Epidemiology and Comorbidities

1

Contents

Abbreviations

^{1}H-MRS	Proton magnetic resonance spectroscopy
AARP	American Association of Retired Persons
AGE	Advanced glycation end
ALT	Alanine aminotransferase
AMP	Adenosine monophosphate
AMPK	AMP-activated protein kinase
APACHE	Acute Physiology and Chronic Health Evaluation
AST	Aspartate aminotransferase

E. M. H. Mathus-Vliegen, J. Dargent, *Bariatric Therapy*,
https://doi.org/10.1007/978-3-319-90074-2_1

ATBC	Alpha-tocopherol beta-carotene
ATP	Adenosine triphosphate
BEACON	Barrett and Esophageal Adenocarcinoma Consortium
BIA	Body impedance analysis
BMI	Body mass index
COX	Cyclooxygenase
CRC	Colorectal cancer
CRP	C-reactive protein
CT	Computed tomography
CVD	Cardiovascular disease
DEXA	Dual-energy X-ray absorptiometry
EPIC	European Prospective Investigation into Cancer and Nutrition
ERCP	Endoscopic retrograde cholangiopancreaticography
ERK	Extracellular signal-regulated kinase
GI	Gastrointestinal
GORD	Gastro-oesophageal reflux disease
GTT	Glucose tolerance test
H. pylori	*Helicobacter pylori*
HCC	Hepatocellular carcinoma
HDL	High-density lipoprotein
HFCS	High-fructose corn syrup
HMW	High molecular weight
HOMA	Homeostatic model assessment
Hp	*Helicobacter pylori*
HR	Hazard ratio
IGF-1	Insulin-like growth factor-1
IGFBP	Insulin-like growth factor-binding protein
IHTG	Intrahepatic triglyceride content
IL	Interleukin
IR	Insulin resistance
LCD	Low-calorie diet
LDL	Low-density lipoprotein
LMW	Low molecular weight
LOS	Lower oesophageal sphincter
LOSP	Lower oesophageal sphincter pressure
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
MetS	Metabolic syndrome
MMW	Middle molecular weight
MOD	Multi-organ dysfunction
MOF	Multiple organ failure
MR	Magnetic resonance
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
MUFA	Mono-unsaturated fatty acid
NAFL	Non-alcoholic fatty liver
NAFLD	Non-alcoholic fatty liver disease

NAS	NAFLD Activity Score
NASH	Non-alcoholic steatohepatitis
NCD-RisC	NCD Risk factor collaboration
NCI	National Cancer Institute
NDDM	non-insulin dependent diabetes mellitus
Nf-κB	Nuclear factor kappa B
NHANES	National Health and Nutrition Examination Survey
NHI	National Institutes of Health
NSAID	Non-steroidal anti-inflammatory drug
OGD	Oesophagogastroduodenoscopy
OR	Odds ratio
PAI	Plasminogen activator inhibitory protein
PCOS	Polycystic ovary syndrome
PI3K	Phosphatidyl inositol 3-kinase
PAR	Peroxisome proliferator-activated receptor
PET	Position emission tomography
PUFA	Polyunsaturated fatty acid
PYY	Polypeptide Y
RR	Relative risk
ROS	Reactive oxygen species
SAT	Subcutaneous adipose tissue
SEER	Surveillance epidemiology and end results
SHBG	Sex hormone binding globuline
SIM	Specialised intestinal metaplasia
SIR	Standardised incidence ratio
SIRS	Systemic inflammatory response syndrome
SRR	Summary relative risk
T2DM	Type 2 diabetes mellitus
TNF-α	Tumour necrosis factor-alpha
TLOSR	Transient lower oesophageal sphincter relaxation
US	Ultrasound
VAT	Visceral adipose tissue
VEGF	Vascular endothelial growth factor
VLCD	Very-low-calorie diet
VLDL	Very-low-density lipoprotein
WHO	World Health Organisation
WHR	Waist-to-hip ratio

1.1 Introduction and Epidemiology

Overweight and obesity have reached epidemic proportions and globally there are now more people who are obese than underweight. This is the case in every region except parts of sub-Saharan Africa and Asia [1]. In 2014 266 million men and 375 million women were obese compared to only 34 million men and 71 million women in 1975 and 58 million men and 126 million women suffered from severe obesity.

