Obesity is a chronic disease requiring long-term management

- Dr Khalilzadeh
- Endocrinologist

Introduction

- The mortality and morbidity associated with being overweight or obese have been known to the medical profession for more than 2000 years

- Adult obesity is associated with a striking reduction in life expectancy for both men and women. It has been suggested that the steady rise in life expectancy seen during the past two centuries may end because of the increasing prevalence of obesity

- N Engl J Med 2005; 352:1138/Ann Intern Med 2003; 138:24

- In the United States, rates of obesity became worrisome in the 1990s as overweight and obesity increased in the population. Until the past two decades, rates of both were higher in the United States than in other countries. Recently other nations have caught up, and prevalence is higher now in Mexico and countries in the Middle East than in the United States. Considering that the genetics of the population has not changed over the interval during which the dramatic rise in rates of obesity have occurred, the increase must result from a complex interplay of genes and environment. Many individuals have a predisposition toward eating and storing calories when they are available

- Mammals have evolved to acquire food and store it as fat against times of food scarcity. Until the modern era, food scarcity had been a substantial threat to existence over excess calories. A pound of fat, containing 3500 calories, may provide 2 to 4 days of survival for an individual without any food supply. In a very calorie restricted environment, 50 pounds of extra fat would make a substantial survival difference. Lean persons will die after only approximately 60 days of starvation, when more than 35% of body weight is lost. Obese persons can tolerate longer fasts, even for more than 1 year, without major adverse effects. In the longest reported fast, a 456-pound (207-kg) man ingested only acaloric fluids, vitamins, and minerals for 382 days and lost 278 pounds (126 kg), or 61% of his initial weight.

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/m^2)
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/

PREVALENCE

- In 2015, approximately 108 million children and 604 million adults globally were obese; this represents an increase in prevalence of obesity in almost all countries since 1980 and a doubling in prevalence in 70 countries.
- Based upon data collected for NHANES from 1988 to 1994, 1999 to 2000, and 2015 to 2016, the age-adjusted prevalence of obesity in the United States increased progressively from 22.9 to 30.5 to 39.6 percent. In 2015 to 2016, the prevalence of obesity in men was 37.9 percent, and the prevalence of obesity in women was 41.1 percent.

Ann Intern Med 2003; 138:24/ JAMA 2018; 319:1723.

Obesity is recognised as a disease and health issue

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"[1]

World Obesity Federation

OC

"Obesity is characterized by excess body fat that can threaten or affect your health. Many organizations including Obesity Canada, now consider obesity to be a chronic disease."[4]

Obesity Canada

AMA

"American Medical Association recognizes obesity and overweight as a chronic medical condition (de facto disease state) and urgent public health problem…and work towards the recognition of obesity intervention as an essential medical service…"[2]

American Medical Association

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…"[5]

European Association for the Study of Obesity

FDA

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

The US Food and Drug Administration

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"[6]

European Medicines Agency

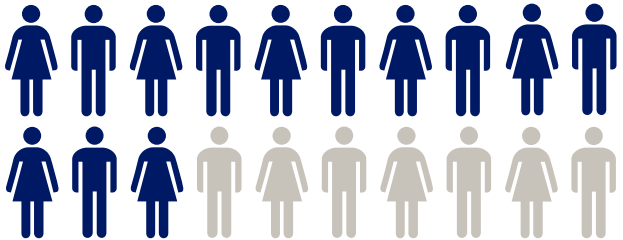
Bray *et al*. *Obes Rev* 2017;18:715–23; 2. AMA resolutions. June 2012. Available here; 3. Food and Drug Administration. Guidance for Industry Developing Products for Weight Management 2007 Available here; 4. Obesity Canada. Available here; 5. EASO: 2015 Milan Declaration: A Call to Action on Obesity. Available here; 6. EMA Draft Guideline on clinical evaluation of medicinal products used in weight control EMA/CHMP/311805/2014. Available here.

Obesity disease recognition

Results from the US ACTION study

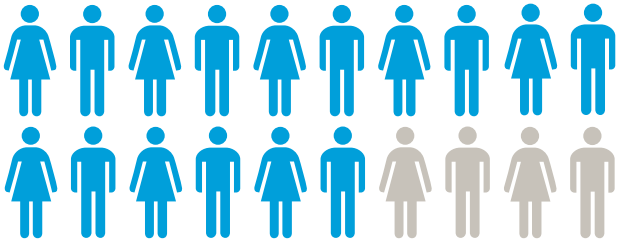
65% of PwO

recognise obesity as a disease



80% of HCPs

recognise obesity as a disease



HCP, healthcare provider; PwO, people with obesity

Kaplan *et al. Obesity (Silver Spring).* 2018;26:61-69

Obesity meets common criteria of a disease

AMA	• An impairment of the normal functioning of some aspect of the body • Characteristic signs or symptoms • Harm or morbidity

Obesity

- Appetite dysregulation
- Abnormal energy balance
- Endocrine dysfunction

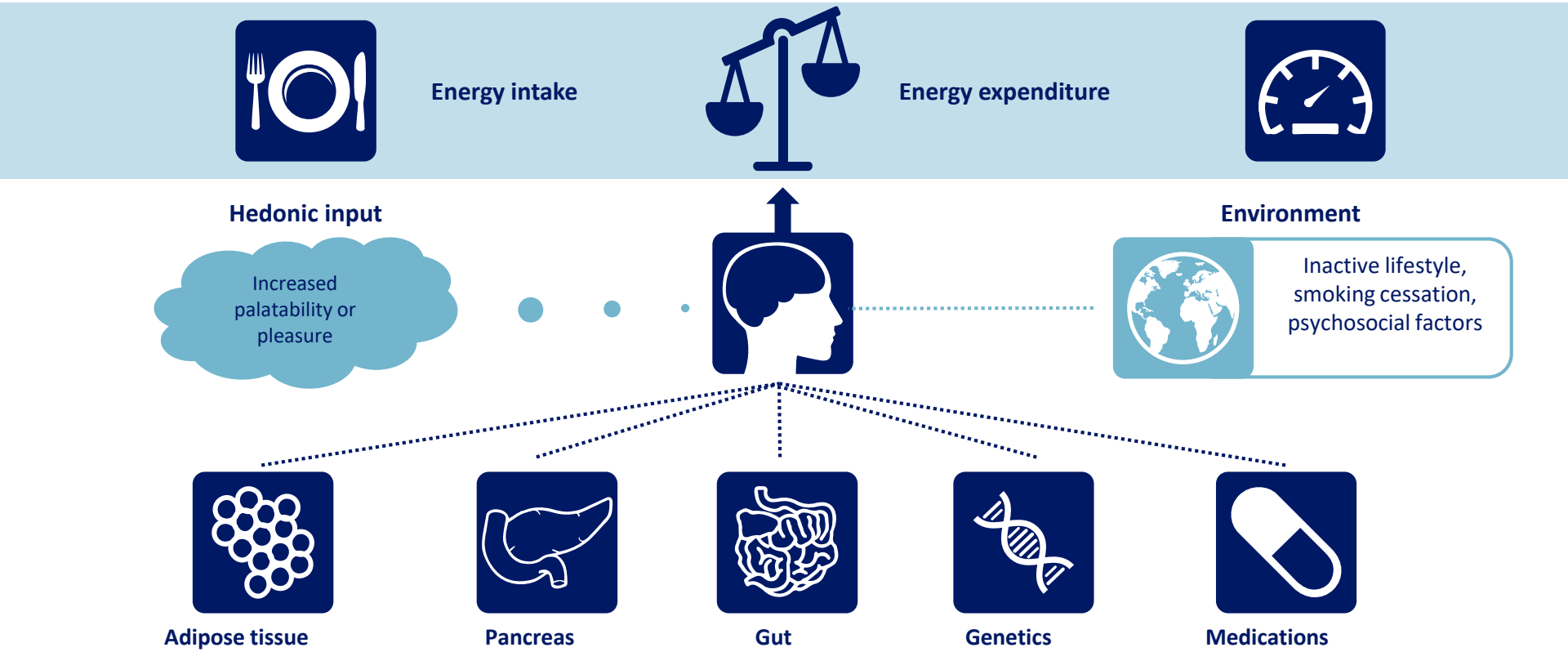
- Increased body fat
- Symptoms associated with increased body fat including:
  - Joint pain
  - Immobility
  - Sleep apnoea

