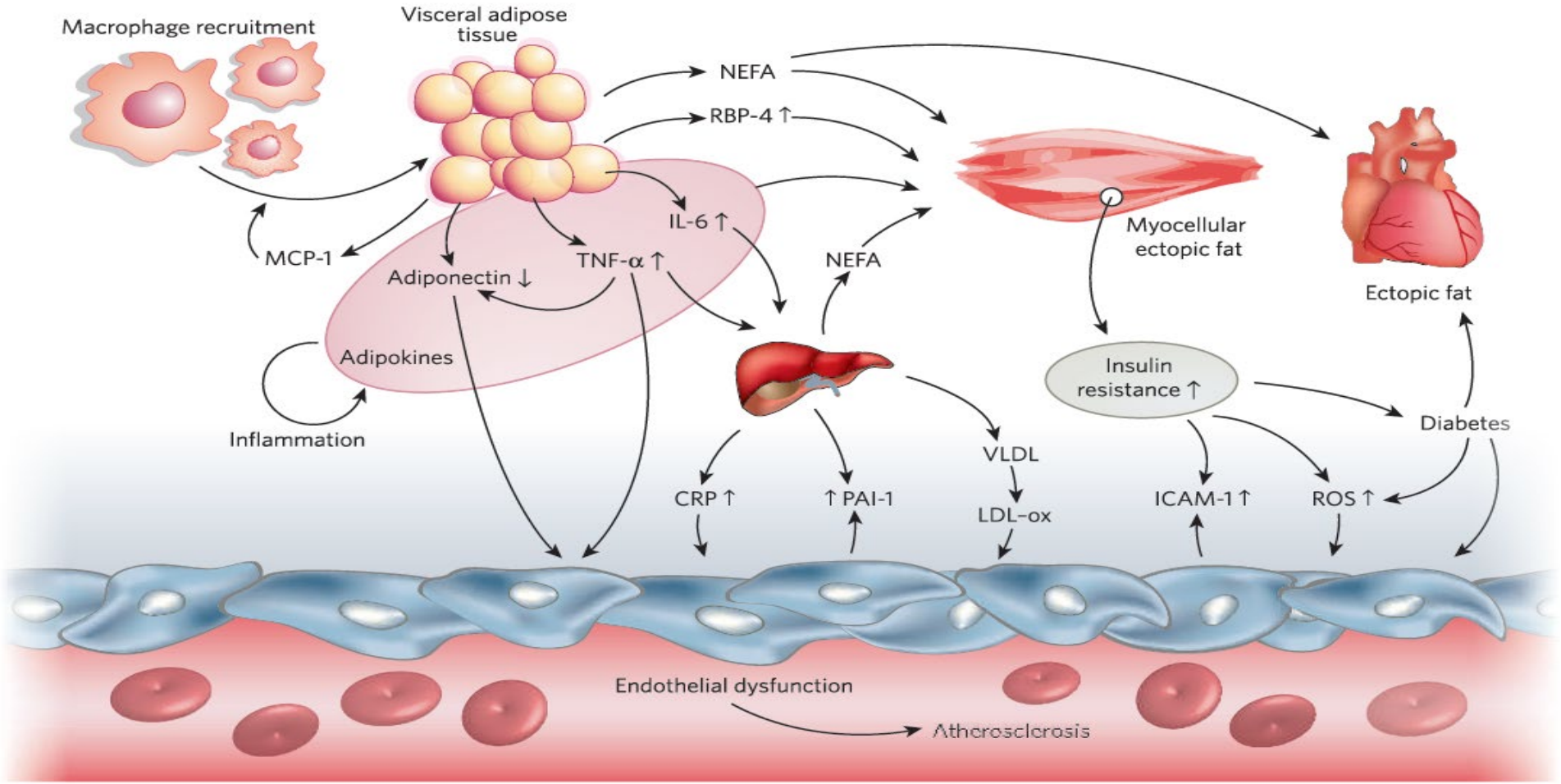


Circulation. 2007 Oct 23;116(17):1942-51



Nat Rev Dis Primers. 2017 Jun 15;3:17034.

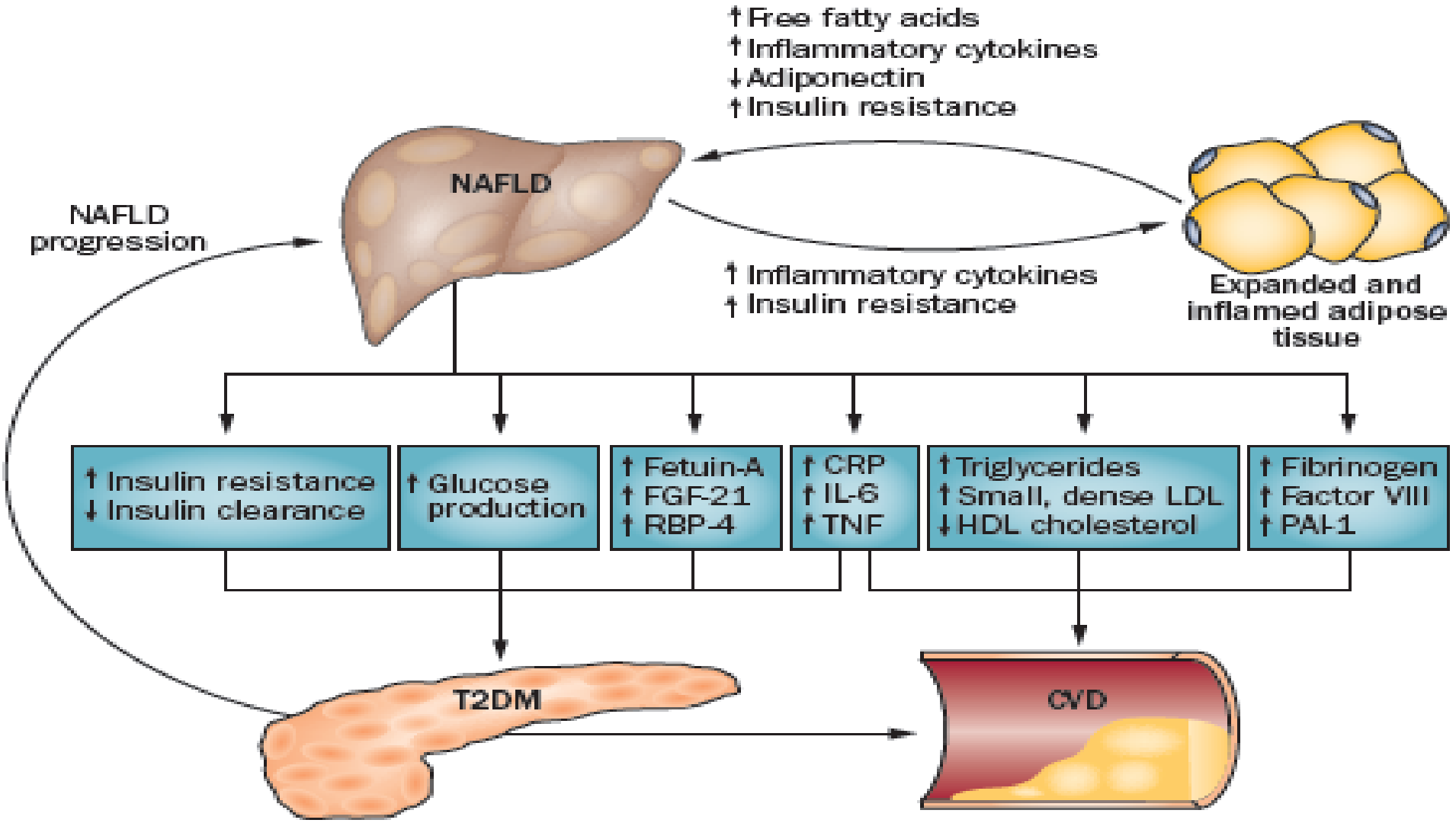
A link between obesity, inflammation and cardiovascular disease: the role of ectopic fat



CRP, c-reactive protein; ICAM-1, intercellular adhesion molecule 1; IL-6, interleukin 6; LDL-ox, oxidised low-density lipoprotein; MCP-1, monocyte chemoattractant protein 1; NEFA, non-esterified fatty acids; PAI-1, plasminogen activator inhibitor-1; RBP-4, retinol binding protein 4; ROS, reactive oxygen species; TNF-α, tumor necrosis factor α; VLDL, very low-density lipoprotein

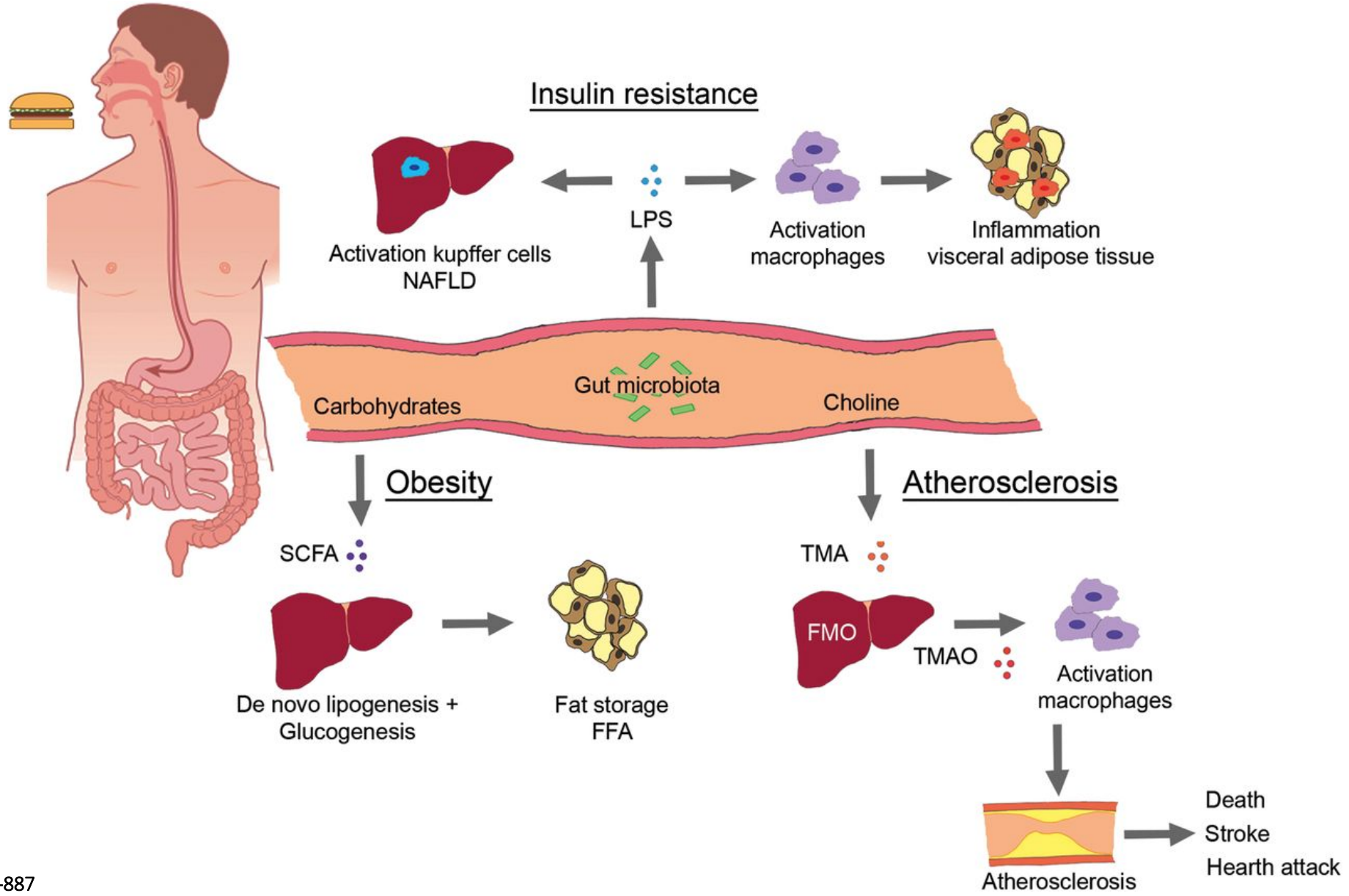
Van Gaal LF et al. *Nature* 2006;444:875–80