In 2016 the Non-Communicable Disease Risk factor Collaboration (NCD-RisC) evaluated 1698 population-based worldwide data sources from 200 countries with more than 19.2 million (9.9 million men and 9.3 million women) participants aged 18 years and older to estimate trends in overweight and obesity from 1975 to 2014 [1]. Over this period the global age-standardised mean Body Mass Index (BMI) in men increased from 21.7 kg/m^2 in 1975 to 24.2 kg/m^2 in 2014, and in women from 22.1 kg/m^2 to 24.4 kg/m^2. The mean increases per decade were 0.63 kg/m^2 for men and 0.59 kg/m^2 for women, signifying an increase in body weight per decade of 1.5 kg. There were large regional differences. The largest increase in men's mean BMI was in high-income English-speaking countries and in women in central Latin America. The prevalence of obesity (BMI ≥30 kg/m^2) increased from 3.2% in 1975 to 10.8% in men and from 6.4% to 14.9% in women (Fig. 1.1). Severe obesity (BMI ≥35 kg/m^2) was present in 2.3% of men and in 5.0% of women and morbid obesity (BMI ≥40 kg/m^2) in 0.64% and 1.6%, respectively. In 2014 more men were obese in 68% of 200 countries and severely obese in 56.5% of countries than underweight. Similar data were 83% and 67.5%, respectively, for women. In 2014 slightly more obese people live in China than in the USA and China moved to the second rank for severe obesity. Notwithstanding this, more than one out of four severely obese men and almost one in five severely obese women in the world live in the USA.

The probability of reaching the global target of halting the rise in obesity by 2025 at the 2010 obesity level is virtually zero. By 2025, the global obesity prevalence will reach 18% in men and surpass 21% in women and severe obesity will surpass 6% in men and 9% in women. If recent trends continue it has been estimated that in 2030 60% of the world's population will be overweight with 3.3 billion people of whom 2.2 billion are overweight and 1.1 billion are obese.

Forty-one million children under the age of five were overweight or obese in 2014 [2, 3]. In Africa, the number of children who are overweight or obese has nearly doubled from 5.4 million in 1990 to 10.6 million in 2014. Nearly half of the children under five who were overweight or obese in 2014 lived in Asia. In European countries the prevalence of overweight and obesity in adults is 50% [4, 5]. Within the range of obesity the segment with a BMI ≥35 kg/m^2 is rapidly growing. In the USA a BMI >35 kg/m^2 is present in 15% of the adult population.

These alarming data signify an enormous burden of well-known obesity-associated diseases such as type 2 diabetes mellitus (T2DM), hypertension, dyslipidaemia, metabolic syndrome, cardiovascular disease, sleep apnoea syndrome and certain cancers. Overweight and obesity are the strongest established risk factor for diabetes which is associated with a 2–3-fold increased risk of mortality [6]. The International Diabetes Federation (IDF) estimated that the cost of caring for diabetes worldwide was at least $673 billion in 2015. The NCD-RisC also estimated the trend in diabetes between 1980 and 2014, without differentiating between type 1 and type 2 diabetes, in 751 studies including almost 4.4 million participants [7]. Global age-standardised diabetes prevalence doubled from 4.3% in 1980 to 9.0% in men and increased by 60% from 5.0% to 7.9% in women. The number of adults with diabetes increased from 108 million in 1980 to 422 million in 2014, a near quadrupling of the number of adults. This impressive increase could be explained for 28.5% due to the rise in prevalence, 39.7% due to population growth and 31.8%