- Type 2 diabetes
- Cardiovascular disease
- Cancer
- Osteoporosis
- Polycystic ovary syndrome

AMA, American Medical Association, NAFLD, non-alcoholic fatty liver disease

American Medical Association Resolution: 420 (A-13). Available at: http://www.npr.org/documents/2013/jun/ama-resolution-obesity.pdf.

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

Energy homeostasis, defined as the balance between energy intake
and energy expenditure, is regulated by complex molecular and
physiologic processes. Control of energy homeostasis requires
physiologic integration of biologic signals from different organs
including fat, muscle, liver, gut, and brain; nutrient-related
signals; and postprandial neural and hormonal influences

Central Nervous System Regulation of Appetite

- The hypothalamus is an important area for integrating complex signals that govern food ingestion. Pro-orexigenic neurons in the arcuate nucleus, which express neuropeptide Y (NPY) and agoutirelated protein (AgRP), and appetite inhibiting neurons, which express the proopiomelanocortin (*POMC*) gene and process its product to α-melanocyte-stimulating hormone (αMSH), are two well-studied hypothalamic networks that inversely regulate weight.

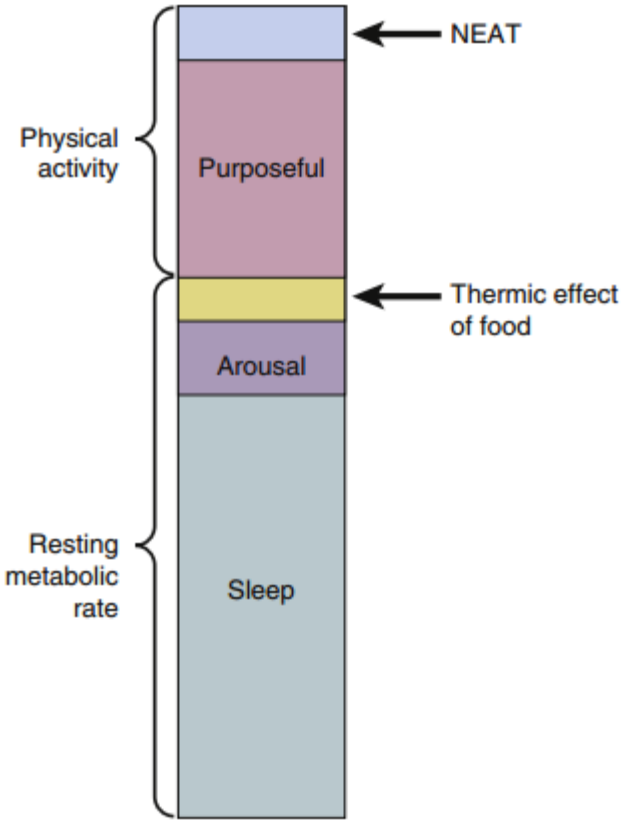
Signals From the Periphery Regulating Appetite

- Multiple peripheral signals regulate energy homeostasis. Leptin, the product of the *ob* gene, is critically important for weight maintenance. Leptin absence, resulting from gene mutations, is associated with absent appetite control resulting in morbid obesity in mice, rats, and humans. Although leptin is necessary for weight maintenance, it is not sufficient. As rodents become obese, adipose tissue synthesizes increased leptin, causing increased levels in the circulation. However, the increased levels fail to decrease food intake. Likewise, most overweight and obese humans have high circulating leptin concentrations. Thus, most obesity is associated with resistance to leptin action

- Most other peripheral signals that participate in energy balance are derived from the gut. Of these, ghrelin is an orexigenic factor derived from the stomach that increases before meals and decreases after feeding. Most other gut peptides, secreted by enteroendocrine cells, inhibit appetite. Of these, glucagon-like peptide 1 (GLP1), derived from pre-proglucagon, is secreted by the L cells of the intestine that also secrete peptide YY. GLP1 and peptide YY are co-secreted after a meal and induce satiety,14 and GLP1, when infused directly into the rat ventricle, opposes the actions of orexigenic peptides including MCH and NPY.15 Cholecystokinin, another gut peptide, is distributed throughout the gastrointestinal tract. It stimulates bile release from the gallbladder after a meal but likely also contributes to satiety

Energy Expenditure

- Energy expenditure is a key component critical for weight homeostasis. Several factors contribute to total daily energy expenditure
  The largest component is basal or resting energy expenditure, defined as the energy required in the basal state for normal
  cellular and organ function; it has also been termed *basal metabolic rate*. Resting energy expenditure accounts for approximately 70%
  of total energy expenditure


NEAT
Physical activity
Purposeful
Thermic effect of food
Arousal
Resting metabolic rate
Sleep

- Components of energy expenditure. The largest component is heat generated by biochemical reactions and physiologic processes occurring at rest that are required for systemic homeostasis, including respiration, circulation, and excretion. The process of arousal increases resting energy expenditure as posture needs to be supported. Resting energy expenditure is regulated by hormones, output from the central nervous system, and sympathetic activity. Eating also requires energy, and postprandial processes involved in digestion and absorption and distribution of nutrients contribute to the thermic effect of food. Physical activity is a smaller component of energy expenditure and includes the energy expended toward purposeful activities and nonexercise activity thermogenesis (NEAT), such as fidgeting

Pathogenesis of Obesity: Genes and Environment

- It is challenging to identify causal factors of obesity because there are few monogenetic forms of obesity, and many single nucleotide polymorphisms (SNPs) associated with excess weight are in noncoding regions of the genome. In addition, there are substantial social and environmental determinants of weight. Food environments are complex and include not just food availability but food cost, cultural perspectives of weight, and an individual's social network.