From NAFLD or NASH to diabetes and CVD



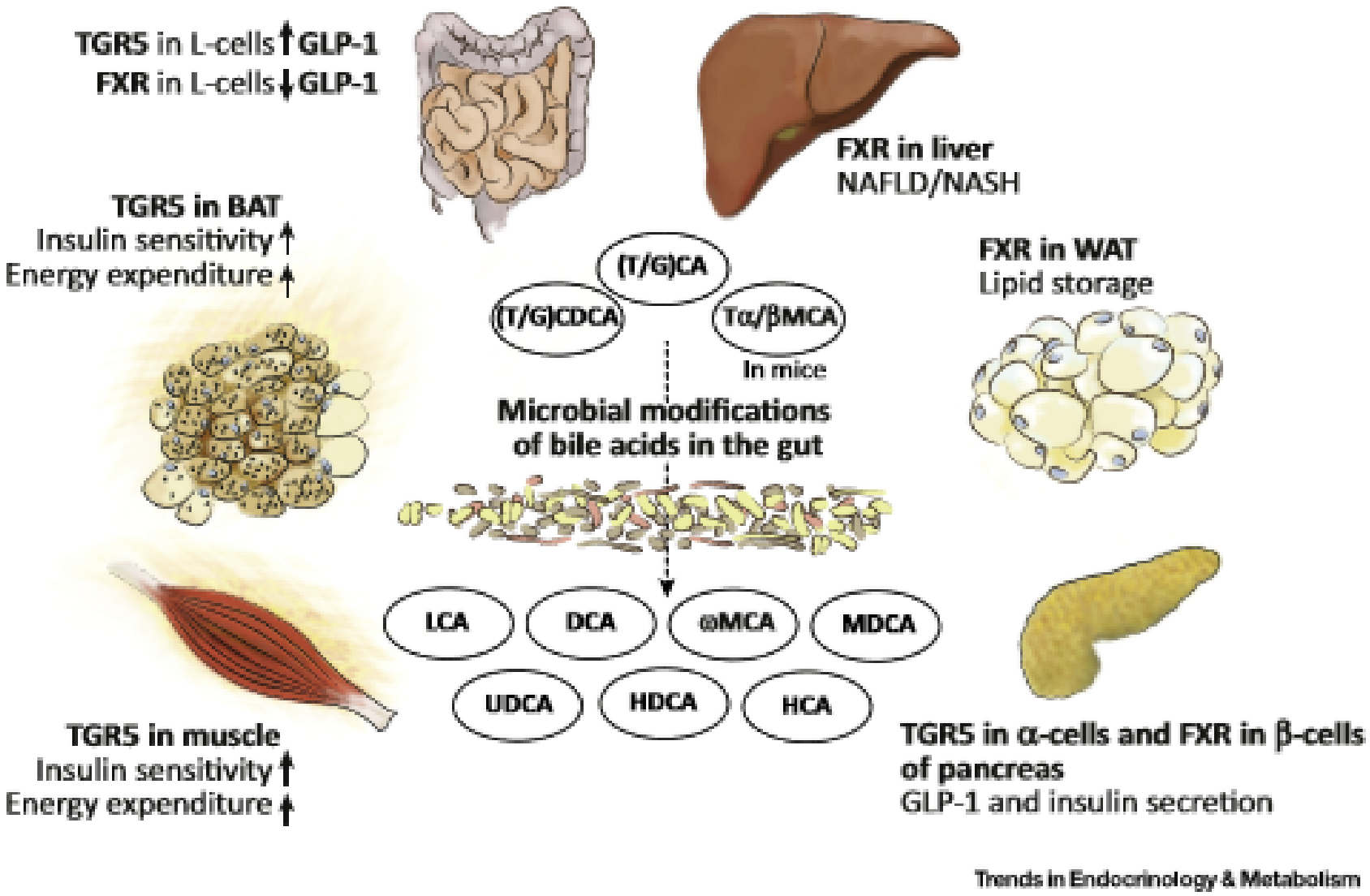
Anstee QM et al Nat Rev Gastroenterol Hepatol 2013

Intestinal microbiota can alter human cardio-metabolism.



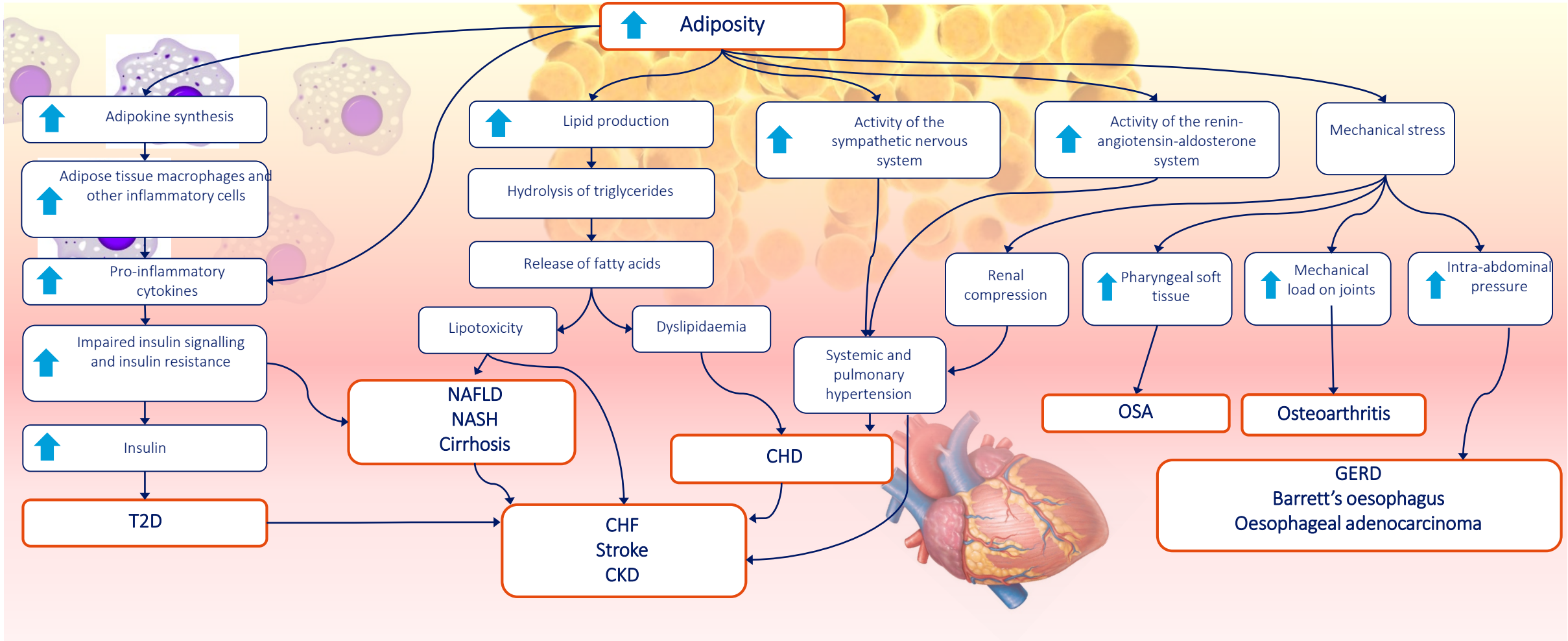
Sarah Vinjé et al. Eur Heart J 2014;35:883-887

Microbial Modification of Bile Acids and Its Metabolic Effect



Trends Endocrinol Metab. 2018 Jan;29(1):31-41

Excess adiposity leads to major risk factors and common chronic diseases



CHD, coronary heart disease; CHF, coronary heart failure; CKD, chronic kidney disease; GERD, gastroesophageal reflux disease; NAFLD, non-alcoholic fatty liver disease, NASH, non-alcoholic steatohepatitis; OSA, obstructive sleep apnoea; T2D, type 2 diabetes

Heymsfield SB & Wadden TA. *N Engl J Med* 2017;376:254–66

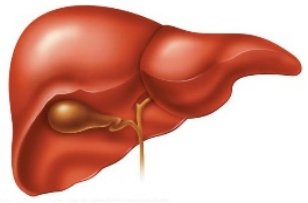
Can weight loss prevent or even cure diabetes?

What are the effects of weight loss?

Benefits of 5–10% weight loss

- Reduction in risk of type 2 diabetes[1,2]
- Improvements in blood lipid profile[3]
- Improvements in blood pressure[4]
- Improvements in abnormal NAFLD liver histology[5,6]
- Improvements in health-related quality of life[7,8]
- Improvements in severity of obstructive sleep apnoea[9,10]
- Reduction in CV mortality[11]

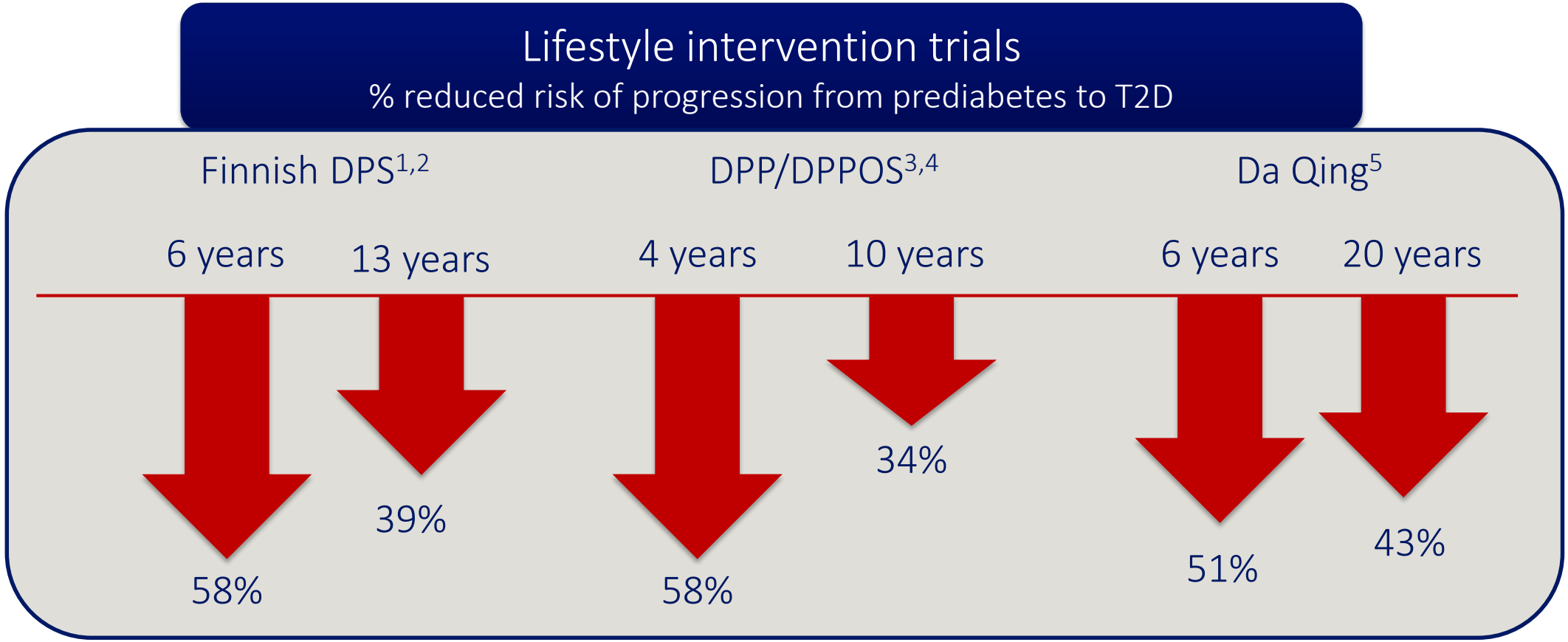



CV, cardiovascular; NAFLD, non-alcoholic fatty liver disease

1. Van Gaal L et al. *Int J Obes* 1989;13 Suppl 2:47–9; 2. Knowler WC et al. *N Engl J Med* 2002;346:393–403; 3. Dattilo AM & Kris-Etherton PM. *Am J Clin Nutr* 1992;56:320–8; 4. Wing RR et al. *Diabetes Care* 2011;34:1481–6; 5. Dixon JB et al. *Hepatology* 2004;39:1647-54; 6. Patel AA et al. *J Clin Gastroenterol* 2009;43:970-4; 7. Warkentin LM et al. *Obes Rev* 2014;15:169–82; 8. Wright F et al. *J Health Psychol* 2013;18:574–86; 9. Foster GD et al. *Arch Intern Med* 2009;169:1619–26; 10. Kuna ST et al. *Sleep* 2013;36:641–9; 11. Li G et al. *Lancet Diabetes Endocrinol* 2014;2:474–80