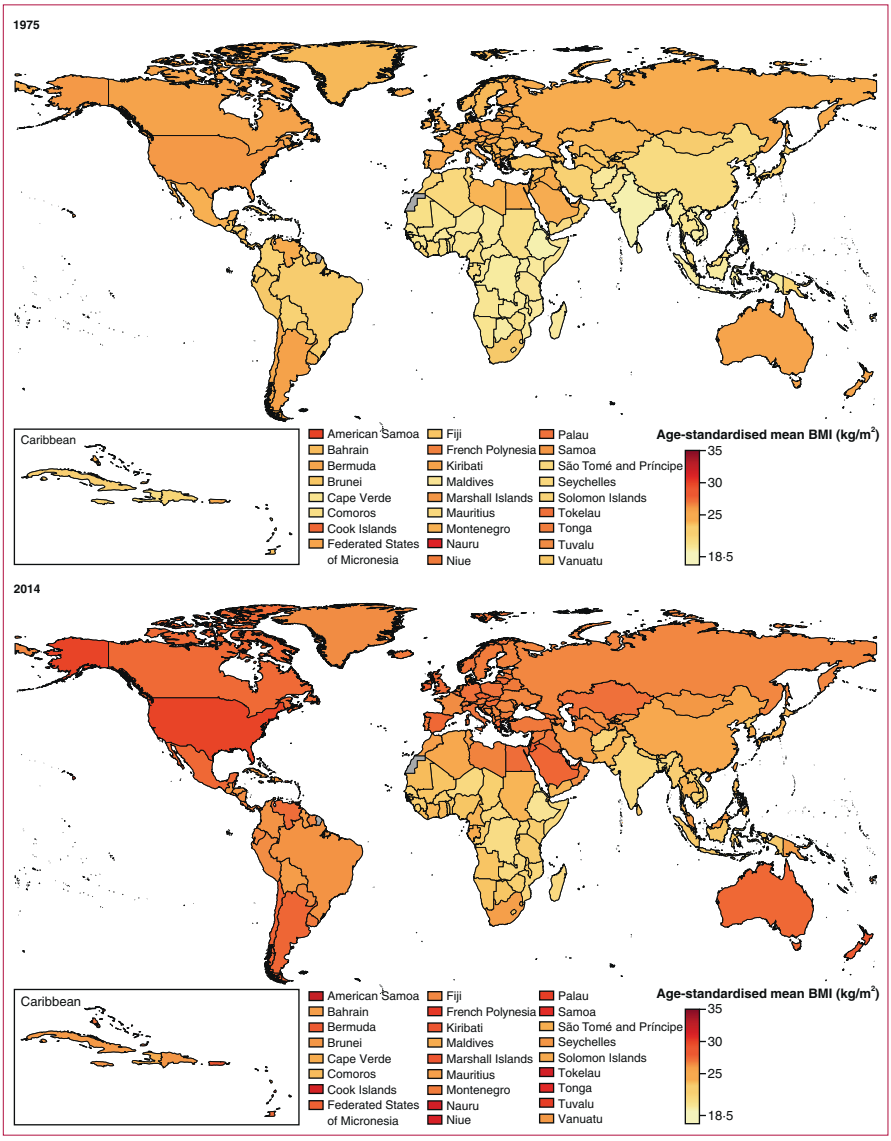

Fig. 1.1 Age-standardised mean BMI in women in 1975 and 2014 worldwide (printed with permission of the editors of the Lancet) [1]

due to the interaction of these two factors. The probability of reaching the goal of halting diabetes at the 2010 level in 2025 is less than 1% in men and is 1% in women. If the trend continues the age-standardised prevalence of diabetes by the year 2025 will be 12.8% in men and 10.4% in women, surpassing a number of 700 million people.

Obesity is an established risk factor for at least ten cancers (oesophagus adenocarcinoma; liver, gallbladder, colorectum and pancreas cancer; kidney

cancer; and in males advanced prostate cancer and in females postmenopausal breast cancer and cancer of the endometrium and ovaries) [8]. Besides the already mentioned gastrointestinal (GI) cancers, the GI tract is involved with gastro-oesophageal reflux disease (GORD) with its complications of erosive oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma, gallstone disease, acute pancreatitis, non-alcoholic fatty liver disease (NAFLD) and colon adenomas.

Apart from these serious comorbidities which may lead to a reduced life expectancy, a range of debilitating conditions such as osteoarthritis, respiratory difficulties, infertility and psychosocial problems, with stigmatisation and discrimination, have a negative impact on the quality of life and result in work absenteeism and disability. Both the life-threatening comorbidities and the impaired quality of life are depicted in the obesity web (Fig. 1.2). Obesity is responsible for 10–13% of deaths. Furthermore, the WHO has emphasized that 44% of T2DM burden, 23% of ischaemic heart disease burden and 7–41% of certain cancer burdens are related to overweight and obesity [2]. In European countries overweight and obesity are

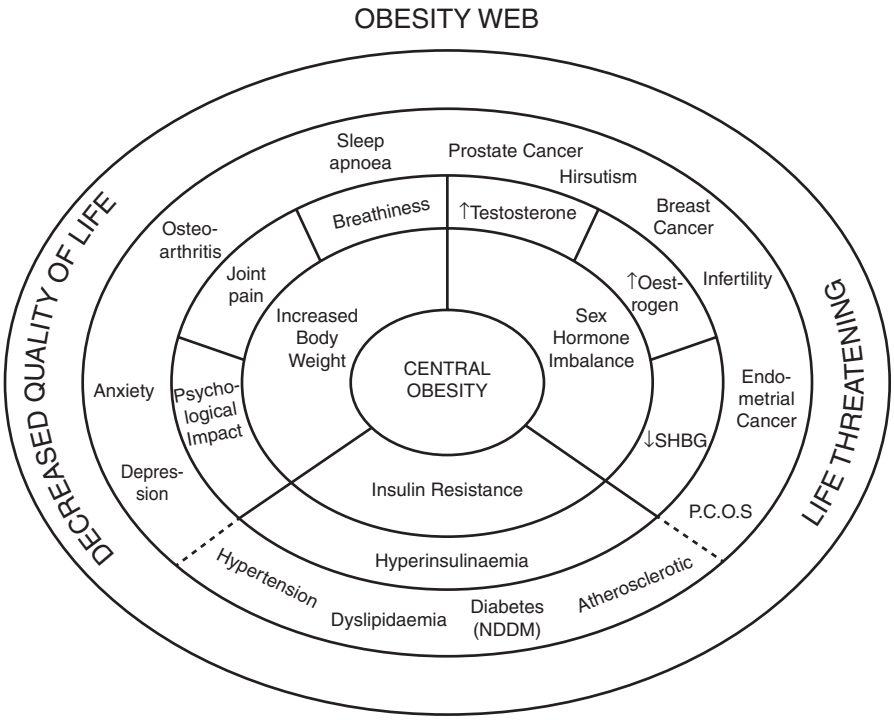

Fig. 1.2 The obesity web illustrates the diverse range of conditions associated with obesity. Furthermore it shows how these conditions are linked in terms of physiological and biochemical mechanisms and how obesity and central obesity may threaten health and cause a decreased quality of life