Influences of Childhood and Parental Obesity

- Childhood obesity increases the risk of becoming an obese adult, as does having at least one obese parent. The risk of adult obesity increases with increasing age and with the severity of obesity in childhood. For example, the risk of being obese at 21 to 29 years of age ranged from 8% for persons who were obese at 1 to 2 years of age and had nonobese parents to 79% for persons who were obese at 10 to 14 years of age and had at least one obese parent, with multiple permutations between these extremes.

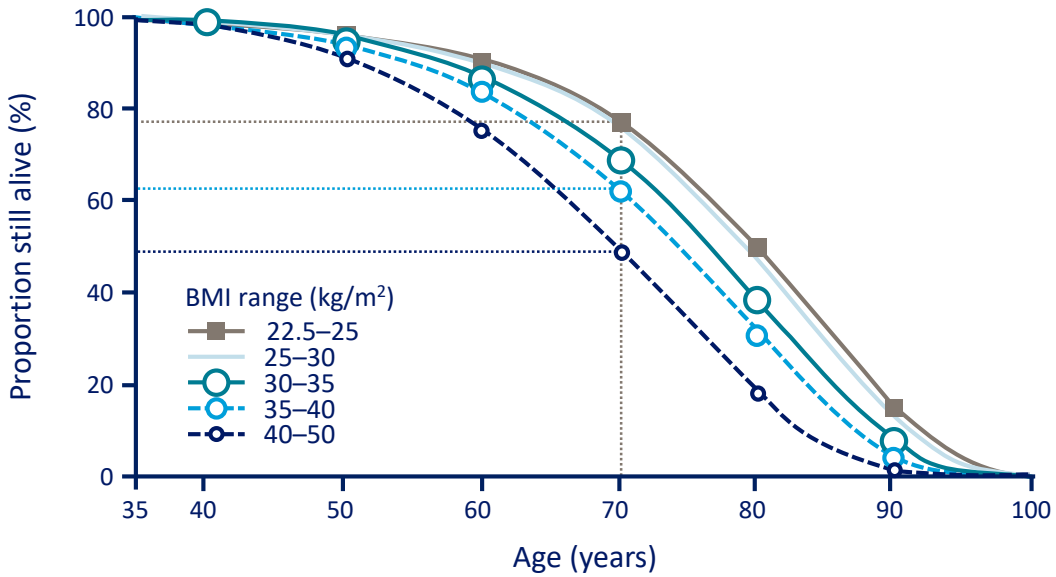
Environmental Effects in High-Risk Populations

A striking example of the effects of modern diet on obesity is seen in Pima Indians living in Arizona. A combination of diet and lifestyle changes starting in the 1950s resulted in an epidemic of both obesity and diabetes.

Adverse Consequences of Obesity

Obesity as a Disease Risk Factor

Life expectancy decreases as BMI increases



Normal BMI =
almost 80% chance
of reaching age 70

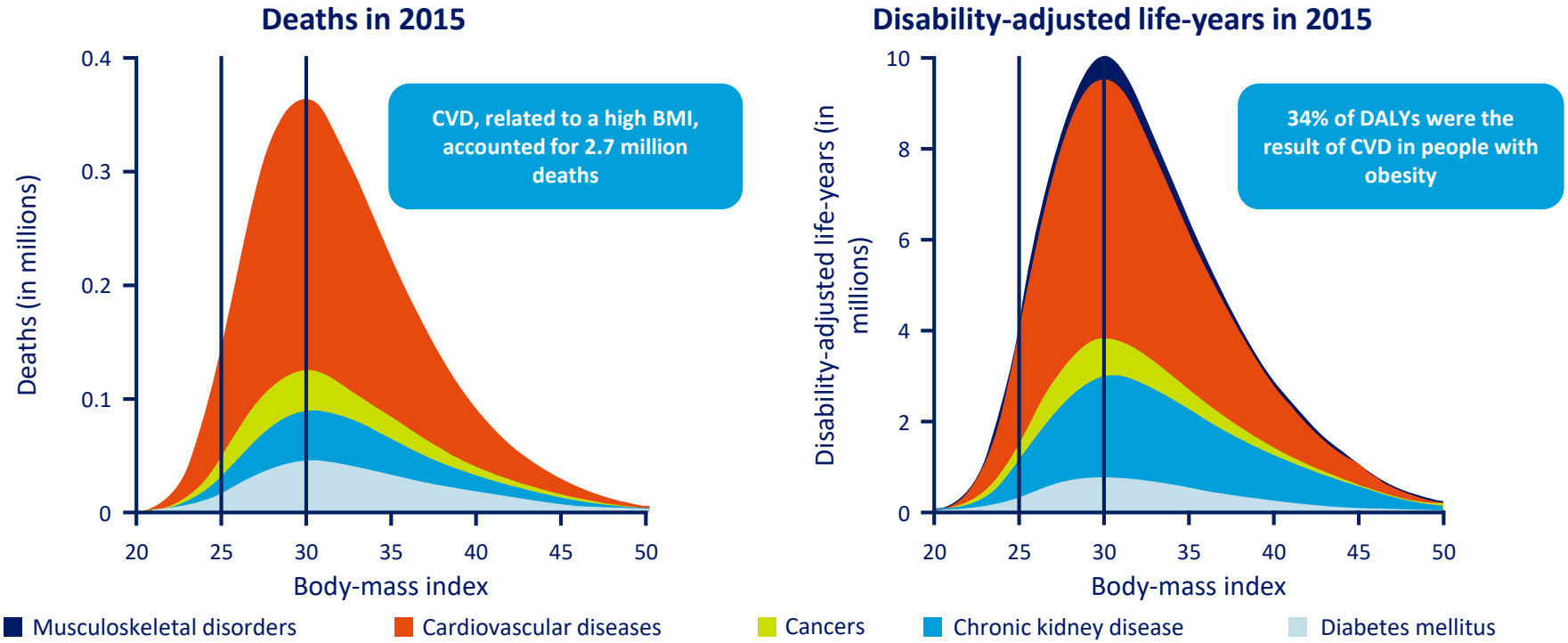
BMI 35–40 =
~60% chance of reaching age 70