Weight loss can reduce progression to T2D

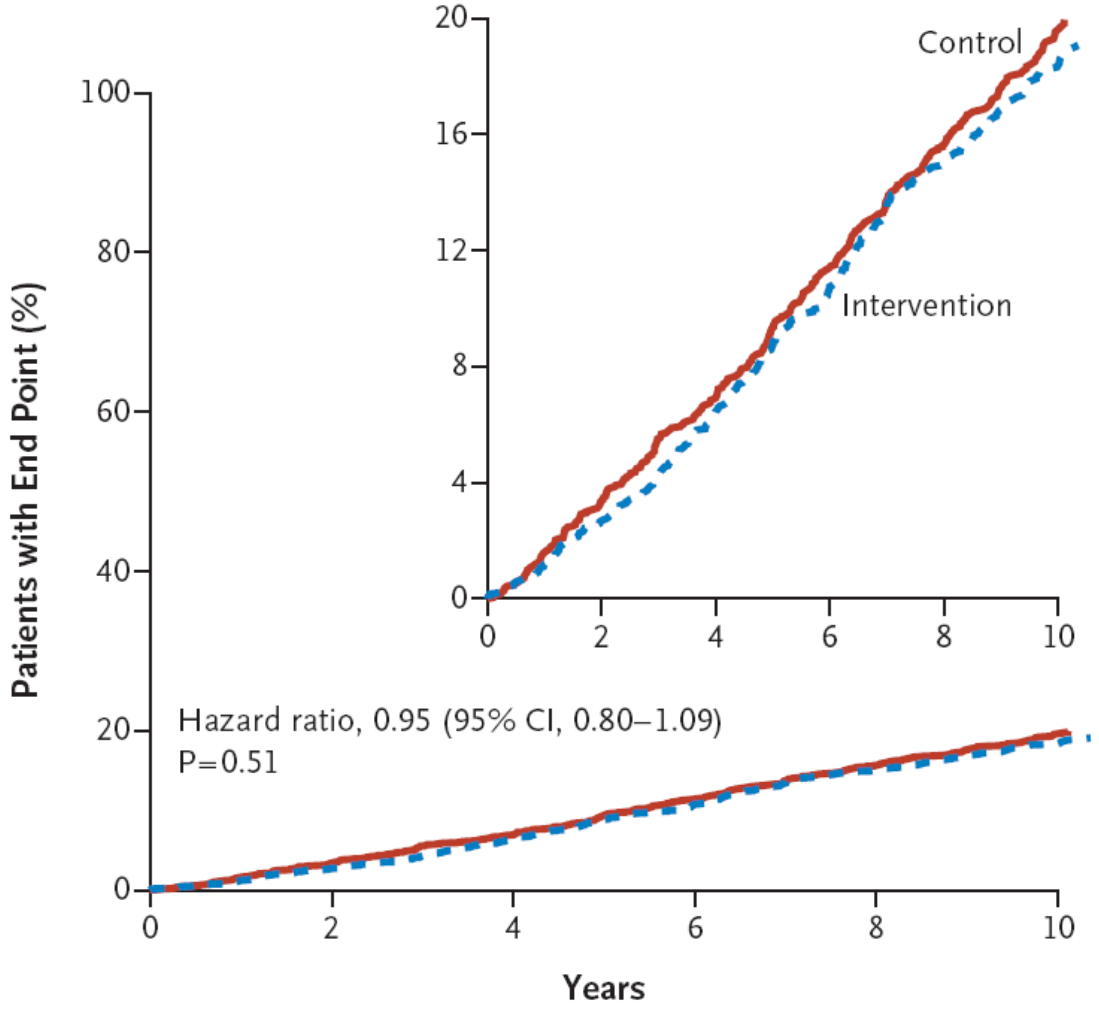


Years are duration of trial or follow-up. Data are versus placebo and not directly comparable due to differences in study design

DPP, Diabetes Prevention Programme; DPPOS, Diabetes Prevention Programme Outcomes Study; DPS, Diabetes Prevention Study; T2D, type 2 diabetes

1. Tuomilehto et al. *N Engl J Med* 2001;344:1343–50; 2. Lindström et al. *Lancet 2006;368:1673–9*; 3. Knowler et al. *N Engl J Med* 2002;346:393–403; 4. Knowler et al. *Lancet* 2009;374:1677–86; 5. Li et al. *Lancet* 2008;371:1783–9

Look AHEAD: NO cardiovascular benefit, unless …



No. at Risk

Control	2575	2425	2296	2156	2019	688
Intervention	2570	2447	2326	2192	2049	505

Weight-loss responders have improved CV outcomes

A *post-hoc* analysis of the Look AHEAD randomised clinical trial

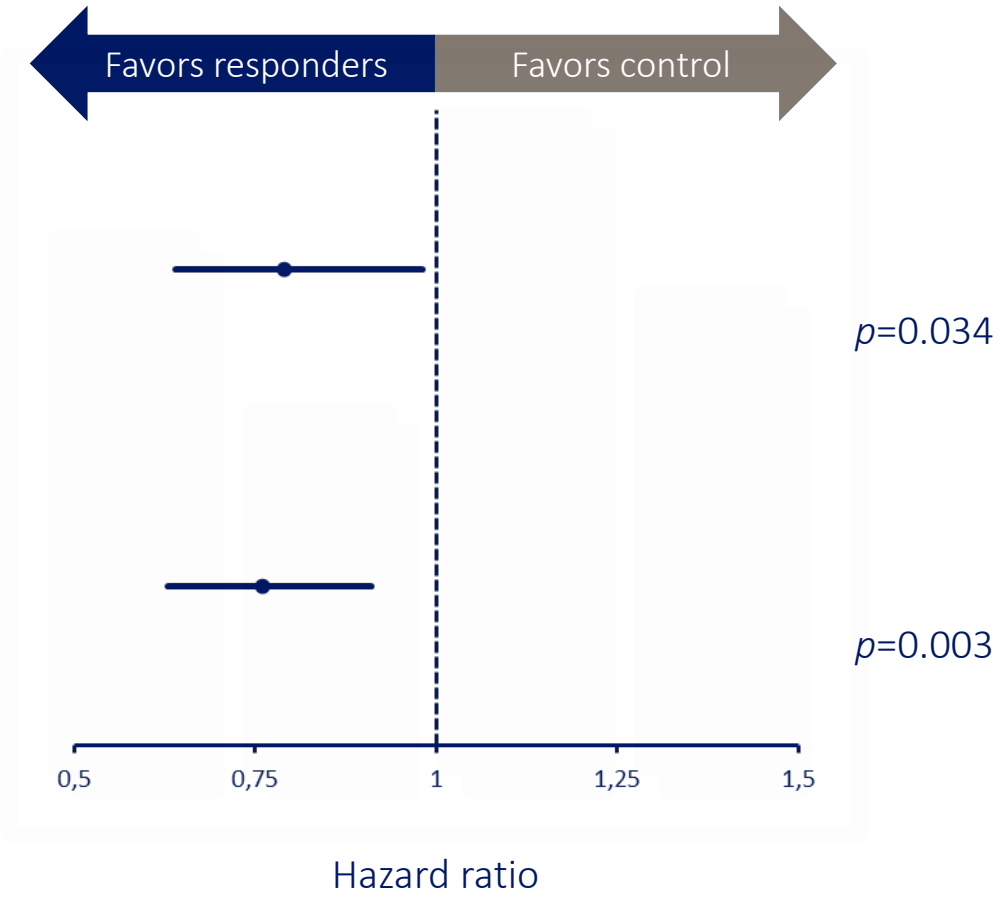
Responder: lost at least 10% of their bodyweight in the 1st year of the study

Primary outcome - 21% lower

CV death, non-fatal acute MI, non-fatal stroke, or admission to hospital for angina

Secondary outcome - 24% lower

As above plus CABG, carotid endartectomy, PCI, hospitalisation for CHF, peripheral vascular disease, or total mortality

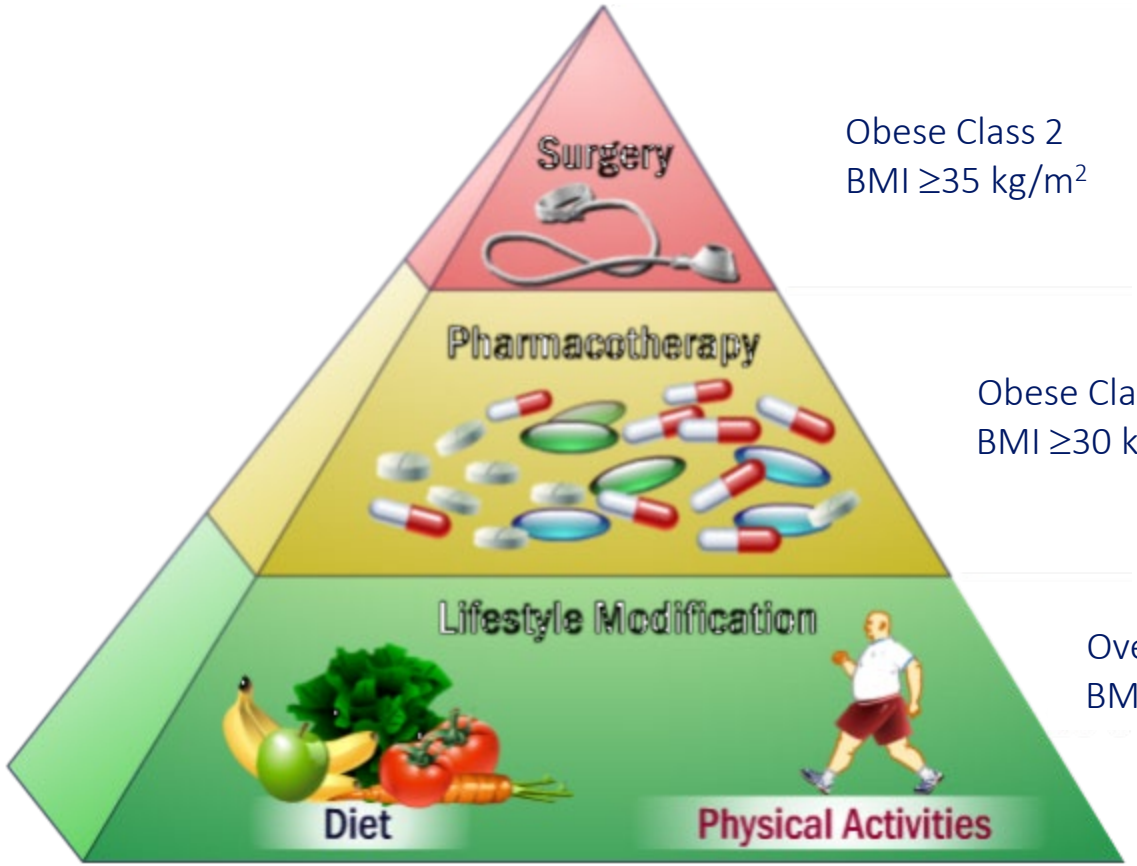


N=4406 participants with T2D to an intensive lifestyle intervention or diabetes support and education