responsible for 80% of cases of T2DM, 35% of ischaemic heart disease and 55% of hypertension among adults [4].

1.2 Definition and Classification

The term overweight refers to an excess of body weight in relation to height and–in children–age [9]. An excess of body weight may involve water, muscle, osseous and adipose tissue but most overweight people will have an excess of adipose tissue. The terms obesity and adiposity refer specifically to an absolute or a relative excess in body fat mass. This excess fat storage, in addition to the way in which the fat is distributed in the body, places the individual at risk of premature death and many obesity-associated comorbidities. Quantification of the amount of adipose tissue and its distribution is important. For everyday use the body mass index (BMI, calculated by dividing weight in kilogram by height in meters squared, kg/m^2) suffices, which is largely independent of height and, at least in adult Caucasians, correlates closely with the mass of body fat.

The World Health Organisation (WHO) classified people according to their BMI into classes of underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight or pre-obesity (BMI 25.0–29.9 kg/m^2) and obesity (BMI ≥30 kg/m^2) with obesity class I (BMI 30–34.9 kg/m^2), class II (BMI 35.0–39.9 kg/m^2) and class III (≥40 kg/m^2) (Table 1.1) [10–14]. For Asian countries different BMI categories have been defined as a similar level of BMI in South East Asians is associated with higher risks of comorbidities than in Caucasians [10–14]. The threshold for obesity is 2 kg/m^2 lower (Table 1.1). The term morbid obesity refers to the category of BMI ≥40 kg/m^2.

BMI is known to be an imperfect predictor of metabolic risks [15]. Some individuals with a normal BMI have a metabolic pattern characteristic of those with overweight or obesity. Some with high BMI appear to have a healthy metabolic pattern, the so-called healthy obese, suggesting that the disease risks associated with obesity may not be uniform and that apparently a subgroup of obese patients is resistant to the development of obesity-associated diseases [16]. The meta-analysis by Kramer and colleagues tried to determine the effect of the metabolic status on all-cause mortality and cardiovascular events in adults with data available on the three categories of BMI, all-cause mortality, fatal and non-fatal cardiovascular events and being metabolically healthy or unhealthy defined by the presence of metabolic syndrome components [17, 18]. A total of 61,386 persons in 8 studies, followed over 10 years or more, were included. They concluded that metabolically unhealthy persons, regardless of BMI, were at 2.5–3 times increased risk of death. However, the metabolically healthy obese group was also at risk, although the risk was smaller, 24% higher, thereby casting doubt on the existence of metabolically healthy obesity [17, 18]. Unfortunately, carefully conducted basis scientific studies that tried to determine the beneficial phenotype of obesity were not considered such as studies with euglycaemic insulin clamps and studies with careful measurement of total body, visceral and subcutaneous fat by

Table 1.1 Comparison of cut-offs of BMI, waist circumference and several components of the metabolic syndrome in Western and Asian countries [10–14]

	Western countries	Asian countries[a]
BMI normal weight	18.5–24.9 kg/m^2	18.5–22.9 kg/m^2
BMI overweight	25–29.9 kg/m^2	23.0–27.4 kg/m^2
BMI obesity	≥30 kg/m^2	≥27.5 kg/m^2
BMI obesity class I	30–34.9 kg/m^2	27.5–32.4 kg/m^2
BMI obesity class II	35–39.9 kg/m^2	32.5–37.4 kg/m^2
BMI obesity class III/morbid obesity	≥40 kg/m^2	≥37.5 kg/m^2
BMI obesity super-morbid obesity	≥50 kg/m^2	
Waist circumference, males Overweight Obese	 ≥94 cm ≥102 cm	
Waist circumference, females Overweight Obese	 ≥80 cm ≥88 cm	
Metabolic syndrome		
Waist circumference, males	≥94 cm	≥90 cm
Waist circumference, females	≥80 cm	≥80 cm
Arterial blood pressure	≥130/85 mmHg or treatment for hypertension	≥130/85 mmHg or treatment for hypertension
Fasting glucose	≥5.6 mmol/L or treatment for T2DM	≥5.6 mmol/L or treatment for T2DM
Serum triglycerides	≥1.7 mmol/L or treatment for hyperlipidaemia	≥1.7 mmol/L or treatment for hyperlipidaemia
HLD cholesterol levels, males	<1.03 mmol/L or treatment	<1.03 mmol/L or treatment
HLD cholesterol levels, females	<1.29 mmol/L or treatment	<1.29 mmol/L or treatment