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

Increasing BMI contributes to death and disability



CVD, cardiovascular disease, DALYs, disability-adjusted life-years

GBD 2015 Obesity Collaborators *N Engl J Med* 2017;377:13–27

Obesity is associated with multiple comorbidities and complications

Metabolic, mechanical and mental

Metabolic

Mechanical

Mental

Depression

Anxiety

Asthma

NAFLD

Gallstones

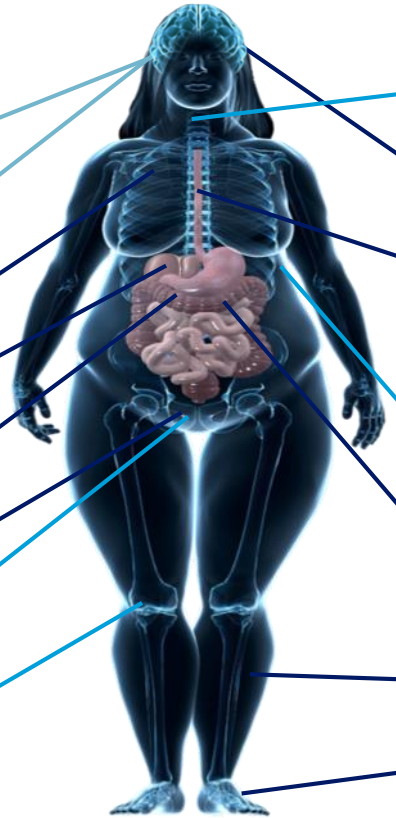
Infertility

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

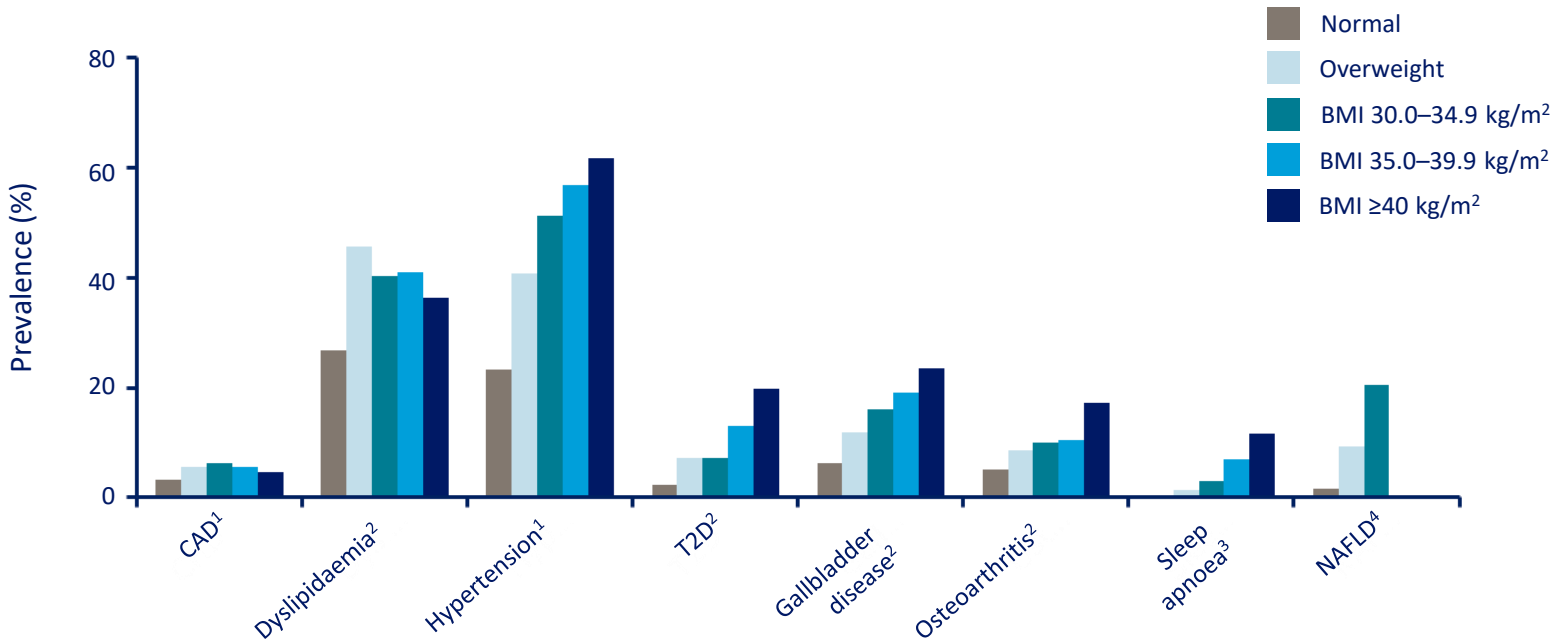
Thrombosis

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

The prevalence of obesity-related comorbidities generally increases with BMI

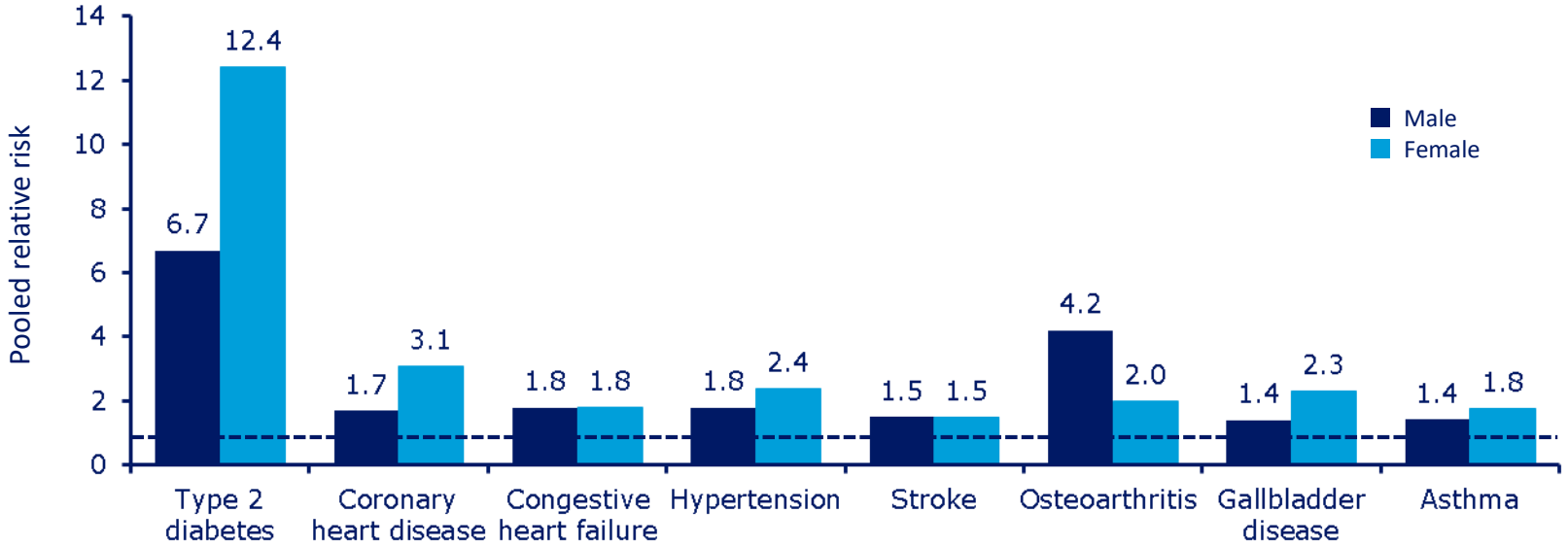


Data taken from the female[1,2,3] and male[4] population.