Look AHEAD Research Group. *Lancet Diabetes Endocrinol*. 2016. [Epub ahead of print]

Pharmacotherapy helps with adherence to a lifestyle change

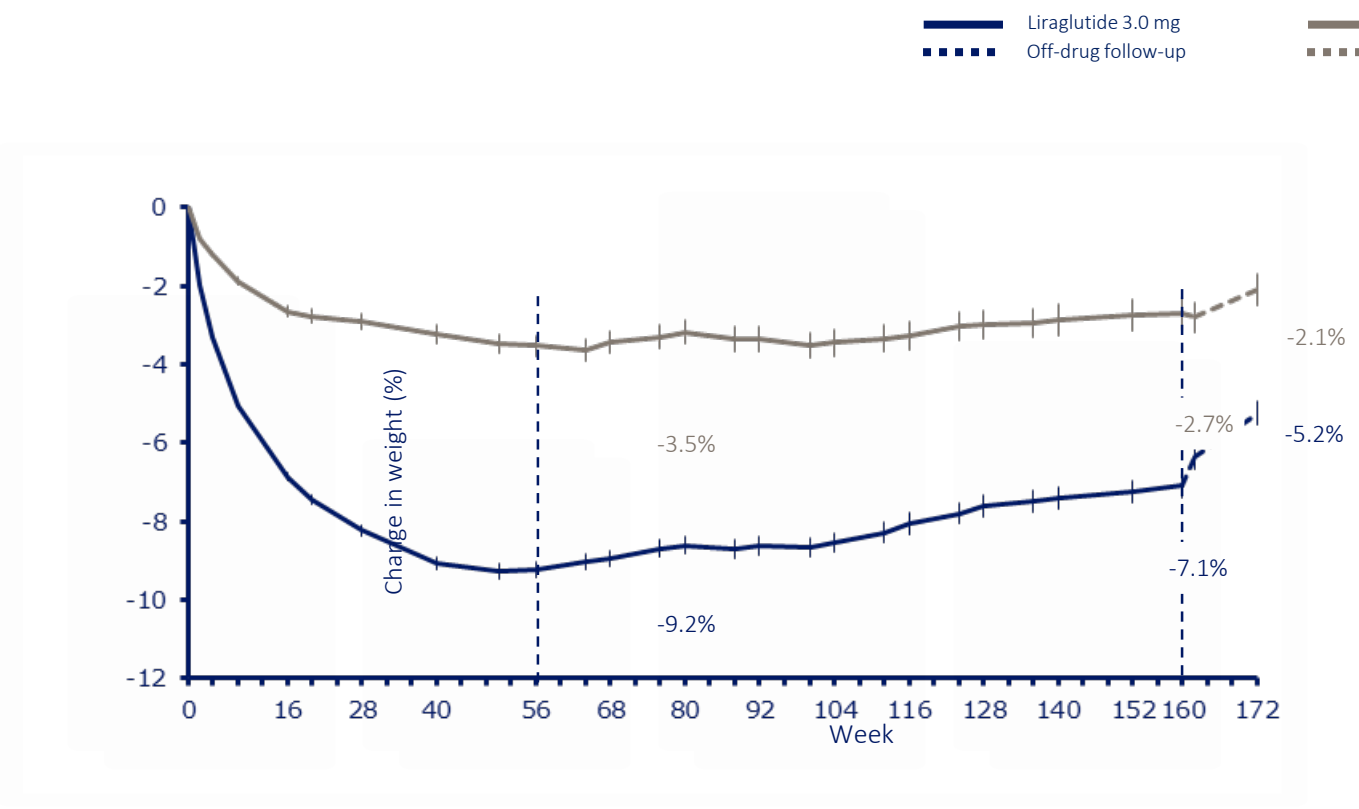
1. Increase the number of patients responding to lifestyle modification
2. Increase the magnitude of the response
3. Increase the duration of the response



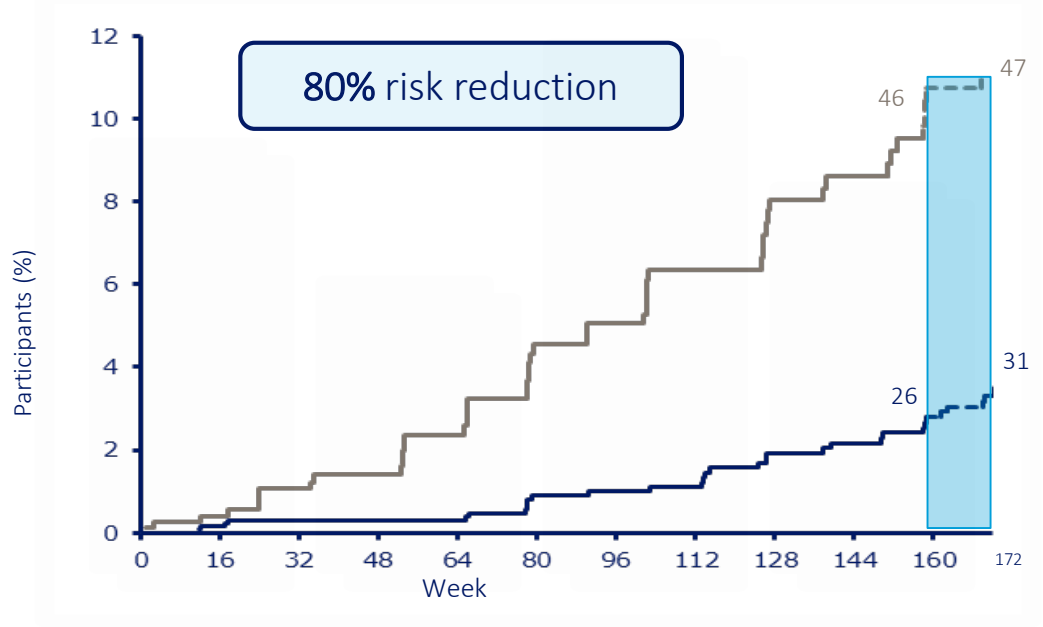
Adapted from Lau DCW et al. *CMAJ* 2007;176:S1–S13

Liraglutide 3.0 mg: Weight loss and progression to T2DM

SCALE Obesity and Prediabetes: 3 years



Full analysis set, fasting-visit data only. Line graphs are observed means (±SE).

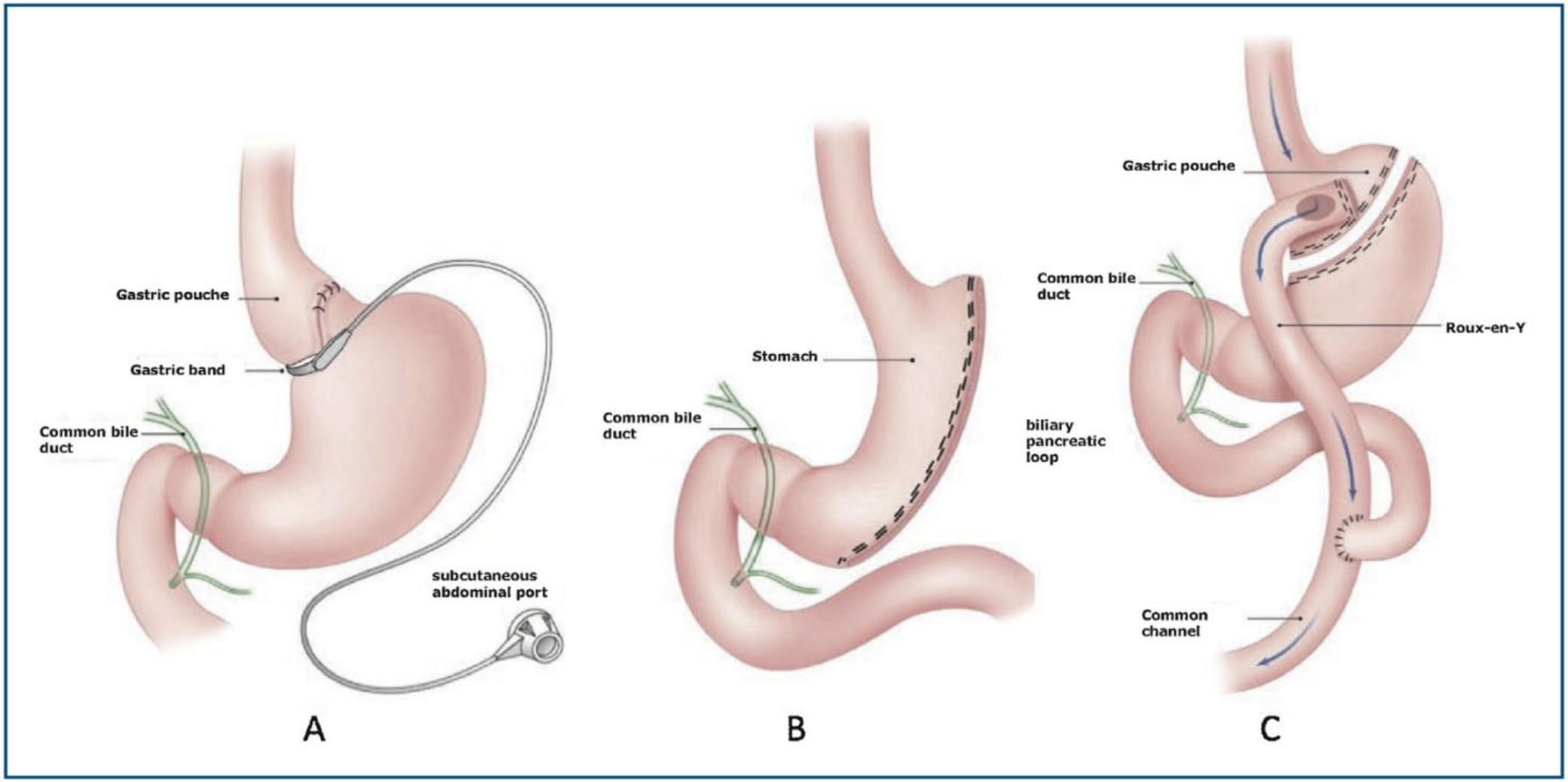


Full analysis set. Numbers in the figure correspond to the accumulated number of diagnosed participants.

*Derived from the primary Weibull analysis. ETD, estimated treatment difference; LOCF, last observation carried forward; SCALE, Satiety and Clinical Adiposity – Liraglutide Evidence in individuals with and without diabetes; SE, standard error; T2D, type 2 diabetes; WL, weight loss.

le Roux CW, Van Gaal L et al. *Lancet* 2017 Apr 8;389(10077):1399-1409.