[a]Threshold BMI for obesity in South Asians being 2 kg/m^2 lower and waist being 10 cm smaller

magnetic resonance (MR) imaging (MRI) and those measuring fat in muscle and liver by MR spectroscopy [19, 20]. Moreover, a relatively large fat mass may mask a small muscle mass, a condition known as sarcopenic obesity. The sole use of BMI may thus aggregate different people with differences in nutritional status, disability, disease and mortality risk.

Likewise, the surplus value of the distribution of fat is more and more appreciated [9]. Subcutaneous fat in peripheral parts of the body, also named peripheral, gynoid, femorogluteal or lower body obesity, is physiological and not associated with health hazards. In contrast, increased intra-abdominal and visceral fat, also named central, android, abdominal or upper body obesity, is associated with increased health risks. An estimation of the distribution of adipose tissue can be obtained by body circumference measurements, such as the waist circumference, measured halfway the lower rib cage and the upper crest of the pelvis (in cm), or the waist/hip circumference ratio (WHR), in which the waist circumference is divided by the hip circumference, measured over both femur condyles. As such, a waist circumference of 80–88 cm in females and 94–102 cm in males corresponds with overweight [21]. In patients with a BMI between 25 and 34.9 the

measurement of the waist wand waist-to-hip ratio are recommended by current guidelines. Cut-off values to define abdominal obesity and to identify persons at risk are 102 cm for men and 88 cm for women and for the WHR ratio 1.0 in men and 0.85 in women [9, 21]. The WHR is presumably a more specific surrogate for the fat distribution as the WHR is less strongly correlated with BMI as is the waist circumference but mostly the use of the waist circumference has been proposed [9, 21]. In Asians these measures are different: the waist is 10 cm smaller. This has also implications for the definition of the metabolic syndrome, which clusters components predictive for cardiovascular diseases, and which requires the presence of visceral obesity defined by the waist circumference combined with at least two other factors [13]. For Asian populations the new definition for the metabolic syndrome which includes the waist circumference is mentioned in Table 1.1 [11, 12, 14].

Methods to better quantify the absolute amount of adipose tissue and its location are either expensive or only feasible in the context of scientific research [9]. Examples of sometimes readily available methods are ultrasonography, body impedance analysis (BIA), computed tomography (CT), magnetic resonance imaging (MRI) and dual-energy X-ray absorptiometry (DEXA). Magnetic resonance spectroscopy allows the determination of fatty tissues in liver and muscle. Hydrodensitometry and isotope dilution and neutron activation methods are mainly available for scientific purposes and the same holds true for position emission tomography (PET) method to demonstrate brown adipose tissue.

1.3 Pathogenesis of Comorbidities

Treatment of obesity is more than a reduction of excess fat; it is also the treatment of obesity's comorbidities. To better understand the pathogenesis of these comorbidities, both the mechanical load by the excess body mass and the role of the adipose tissue itself should be taken into consideration.

Adipose tissue is no longer considered to be an inert tissue. Brown adipose tissue, being found principally in neonates but also in the neck-scapular region in adults with distinct differences between normal-weight and obese individuals, is mainly involved in the temperature regulation [22–24]. When exposed to cold, for instance 16 °C, the energy expenditure increases by approximately 160 kcal per day and this is likely through brown adipose tissue thermogenesis [23, 24]. White adipose tissue is now considered to constitute an endocrine organ in its own right, being an important mediator of metabolism and inflammation [25, 26] (Fig. 1.3). It secretes adipokines which are divided into *hormone-like adipokines* such as leptin, resistin, adiponectin, visfatin, apelin, vaspin, hepcidin, chemerin, omentin and angiopoietin-like peptide 4, and *inflammatory cytokines*, which include tumour necrosis factor alpha (TNF-α), interleukins such as interleukin-1 (IL-1), IL-6 and IL-10, plasminogen activator protein (PAI) and monocyte chemoattractant protein-1 (MCP-1).