BMI, body mass index; CAD, coronary artery disease; NAFLD, non-alcoholic fatty liver disease; T2D, type 2 diabetes

1. Pantalone *et al. BMJ Open. 2017;7:e017583*; 2. Must *et al. JAMA* 1999;282:1523–9; 3. Li *et al. Prev Med* 2010;51:18–23;
4. Church *et al*. *Gastroenterology* 2006;130:2023–30

Obesity is associated with multiple comorbidities

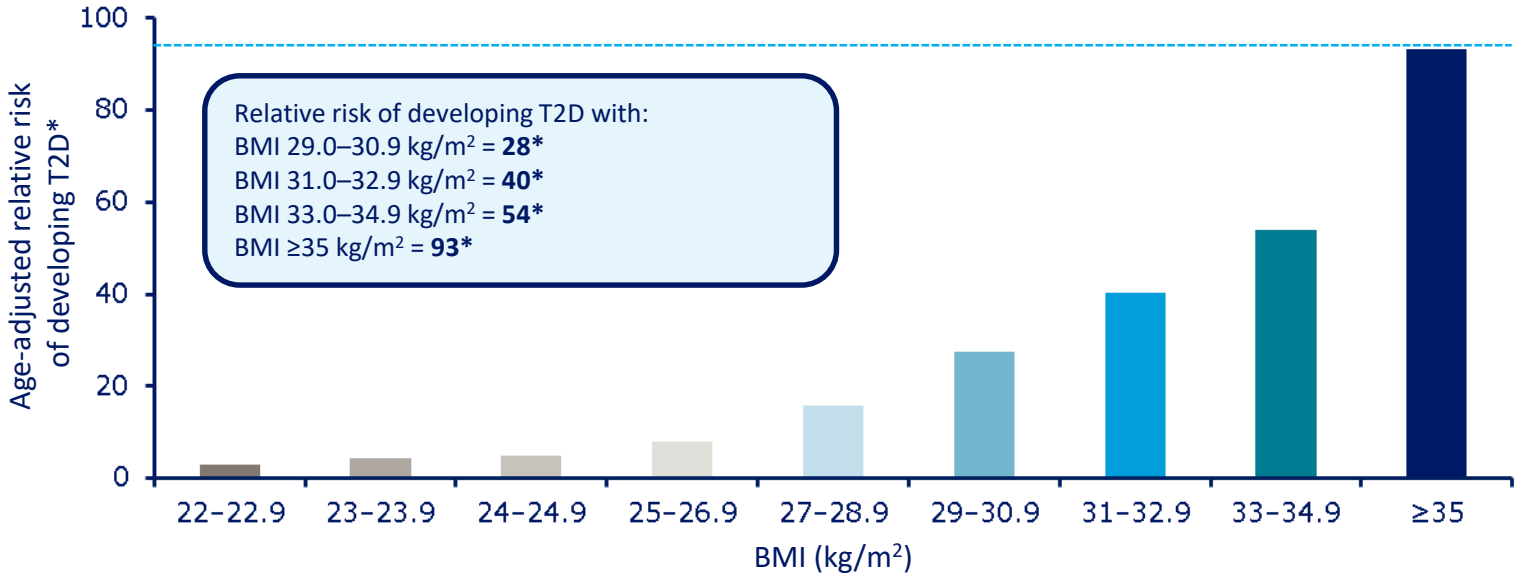
Relative risk of comorbidities compared to individuals with normal BMI



Study-specific unadjusted relative risks (RRs) on the log scale comparing overweight with normal and obesity with normal were weighted by the inverse of their corresponding variances to obtain a pooled RR with 95% confidence intervals (CI). Dotted line indicates relative risk in the normal population.