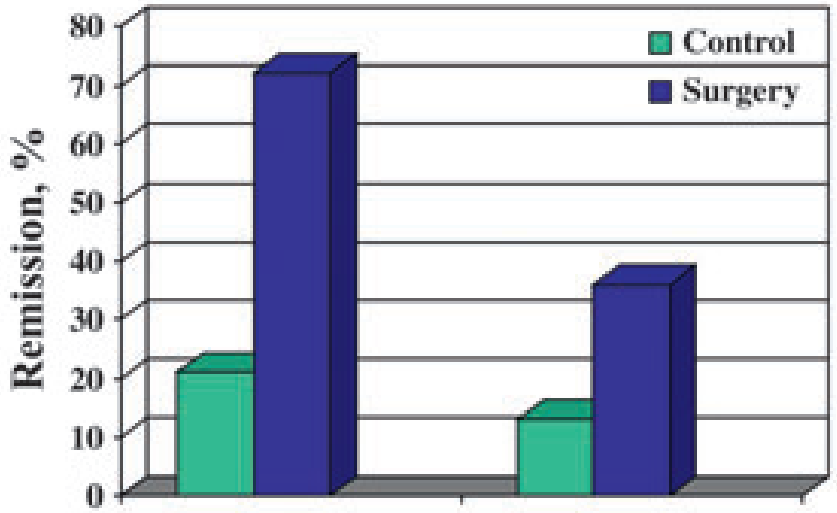
Different surgical procedures?



Caiazzo R and Patou F J Visc Surg 2013

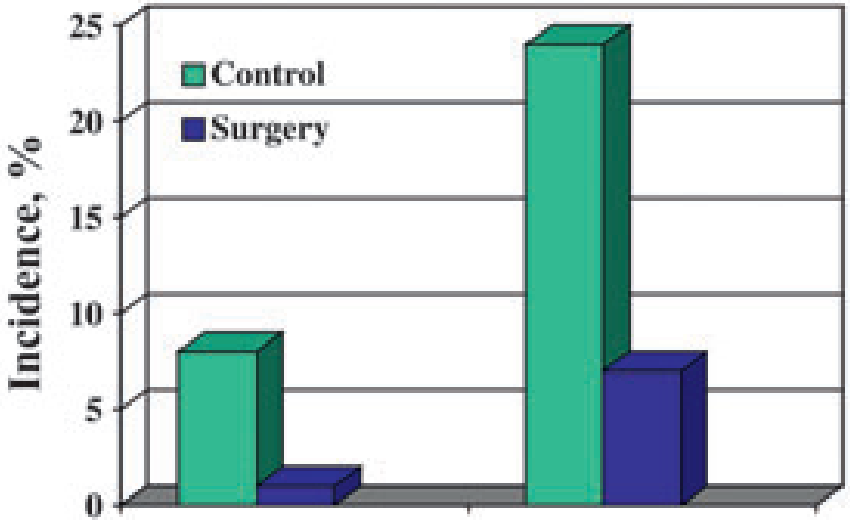
Reduction of incidence and remission from diabetes in SOS study

(a) SOS. Remission from diabetes over 2 and 10 years



Number of subjects:	2 year	10 year
Control	248	84
Surgery	342	118
Adjusted Odds ratio	8.42	3.45
95% CI	5.68 - 12.5	1.64 - 7.28
P value	<0.001	<0.001

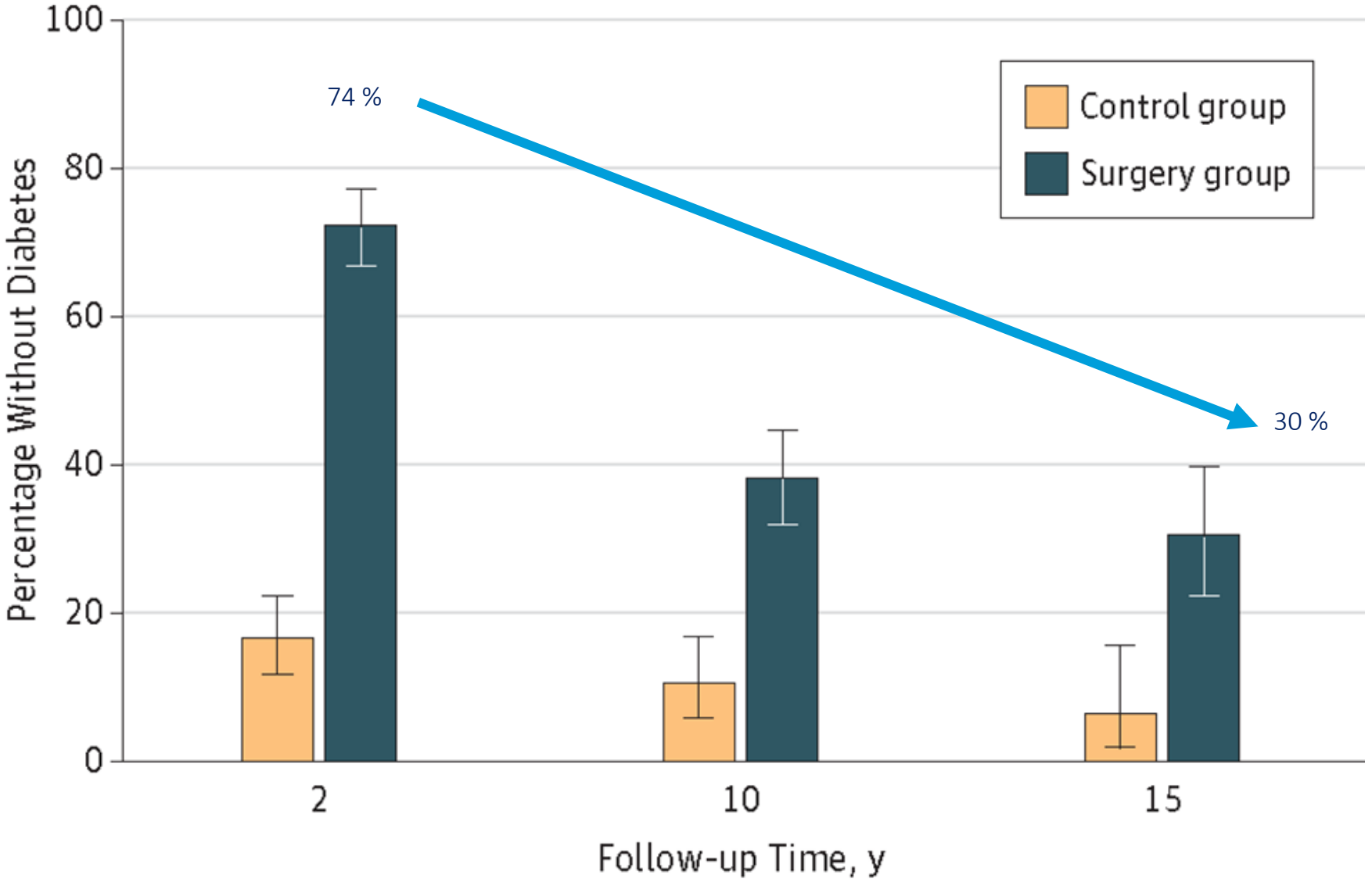
(b) SOS. Incidence of diabetes over 2 and 10 years



Number of subjects:	2 year	10 year
Control	1402	539
Surgery	1489	517
Adjusted Odds ratio	0.14	0.25
95% CI	0.08 - 0.24	0.17 - 0.38
P value	<0.001	<0.001

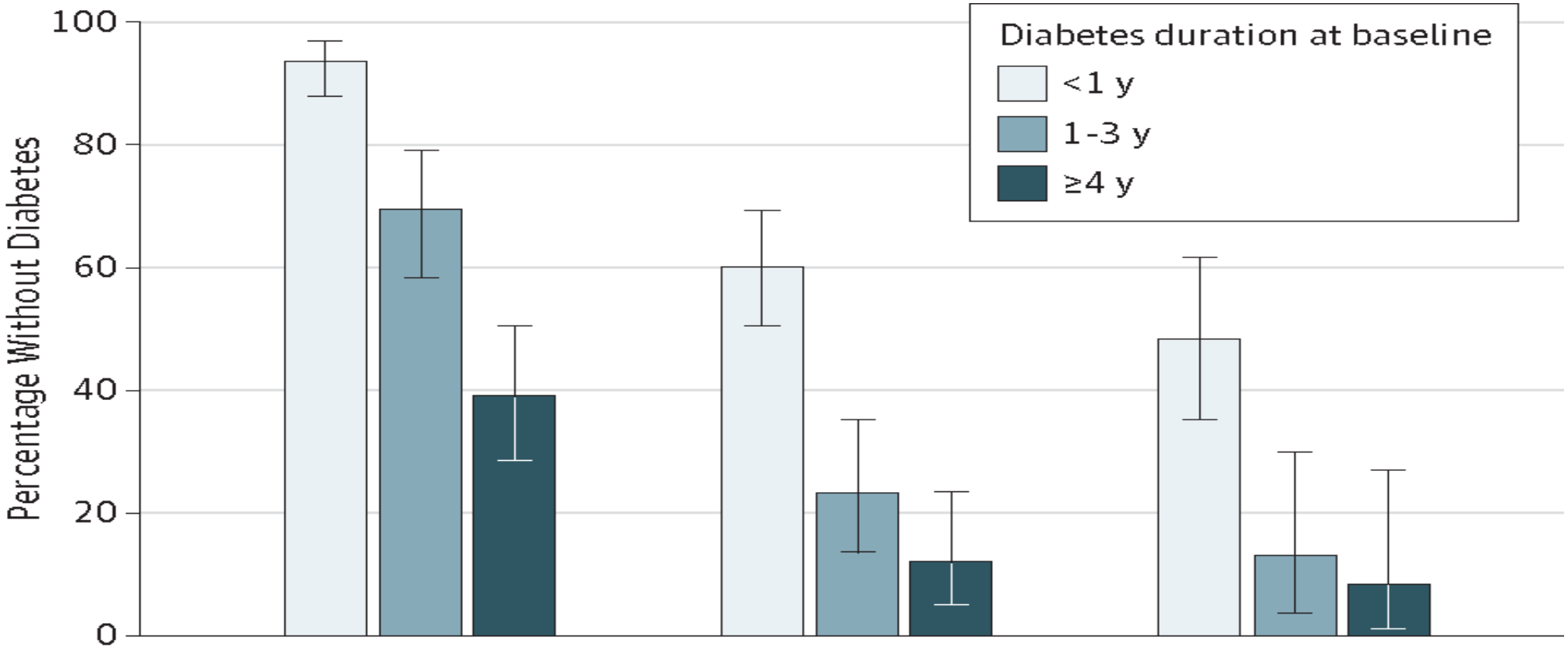
Sjöström L et al N Engl J Med 2004

Effect of ‘metabolic’ surgery – a cure for diabetes?



Sjöström. JAMA. 2014;311(22):2297-2304.