	Effects	Pathways	Involved adipokines and cytokines
White adipose tissue	Metabolism	Energy homeostasis	Leptin, IL-6, IL-1, IL-1Ra
		Adipocyte differentiation	TNF-α, MCP-1, IL-1, IL-1Ra, IL-6
		Insulin sensitivity	IL-1, IL-1Ra, IL-6, TNF-α
	Inflammation	Inflammatory control	IL-1, IL-1Ra, IL-6, IL-8, IL-9, IP-10, TNF-α, MCP-1, PAI, RANTES
		Cardiovascular protection/ Neo-angiogenesis	Adiponectin, IL-1, IL-1Ra, IL-10, VEGF, Leptin, TNF-α
		Vascular inflammation	IL-8, IL-10, MCP-1, RANTES, Resistin

Fig. 1.3 The effects of white adipose tissue on metabolism and inflammation through different pathways with involved adipokines and cytokines [25, 26]. *IL* interleukin, *TNF-α* tumour necrosis factor-alpha, *MCP-1* monocyte chemoattractant protein-1, *PAI* plasminogen activator inhibitory protein, *RANTES* regulated upon activation normal T-cell sequence, *VEGF* vascular endothelial growth factor, *IP-10* interferon-gamma inducible protein 10

These adipokines and cytokines are involved in energy homeostasis, adipocyte differentiation and insulin sensitivity, and thereby have their effect on metabolism. They also exert their influence on inflammation through pathways of inflammatory control, cardiovascular protection, angiogenesis and vascular inflammation. Some hormone-like adipokines and inflammatory cytokines, that are mentioned in a large number of studies, need some more detailed discussion [25, 26].

1.3.1 Hormone-Like Adipokines

Through the hypothalamus *leptin* modulates body weight, food intake and fat stores. High levels of leptin, related to the large fat mass in the obese, do not suppress the appetite because of resistance to the hormone due to leptin receptor signalling defects, downstream blockade in neuronal circuits and defects in leptin transport across the blood-brain barrier. Furthermore, leptin regulates pancreatic islet cell growth, growth hormone levels, immune homeostasis, haematopoiesis, angiogenesis, wound healing, osteogenesis and gastrointestinal function.

Adiponectin has anti-proliferative and anti-atherosclerotic properties and is an antioxidant by decreasing reactive oxygen; it augments endothelial nitrous oxygen production protecting the vasculature by vasodilation and reduced platelet aggregation. Adiponectin concentrations are markedly declined in morbid obesity and a wide array of diseases such as stroke, coronary heart disease, insulin resistance, non-alcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH), and many obesity-related cancers have been associated with decreased adiponectin levels.

	Location	Secretion of	Effects
Local white adipose tissue deposits	Visceral	IL-8, IP-10, MCP-1, RANTES	Local and systemic inflammation
	Muscle	TNF-α, FFA, IL-6	Insulin resistance
	Epicardial	IL-6, IL-1b, TNF-α, MCP-1	Local inflammation and chemotaxis
	Perivascular	IL-1/ IL-1Ra, IL-6, IL-8, IP-10, MCP-1, TNF-α, RANTES	Atherosclerosis and systolic hypertension
	Kidney	Reabsorption of sodium	Increased vascular volume, hypertension

Fig. 1.4 Local effects of white tissue and their secretory products on metabolism and inflammation [25, 26]. *IL* interleukin, *IP-10* interferon-gamma inducible protein 10, *MCP-1* monocyte chemoattractant protein-1, *RANTES* regulated upon activation normal T-cell sequence, *TNF-α* tumour necrosis factor-alpha, *FFA* free fatty acids

1.3.2 Inflammatory Cytokines and Anti-inflammatory Factors

Inflammatory cytokines can be divided into adipocytokines (leptin, resistin, visfatin, adiponectin), interferons (interferon gamma, beta), interleukins (IL-1, IL-5), haematopoietic factors, chemokines (IL-6, IL-10, MCP-1) and growth factors (TNF-α). TNF-α, IL-1 and IL-6 influence growth and immunity, and initiate inflammation, apoptosis and cell division. Anti-inflammatory factors include anti-inflammatory cytokines (IL-4, IL-10, tumour growth factor beta (TGF-β)), receptor antagonists (IL-1Ra), soluble receptors (IL-1RII, sTNFR, sIL-1R) and adipocytokines (adiponectin).

Adding to the complexity is the fact that different fat depots in the body play secrete different sets of adipokines [25, 26] (Fig. 1.4). Whereas visceral adipose tissue can influence both systemic and local inflammatory processes, muscular fat deposits figure more prominently with insulin resistance. Perivascular fat can facilitate the development of atheromas and perirenal fat can contribute to hypertension. In contrast to lean subjects who have normal-sized adipocytes with normal numbers of macrophages with high adiponectin and low leptin levels, obese patients have large adipocytes, more macrophages in their adipose tissue and more apoptotic adipocytes with low adiponectin levels and high leptin levels, promoting atherosclerosis and decreased insulin responsiveness or insulin resistance in liver and muscle.