Guh *et al. BMC Public Health* 2009;9:88

Greater risk of developing T2D with higher BMI

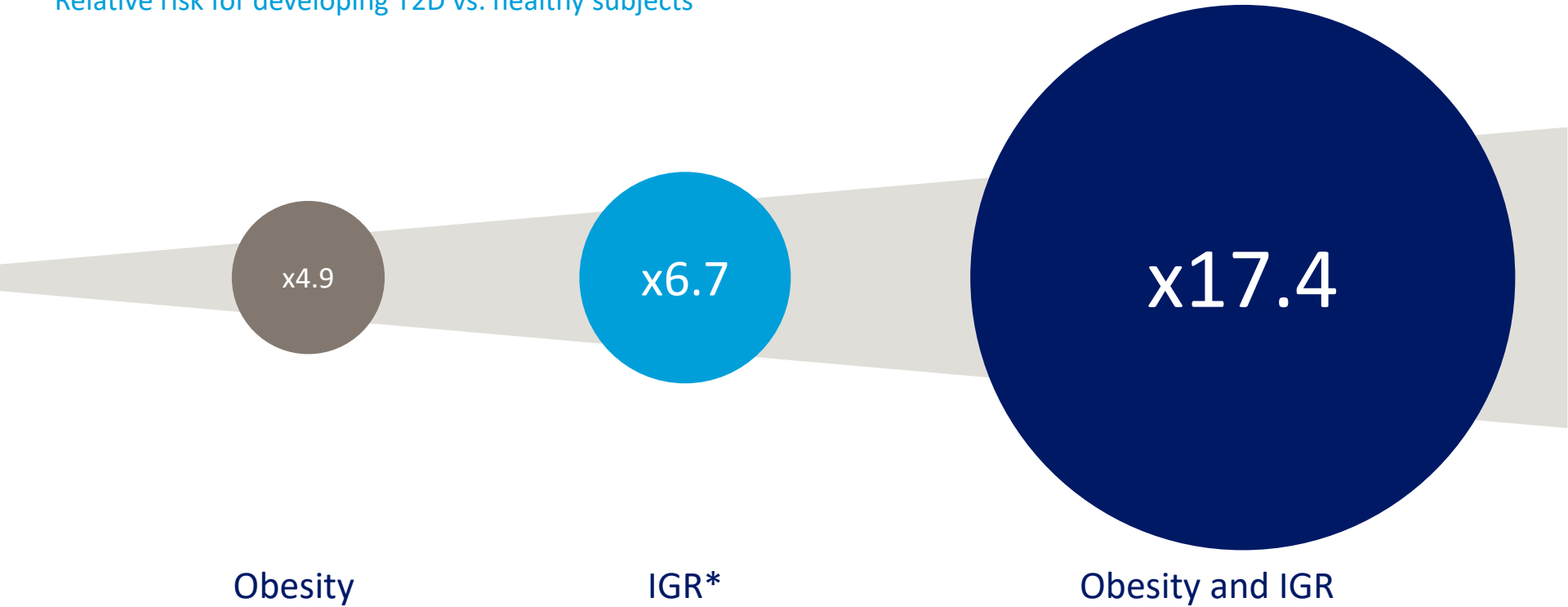


*vs. BMI <22 kg/m²; Data are for women only. n=114,281 female registered nurses aged 30–55 years; T2D, type 2 diabetes

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

Additive risk for T2D with obesity and IGR

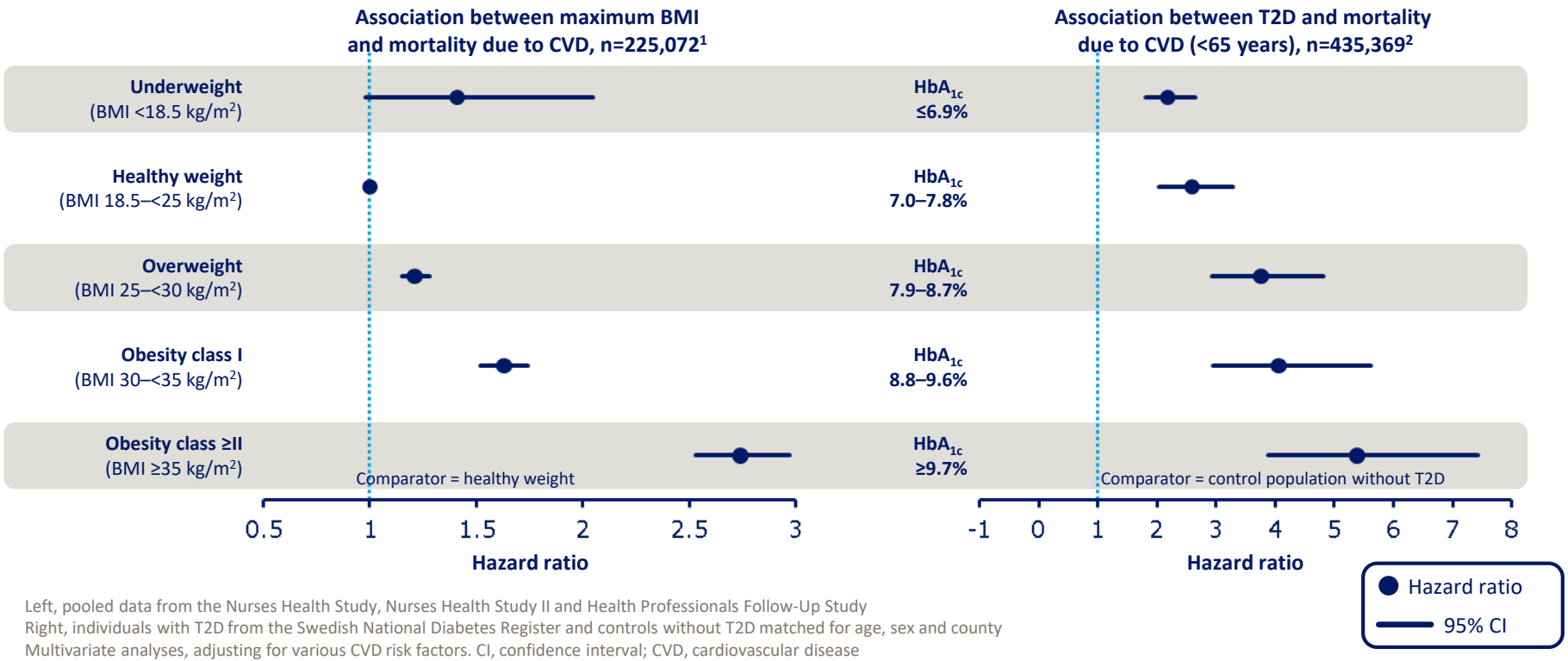
Relative risk for developing T2D vs. healthy subjects



n=4369. *Impaired glucose regulation: fasting plasma glucose concentration 110–126 mg/dL (6.1–6.99 mmol/L) and/or 2-hour plasma glucose concentration 140–200 mg/dL (7.8–11.09 mmol/L). IGR, impaired glucose regulation; T2D, type 2 diabetes

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

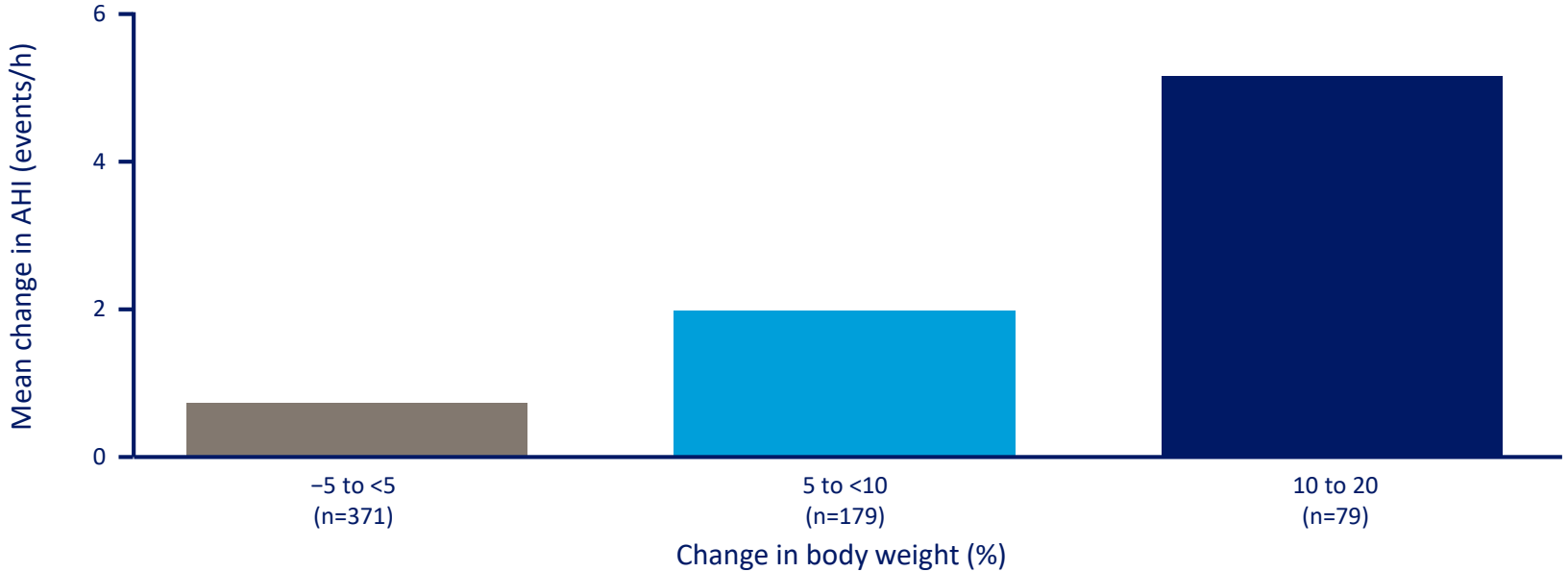
Greater risk of CVD mortality with increased BMI and HbA_{1c}