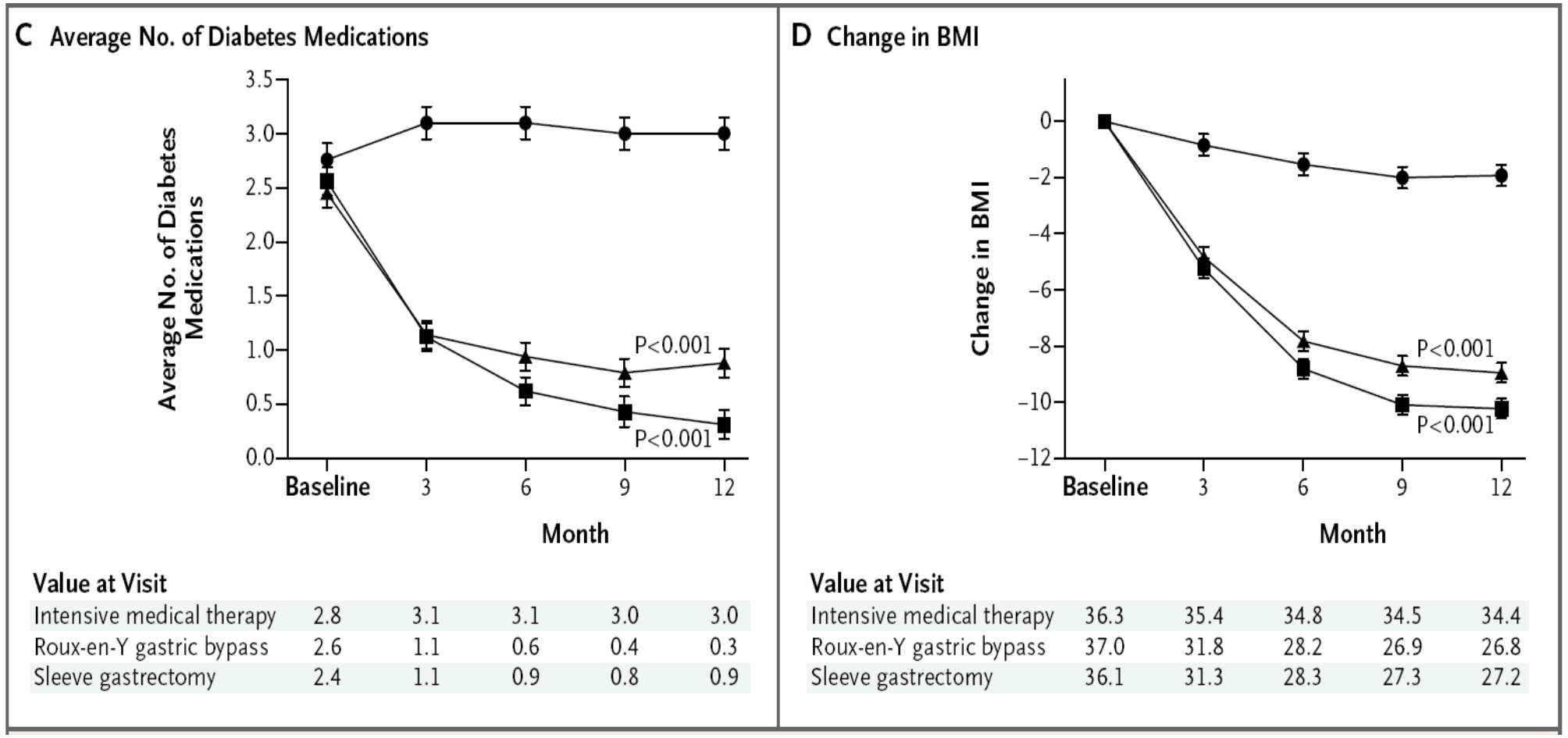
Effect of ‘metabolic’ surgery by duration



Total participants			
<1 y	139	113	60
1-3 y	82	65	31
≥4 y	82	58	24

Sjöström. JAMA. 2014;311(22):2297-2304.

Reduction of diabetes medication

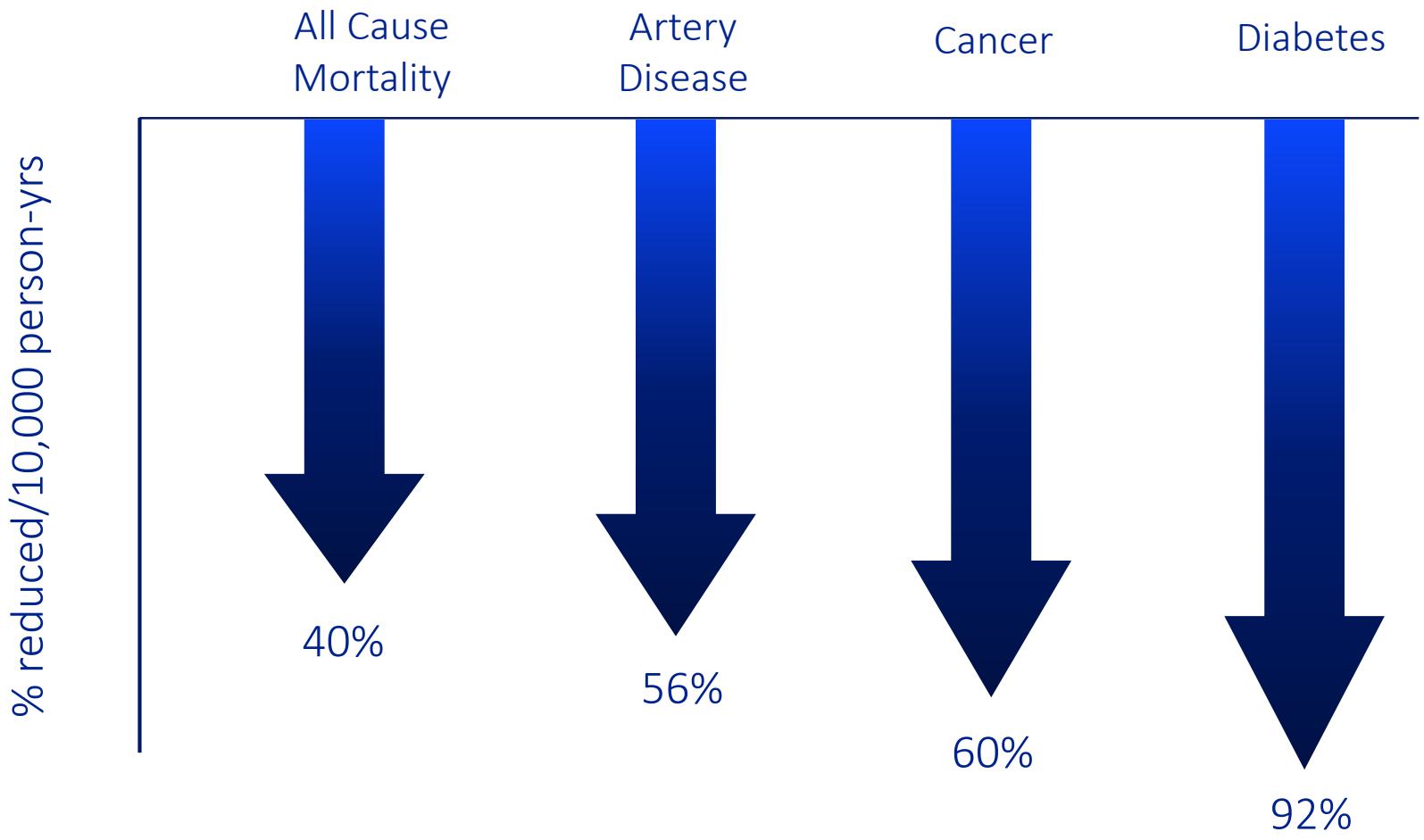


Value at Visit					
Intensive medical therapy	2.8	3.1	3.1	3.0	3.0
Roux-en-Y gastric bypass	2.6	1.1	0.6	0.4	0.3
Sleeve gastrectomy	2.4	1.1	0.9	0.8	0.9

Value at Visit					
Intensive medical therapy	36.3	35.4	34.8	34.5	34.4
Roux-en-Y gastric bypass	37.0	31.8	28.2	26.9	26.8
Sleeve gastrectomy	36.1	31.3	28.3	27.3	27.2

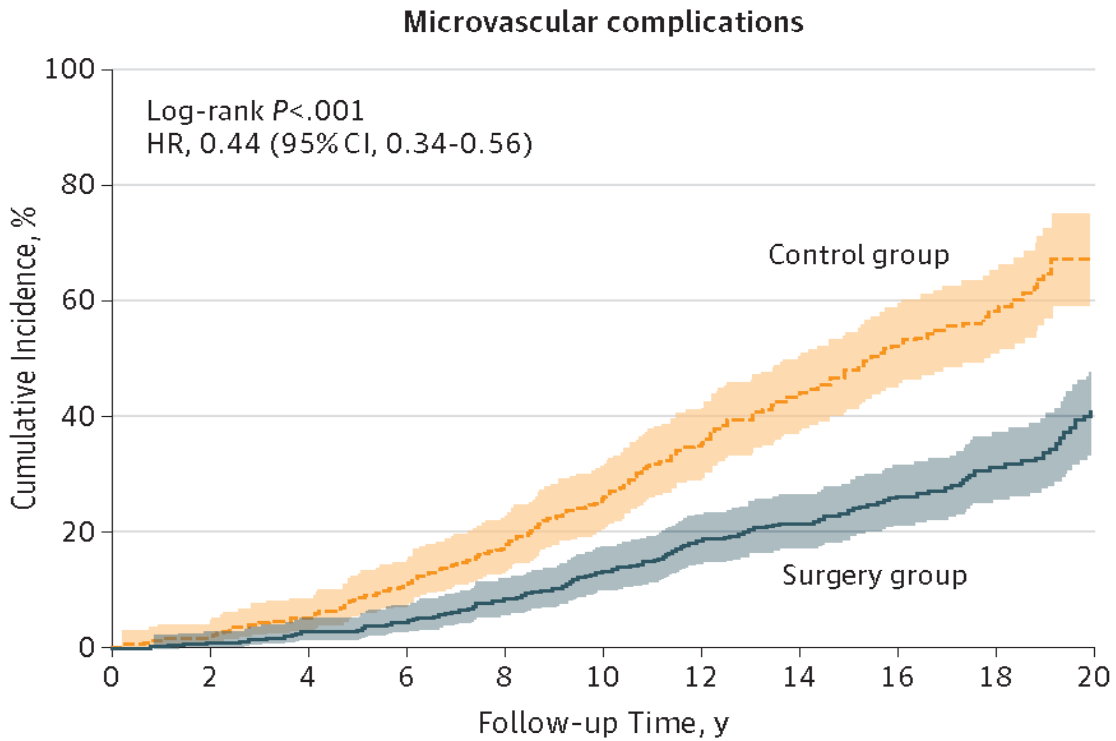
Schauer P., et al. NEJM 2012

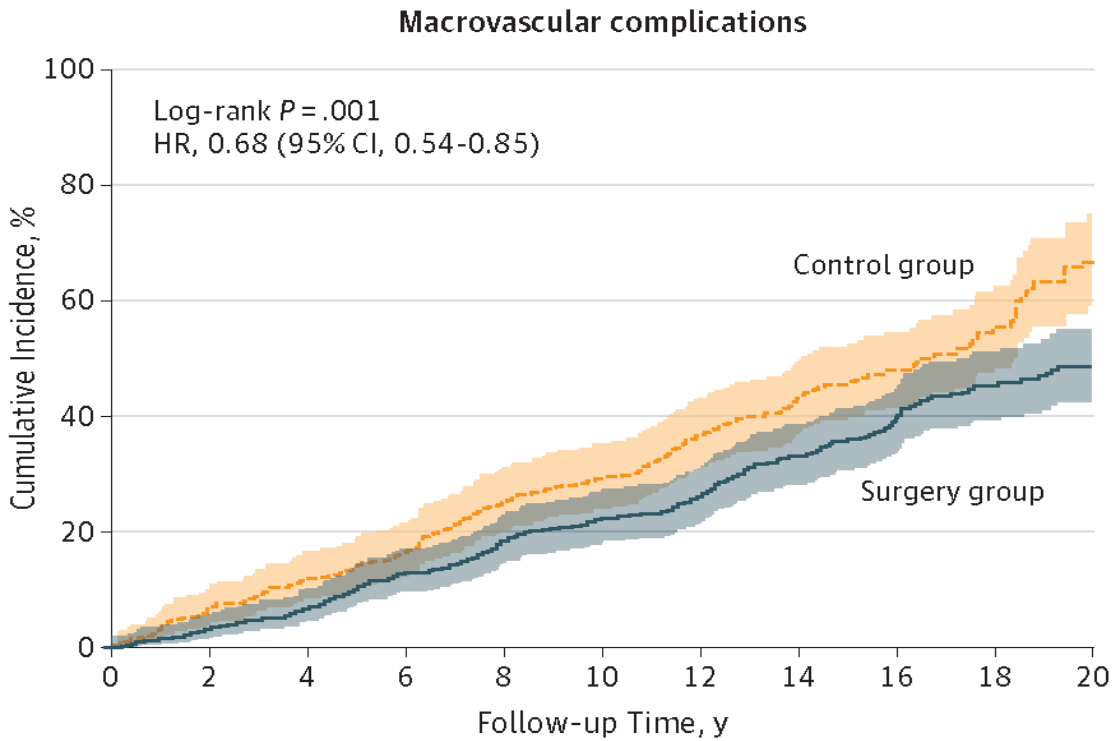
Long-Term Mortality After Gastric Bypass Surgery



