Why treat obesity?
The entity of diabesity

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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

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

Natural history of type 2 diabetes

Genetic susceptibility

Early life events:
- Low birth weight
- Formula feeding

Insulin resistance $\uparrow$

Compensatory insulin secretion

IGT

Intrauterine nutrition
- Inherited $\beta$-cell defect
- Glucotoxicity
- Lipotoxicity

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

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

Relative risk of type 2 diabetes

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

Relative risk for diabetes based on BMI at age 18 and weight gain 18–32 years:

- <4.9
- 5.0–6.9
- 7.0–10.9
- 11.0–19.9
- >20

BMI, body mass index

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-Seon Lim, MD, PhD
Deb Heit, MD, PhD
David R. Jacobs, Jr., PhD

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

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

T. L. M. Hectors · G. Vanparys · K. van der Ven · G. A. Martens · P. G. Jorens · L. E. Van Gaal · A. Covaci · W. De Coen · R. Blust
Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Jotham Suez¹, Tal Korem², David Zeevi², Gili Zilberman-Schapira³, Christoph A. Thaiss¹, Ori Maza¹, David Israeli³, Niv Zmora⁴, Shlomit Gilad⁷, Adina Weinberger², Yael Kuperman⁸, Alon Harmelin⁸, Ilana Kolodkin-Gal⁹, Hagit Shapiro¹, Zamir Halpern⁵, Eran Segal² & Eran Elinav¹
### Sleep restriction and risk of obesity

Sleep duration <5 hours increases risk of obesity

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>OR (95% CI)</th>
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<td>Chaput JP</td>
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<td>Kobayashi D</td>
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<tr>
<td>Nagai M</td>
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<td>Patel SR</td>
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<td><strong>Overall</strong></td>
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<td>1.45 (1.25, 1.67)</td>
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</table>

NOTE: Weights are from random effects analysis

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CI, confidence interval; OR, odds ratio

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
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
From NAFLD or NASH to diabetes and CVD

Anstee QM et al Nat Rev Gastroenterol Hepatol 2013
Intestinal microbiota can alter human cardio-metabolism.

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

**Adiposity**
- Adipokine synthesis
- Adipose tissue macrophages and other inflammatory cells
- Pro-inflammatory cytokines
- Impaired insulin signalling and insulin resistance
- Insulin
- T2D

**Lipid production**
- Hydrolysis of triglycerides
- Release of fatty acids
- Lipotoxicity
- Dyslipidaemia

**Activity of the sympathetic nervous system**
- Systemic and pulmonary hypertension

**Activity of the renin-angiotensin-aldosterone system**
- Renal compression
- Pharyngeal soft tissue

**Mechanical stress**
- Mechanical load on joints
- Intra-abdominal pressure

**Chronic kidney disease (CKD)**

**Obstructive sleep apnoea (OSA)**

**Osteoarthritis**

**Gastroesophageal reflux disease (GERD)**
- Barrett’s oesophagus
- Oesophageal adenocarcinoma

**Cardiovascular diseases**
- CHD, coronary heart disease
- CHF, coronary heart failure
- Stroke
- Cirrhosis
- NAFLD, non-alcoholic fatty liver disease
- NASH, non-alcoholic steatohepatitis
- OSA, obstructive sleep apnoea
- T2D, type 2 diabetes

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
- Improvements in blood lipid profile
- Improvements in blood pressure
- Improvements in abnormal NAFLD liver histology
- Improvements in health-related quality of life
- Improvements in severity of obstructive sleep apnoea
- Reduction in CV mortality

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

Weight loss can reduce progression to T2D

Lifestyle intervention trials
% reduced risk of progression from prediabetes to T2D

Finnish DPS\textsuperscript{1,2}

- 6 years: 58%
- 13 years: 39%

DPP/DPPOS\textsuperscript{3,4}

- 4 years: 58%
- 10 years: 34%

Da Qing\textsuperscript{5}

- 6 years: 51%
- 20 years: 43%

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

Look AHEAD: NO cardiovascular benefit, unless...

Hazard ratio, 0.95 (95% CI, 0.80–1.09)
P = 0.51

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<th>No. at Risk</th>
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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

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

Obese Class 2
BMI ≥35 kg/m²

Obese Class 1
BMI ≥30 kg/m²

Overweight
BMI ≥25 kg/m²

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).


*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.
Different surgical procedures?
Reduction of incidence and remission from diabetes in SOS study

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

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

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

[Sjöström. JAMA. 2014;311(22):2297-2304.]
Effect of ‘metabolic’ surgery by duration

Diabetes duration at baseline
- <1 y
- 1-3 y
- ≥4 y

Percentage Without Diabetes

Follow-up Time, y
- 2
- 10
- 15

Total participants
- <1 y
- 1-3 y
- ≥4 y

Reduction of diabetes medication

C Average No. of Diabetes Medications

D Change in BMI

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<table>
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<td>36.1</td>
<td>31.3</td>
<td>28.3</td>
<td>27.3</td>
<td>27.2</td>
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Long-Term Mortality After Gastric Bypass Surgery

- All Cause Mortality: 40%
- Artery Disease: 56%
- Cancer: 60%
- Diabetes: 92%

Adams TD, et al. NEJM 2007;357:753
Cumulative incidence of diabetic complications after bariatric surgery

Cumulative incidence of diabetic complications by disease duration

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

D Body-Mass Index

<table>
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<th>Month</th>
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<tr>
<td>Gastric bypass</td>
<td>2.5</td>
<td>0.54</td>
<td>0.3</td>
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</tbody>
</table>

Schauer PR et al for the STAMPEDE Investigators NEJM 2014
Mechanisms in bariatric surgery: Gut hormones, diabetes resolution, and weight loss
Are there weight loss-independent therapeutic effects of upper gastrointestinal bypass?

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