Left, pooled data from the Nurses Health Study, Nurses Health Study II and Health Professionals Follow-Up Study
Right, individuals with T2D from the Swedish National Diabetes Register and controls without T2D matched for age, sex and county
Multivariate analyses, adjusting for various CVD risk factors. CI, confidence interval; CVD, cardiovascular disease

1. Yu et al. Ann Intern Med 2017;166:613-620; 2. Tancredi et al. N Engl J Med 2015;373:1720–32

Weight gain increases severity of obstructive sleep apnoea: longitudinal study data

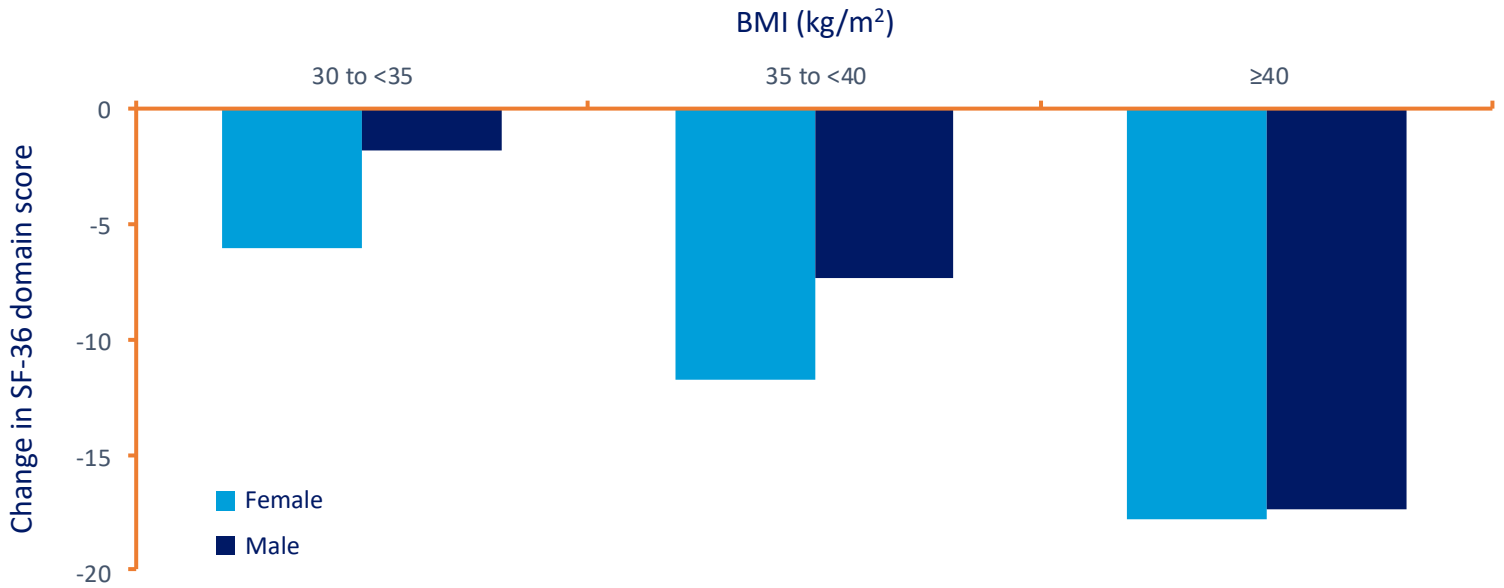


Sleep-disordered breathing includes a wide spectrum of sleep-related breathing abnormalities related to increased upper airway resistance include snoring, upper airway resistance syndrome (UARS), and obstructive sleep apnoea–hypopnoea. AHI, apnoea–hypopnoea index; CI, confidence interval

Peppard *et al. JAMA* 2000;284:3015–21

Obesity is associated with impaired physical function

When compared with normal weight (BMI 18.5–<25 kg/m^2)