Adams TD, et al. NEJM 2007;357:753

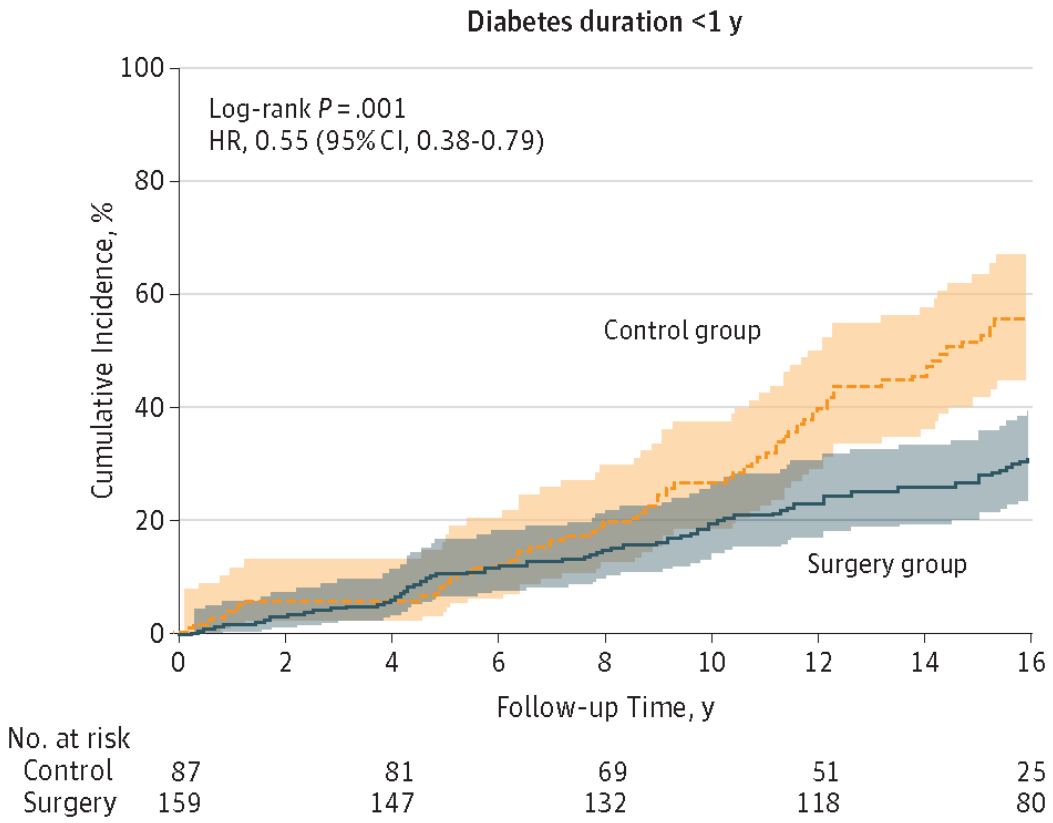
Cumulative incidence of diabetic complications after bariatric surgery

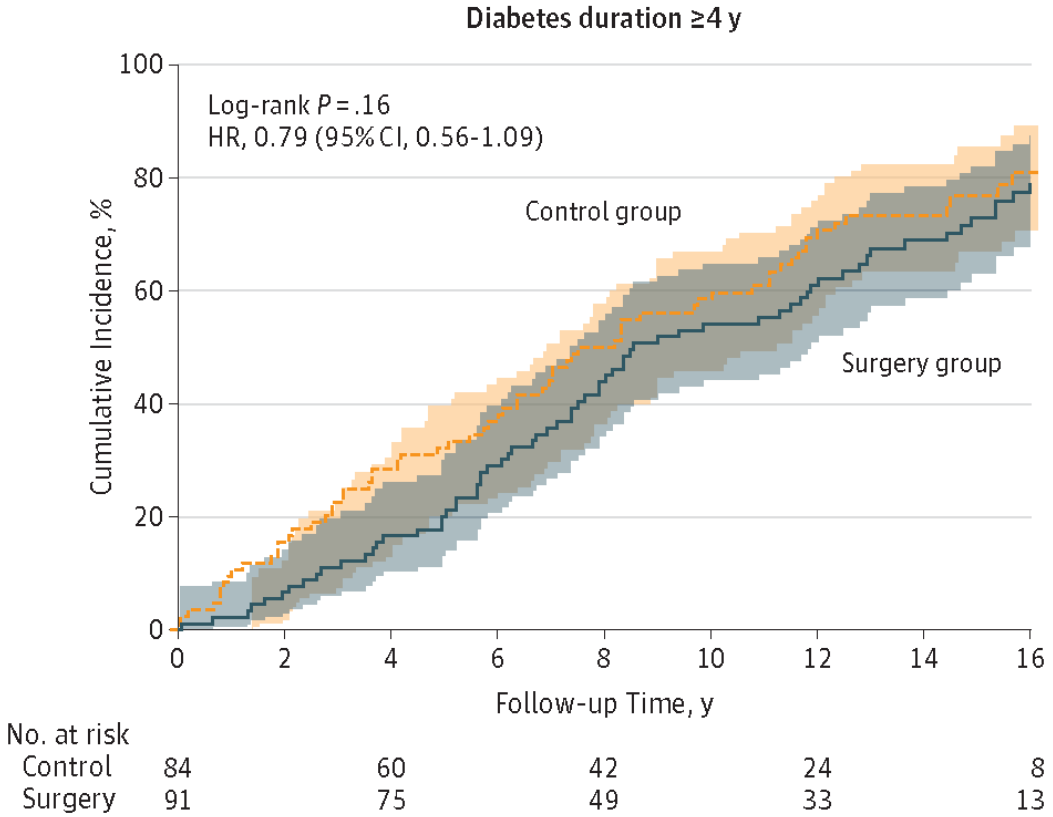




Sjöström L., et al. *JAMA.* 2014;311(22):2297-2304.

Cumulative incidence of diabetic complications by disease duration





Sjöström L., et al. *JAMA.* 2014;311(22):2297-2304.

Bariatric surgery vs conventional therapy in Type 2 diabetes
STAMPEDE Trial

RCT: conventional ↔ Gastric bypass ↔ Sleeve gastrectomie

- 5 kg **- 30 kg** **- 25 kg**

Age: 49±8j

BMI 36.4kg/m²

Duration 8.5±5j

HbA1c 9.2% ± 1.5

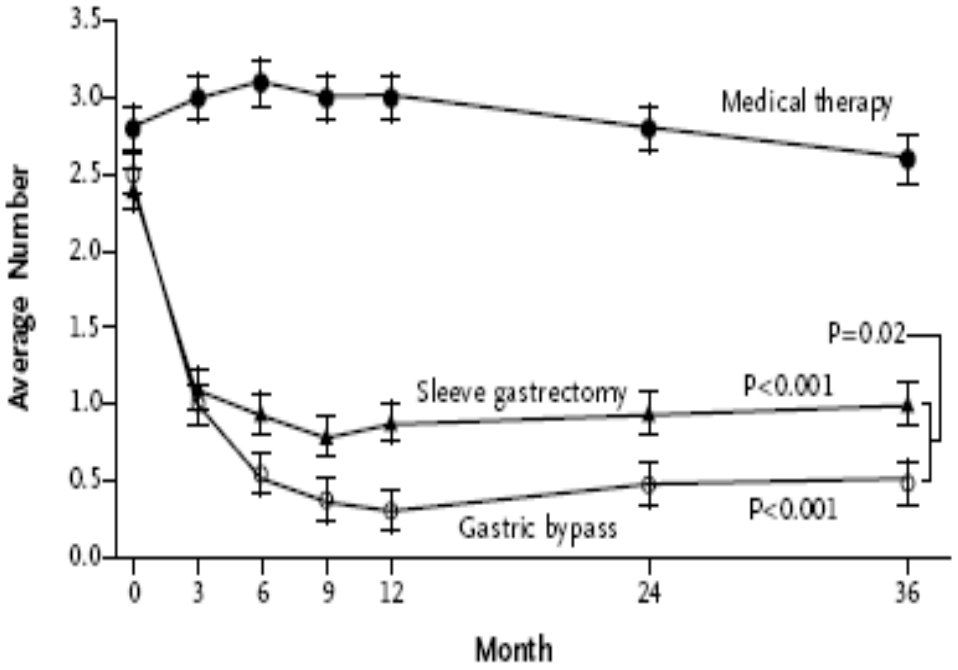
Insulin use 43%

34%: BMI <35kg/m²

Schauer, et al. NEJM 2012;366:1567-76

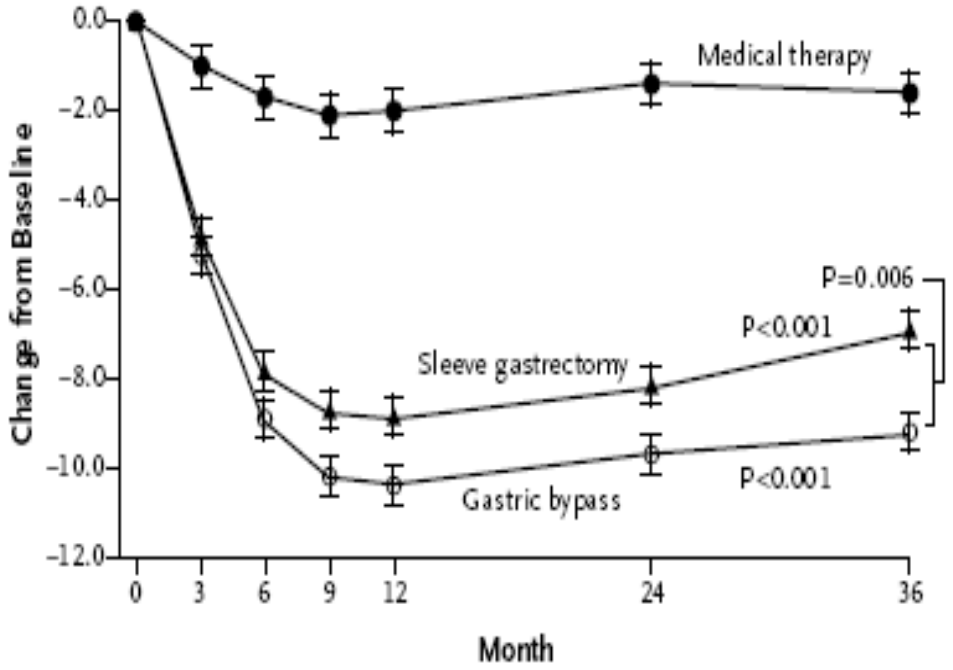
Stampede: surgery vs medical therapy
3 y outcome data