1.4 Decreased Life Expectancy and Mortality

Most of the curves depicting mortality in relationship to increasing BMI values show a J-shaped or U-shaped configuration with excess mortality at both extremes of BMI values, i.e. underweight defined by a BMI <18.5 and overweight/obesity defined by a BMI ≥25 kg/m^2. Reverse causation explains the death at lower BMIs

as pre-existent chronic disease and inadequate control for smoking status can distort the true relation between body weight and risk of death. Smoking is associated with a lower BMI and an increased risk of death and pre-existing disease is linked to both decreased weight and increased risk of death. The studies that investigated the cause of death at low BMIs found mainly a higher mortality from non-cancer, non-cardiovascular diseases such as acute or chronic respiratory diseases, infectious disease and injuries or a higher mortality from cardiovascular disease [21, 27–29]. Others have suggested that the higher mortality is a detrimental effect of a low BMI per se.

In the Framingham Heart Study (1948–1990) life expectancy and premature death before 70 years of age were measured in overweight and obese subjects [30]. Because of being overweight, 40-year-old female non-smokers lost 3.3 years and 40-year-old male non-smokers lost 3.1 years of life expectancy and because of obesity the lost years of life were 7.1 and 5.1 years, respectively. Obese women were 115% more likely and obese men 81% more likely to die before age 70. Obese female smokers lost 7.2 years and obese male smokers lost 6.7 years when compared with normal-weight 40-year-old smokers. The survival advantage by non-smoking in the obese was rather small. Obese female smokers lost 13.3 years and obese male smokers lost 13.7 years when compared with normal-weight non-smokers. So, the double burden of obesity and smoking resulted in losing 13–14 years of life expectancy. These data were confirmed in the large Prospective Studies Collaboration publication with a reduced life expectancy by 2–4 years at BMI 30–35 and by 8–10 years at BMI 40–45 [28].

There are not many studies that investigated the effect of both overall and abdominal adiposity. In the European Prospective Investigation into Cancer and Nutrition (EPIC) with a mean follow-up of 9.7 years in 359,387 subjects the lowest mortality was observed at a BMI of 25.3 for men and 24.3 for women and in smokers at a lower BMI of 24.5 for men and 23.9 for women [21]. After adjustment for BMI, relative risks (RR) for death in the highest quintile of waist (≥102.7 cm in males and ≥89.0 cm in females vs., respectively, <86.0 and <70.1 cm) were 2.05 (95% confidence interval 1.80/2.33) for men and 1.78 (1.56/2.04) for women. In the highest quintile of waist-to-hip ratio the relative risks of death were 1.68 (1.53/1.84) for men and 1.51 (1.37/1.60) for women. BMI remained significantly associated with the risk of death in models that included waist and waist/hip ratio. So, both general and abdominal adiposities are associated with an increased risk of death. For a given BMI an increase in waist by 5 cm increased the risk for death with 17% (1.15/1.20) among men and by 13% (1.11/1.15) among women. Similarly, by a given BMI an increase by 0.1 in WHR resulted in an increased death rate of 1.34 (1.28/1.39) for men and 1.24 (1.20/1.29) for women. Alarmingly, the associations of waist and WHR tended to be stronger in the lower BMI category: among men and women of normal weight the relative risks of death in the highest quintile of waist were, respectively, 2.06 (1.32/3.20) and 1.79 (1.39/2.31) and in the highest quintile of WHR, respectively, 1.79 (1.53/2.10) and 1.53 (1.34/1.75), again emphasising the fact that even normal-weight subjects may be at risk when a visceral fat distribution is present.

The Prospective Studies Collaboration publication of 57 studies with almost 900,000 adults gives more details about the effect of stepwise higher BMI values [28]. In both sexes the mortality was lowest at about BMI 22.5–25 kg/m^2. Each 5 kg/m^2 higher BMI was associated with at least 5 mmHg higher systolic blood pressure and about 4 mmHg higher diastolic blood pressure; it was inversely associated with HDL cholesterol (0.16 mmol/L lower in males and 0.14 mmol/L lower in females) and therefore strongly positively related with the ratio of non-HDL to HDL (males 0.85, females 0.54 higher per 5 kg/m^2). Moreover, each 5 kg/m^2 higher BMI was on average associated with about a 30% higher overall mortality (hazard ratio (HR) per 5 kg/m^2 1.29 (1.27/1.32)), a 40% higher vascular mortality (HR 1.41 (1.37/1.45)), a 40% higher ischaemic heart mortality (1.39 (HR 1.34/1.44)) and a 40% higher stroke mortality (HR 1.39 (1.31/1.48)). In the BMI range of 25–50 kg/m^2, BMI was associated with mortality due to heart failure (HR 1.86 (1.55/2.23)) and hypertensive disease (HR 2.03 (1.75/2.36)), but also with mortality due to diabetes (HR 2.16 (1.89/2.46)), renal disease (HR 1.59 (1.27/1.99)), hepatic disease (HR 1.82 (1.59/2.09)), neoplasia (HR 1.10 (1.06/1.15)) and respiratory diseases and lung cancer (HR 1.20 (1.07/1.34)). For several sites of cancer the hazard ratios were different according to age: for deaths at ages 60–89, cancers of the liver (HR 1.47 (1.26/1.71)), kidney (1.23 (1.06//1.43)) and breast (1.15 (1.02/1.31)) were important, and for death at 35–59 years these were cancer of the endometrium (1.38 (1.08/1.77)), prostate (1.13 (1.02/1.24)) and large intestine only in males (1.29 (1.18/1.40)).