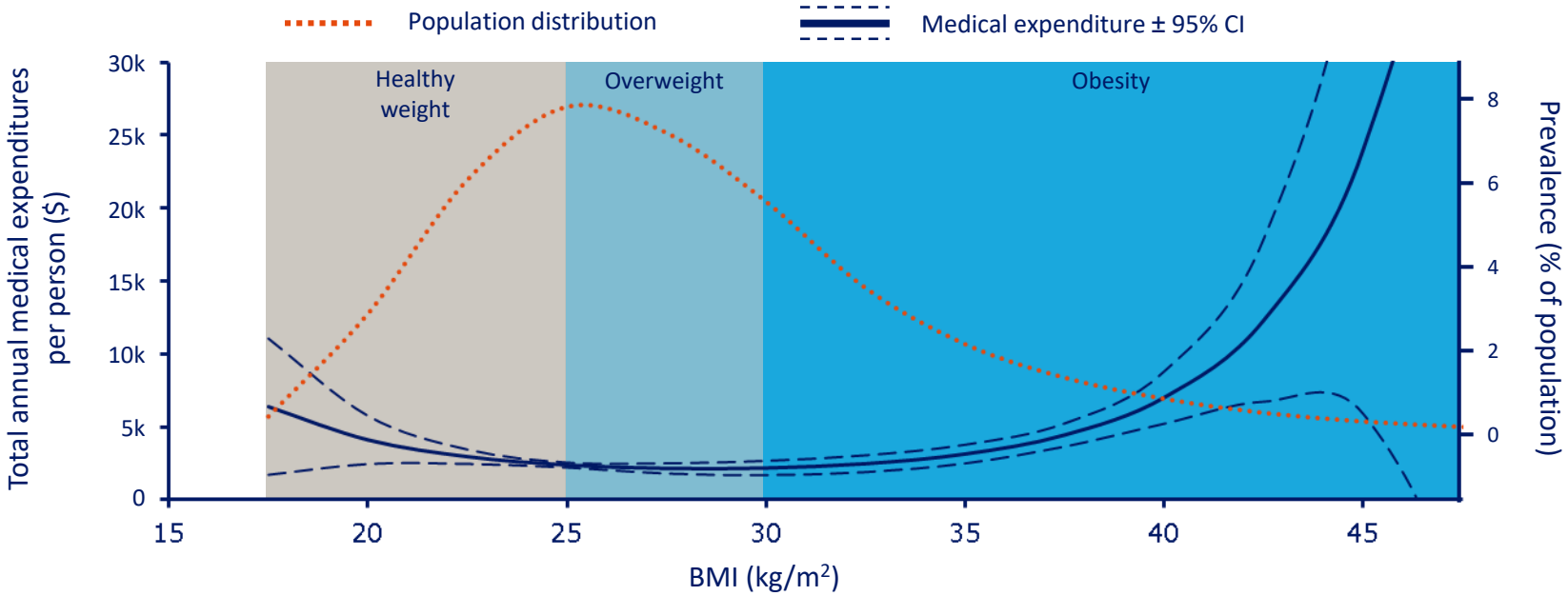


SF-36, Short Form-36

Hopman *et al. Qual Life Res* 2007;16:1595–603

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 comorbidities

Benefits of 5–10% weight loss

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

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

Greater weight loss further improves obesity-related complications

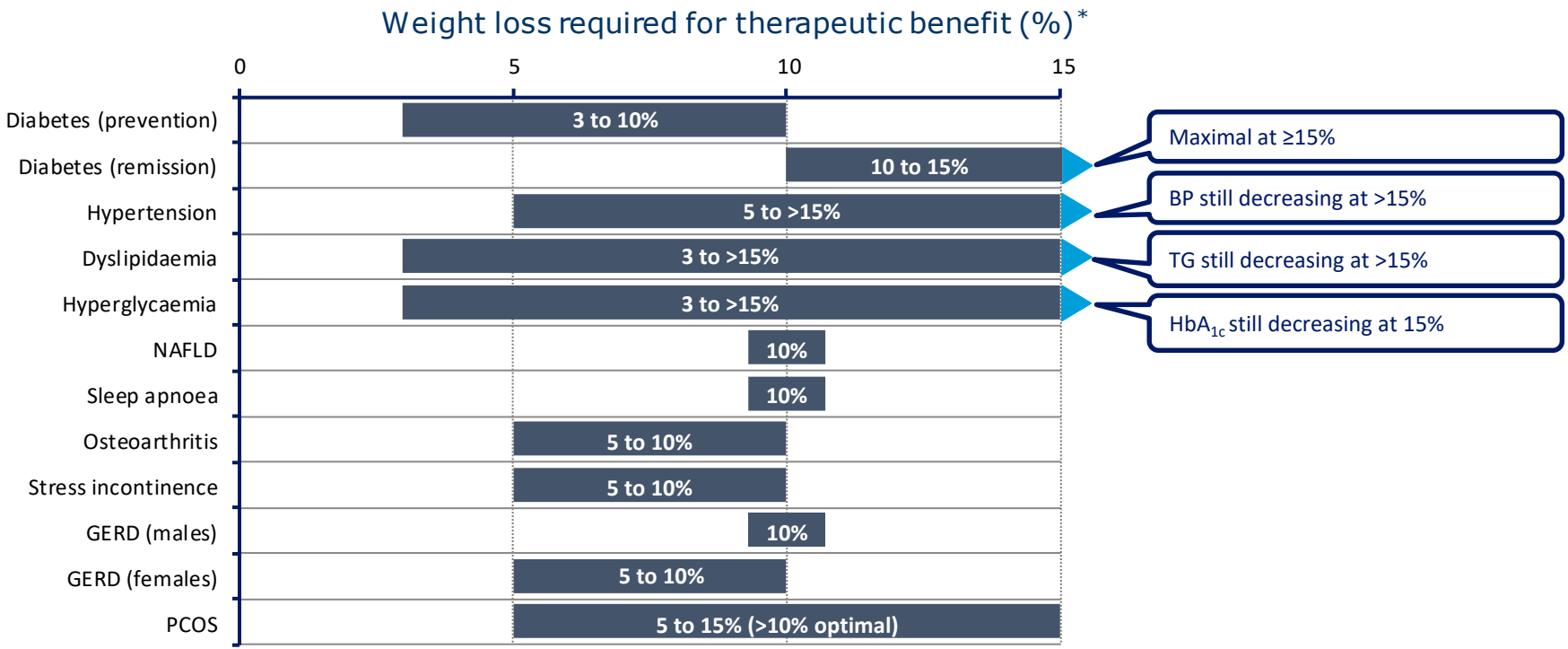


*Figure displays weight loss ranges examined in the studies (impact of >10% weight on NAFLD, and sleep apnoea symptoms was not reported). BP, blood pressure; TG, triglycerides; GERD, gastroesophageal reflux disease; NAFLD, non-alcoholic fatty liver disease; PCOS, polycystic ovary syndrome; TG, triglycerides

Cefalu *et al*. *Diabetes Care* 2015;38:1567–82; Lean *et al*. *Lancet* 2018;391:541–51

Gaps in obesity care

Results from the US ACTION study

PwO (n=3008)

- 82% consider weight loss to be completely their own responsibility
- Only 55% have received a formal diagnosis from their HCP
- Of those receiving a diagnosis, only 24% have a follow-up appointment

HCPs (n=606)

- Most HCPs down-prioritise weight loss discussions due to lack of time or more important matters
- HCPs set unrealistic weight loss targets with their patients (mean target of 19%)
- Little belief in the efficacy of weight loss medications and concerns about side-effects

HCP, healthcare provider; PwO, people with obesity

Kaplan *et al. Obesity (Silver Spring).* 2018;26:61-69

Summary

- Obesity is a chronic and complex medical condition associated with a large number of complications affecting most organs and systems through multiple pathways
- There is now considerable evidence that intentional weight loss is associated with clinically relevant benefits for the majority of these health issues
- Unfortunately , obesity remains underdiagnosed and undertreated


موفقّ باشید