C Diabetes Medications



Value at Visit					
Medical therapy	2.8	3.1	3.0	2.8	2.6
Sleeve gastrectomy	2.4	0.94	0.88	0.94	1.0
Gastric bypass	2.5	0.54	0.3	0.47	0.48

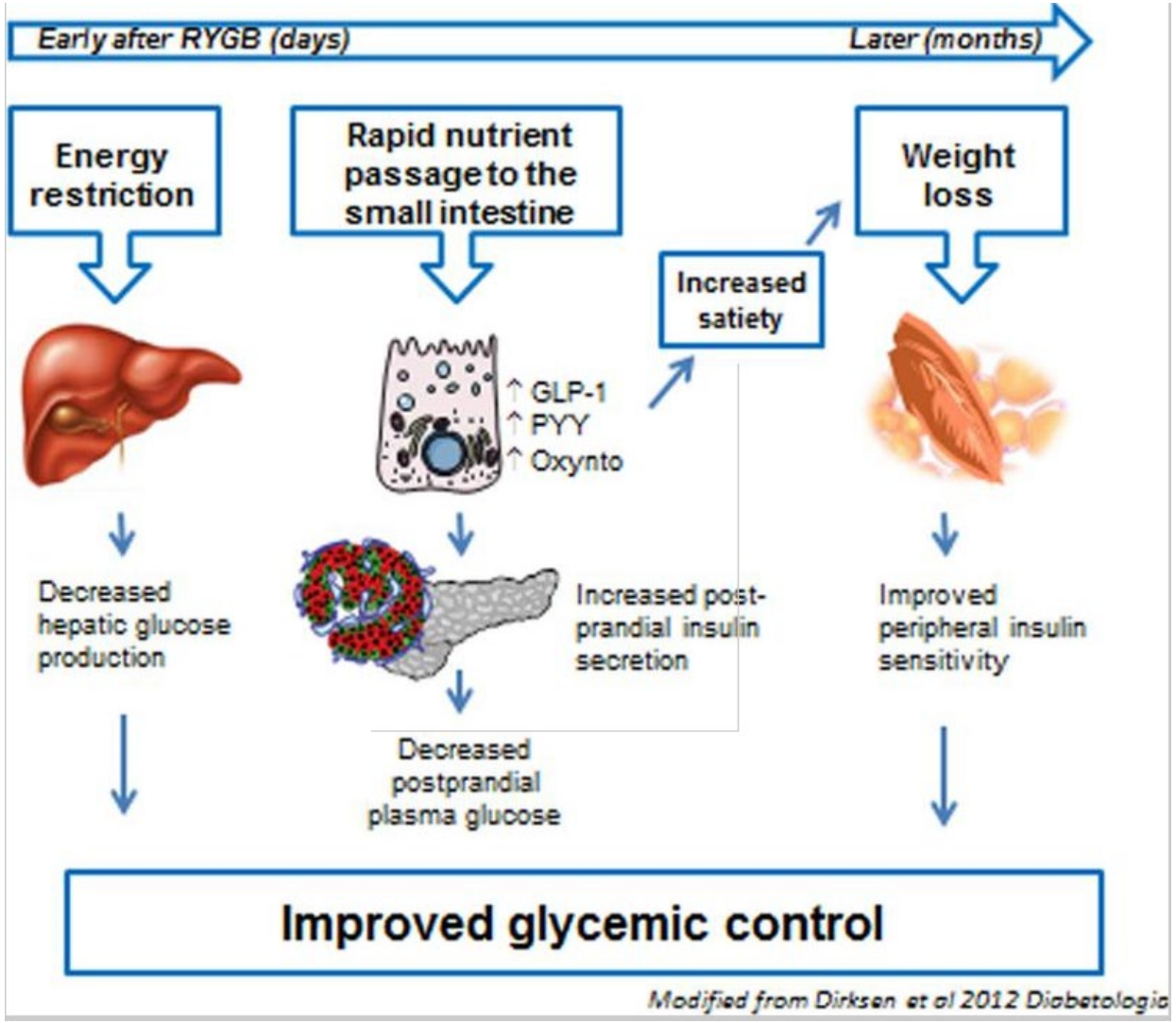
D Body-Mass Index



Value at Visit					
Medical therapy	36.4	34.6	34.2	35.0	34.8
Sleeve gastrectomy	36.1	28.3	27.1	27.9	29.2
Gastric bypass	37.1	28.2	26.7	27.3	27.9

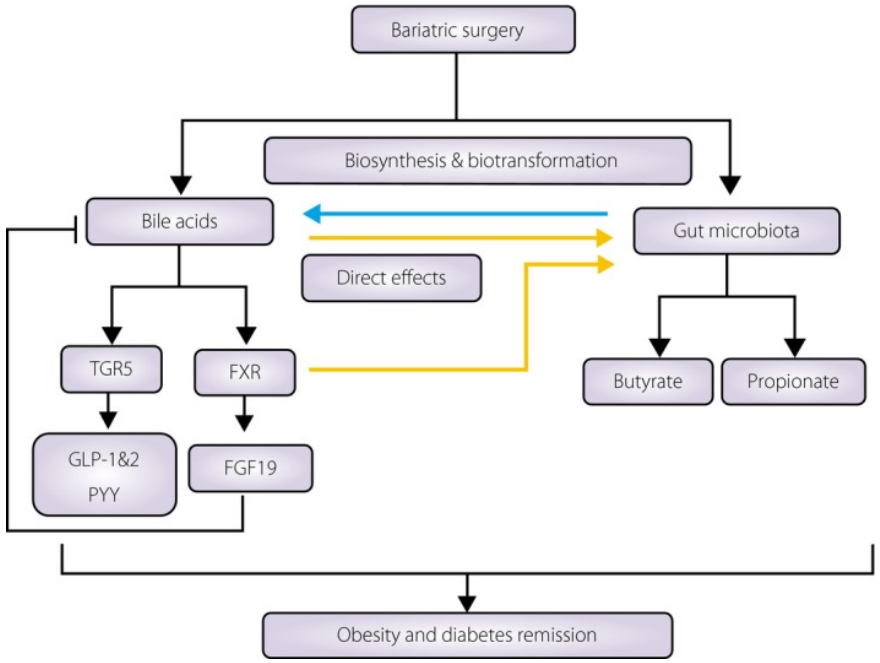
Schauer PR et al for the STAMPEDE Investigators NEJM 2014

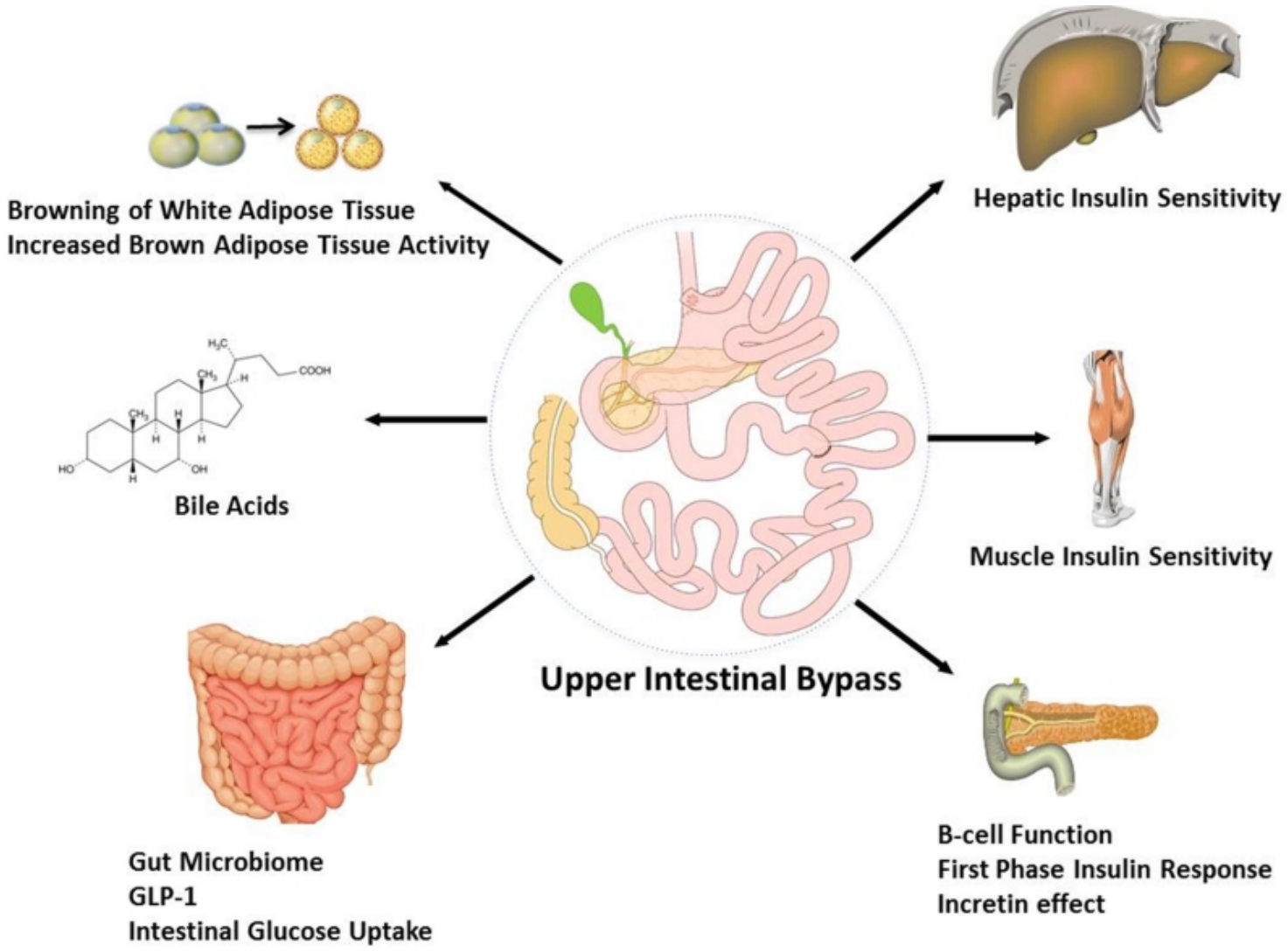
Mechanisms in bariatric surgery:
Gut hormones, diabetes resolution, and weight loss



J. Holst et al. Surg Obes Relat Dis. 2018 May; 14(5): 708–714.

Are there weight loss-independent therapeutic effects of upper gastrointestinal bypass?





J Intern Med. 2016 Nov; 280(5): 476–486.

Metabolic (Bariatric and Nonbariatric) Surgery for Type 2 Diabetes: A Personal Perspective Review

Henry Buchwald[1,2] and Jane N. Buchwald[3]

Diabetes Care 2019;42:331–340 | https://doi.org/10.2337/dc17-2654

Metabolic surgery can cause amelioration, resolution, and possible cure of type 2 diabetes. Bariatric surgery is metabolic surgery. In the future, there will be metabolic surgery operations to treat type 2 diabetes that are not focused on weight loss. These procedures will rely on neurohormonal modulation related to the gut as well as outside the peritoneal cavity. Metabolic procedures are and will always be in flux as surgeons seek the safest and most effective operative modality; there is no enduring gold standard operation. Metabolic bariatric surgery for type 2 diabetes is more than part of the clinical armamentarium, it is an invitation to perform basic research and to achieve fundamental scientific knowledge.

Take home messages

- Obesity and diabetes are closely linked
  - Common environmental and lifestyle triggers
  - Pathogenetic mechanisms link “diabesity” with NASH, CVD and other common diseases
- Diabetes can be prevented by weight loss
- Diabetes remission can be attained through metabolic surgery
  - Mechanisms involved give rise to possible future medical therapies

Dank aan Prof. Van Gaal voor het ter beschikking stellen van zijn slides