The by far largest study published in 2016 by Aune et al. included 230 cohorts with 30.3 million participants and almost 3.8 million deaths [6]. The lowest risk was a BMI of 23–24 in never smokers, 22–23 in healthy never smokers and 20–22 in never smokers with ≥20 years of follow-up. The summary relative risk for all-cause mortality per 5 unit increase in BMI was 1.05 (1.04/1.07) for all participants (228 cohort studies). Due to the large number of participants they could stratify for risk of smoking and several specific causes of early death in the first 1–6 years after inclusion in the study. By doing so they found a summary relative risk per 5 unit increase in BMI of 1.18 (1.15/1.21) for never smokers (53 cohorts), 1.21 (1.18/1.25) for healthy never smokers (26 cohorts) and 1.27 (1.21/1.33) for healthy never smokers with exclusion of early follow-up (11 studies). Their data were at variance with another large study by Flegal et al., a meta-analysis of 97 cohort studies with 2.88 million individuals and more than 270,000 deaths [31]. Flegal et al. found summary hazard ratios of death of 0.94 (0.90/0.97), 0.97 (090/1.04) and 1.34 (1.21/1.47) for BMI categories of 25–30, 30–35 and ≥35, respectively, suggesting a protective effect of overweight on mortality and only severely obese people being at increased risk of mortality. There are two possible explanations to clarify this discrepancy. Flegal et al. defined a normal weight by a wide range of BMI 18.5–24.9 kg/m^2 and used statistical adjustments for smoking and prevalent disease while in the study of Aune et al. stratification for and/or exclusion of smokers and prevalent disease is a more powerful tool but this needs obviously large cohorts [15].

Two other large cohorts were also able to exclude the group of smokers and found data that agreed with the study by Aune et al. The NHI–AARP (National

Institute of Health–American Association of Retired Persons) Diet and Health Study (527,265 participants) found relative risks of death in class I, II and II obesity in non-smoking males of 1.96, 2.46 and 3.82, respectively, and in non-smoking females of 1.99, 2.57 and 3.79, respectively, when compared with a BMI of 23.5–24.9 [32]. In the National Cancer Institute (NCI) Cohort Consortium with 1.46 million white adults, Berrington de Gonzalez et al. excluded patients with smoking and impaired health status [29]. Hazard ratios for death due to overweight were 1.11 (1.07/1.16) for males and 1.13 (1.09/1.16) for females when compared with a BMI 22.5–24.9 as the reference group. In the BMI classes of 30–34.9, 35–39.9 and 40–49.9 hazard ratios of 1.44, 1.88 and 2.51 in women and 1.44, 2.06 and 2.93 for men were reported. Per 5 unit increase in BMI the all-cause mortality HR was 1.31 (1.29/1.33) over the wide BMI range of 25.0–49.9 kg/m^2.

1.4.1 Mortality: All-Cause and Disease-Specific Causes

Obesity is associated with an increase in all-cause mortality and life expectancy is reduced. The impact of obesity on mortality is less in subgroups where competing causes of death are increased such as in elderly and smokers [33]. Flegal et al. combined the data of the three National Health and Nutrition Examination Surveys (NHANES) in the USA and grouped the causes of deaths into three categories: cardiovascular, cancer and all other (non-cardiovascular, non-cancer) [27]. Cancer was further divided into lung cancer; obesity-related cancers such as colon, breast, oesophagus, uterine, kidney, ovarian and pancreas cancer; and other cancers. Obesity was associated with increased all-cause mortality and with increased excess deaths from cardiovascular, coronary heart and non-coronary heart disease (including stroke), from obesity-associated cancers and from the combined presence of diabetes and kidney disease. Overweight was associated with a decreased all-cause mortality with only an increased mortality from diabetes and kidney disease combined, but a decreased mortality from non-cardiovascular, non-cancer disease causes and not associated with cancer and cardiovascular mortality. Similar findings were reported by Berrington de Gonzalez et al. in the NCI Cohort Consortium with overall higher risks for death from cardiovascular disease than for death from cancer [29]. For cardiovascular death these hazard ratios were 1.82 (1.69/1.93) for BMI 30–34.9, 2.63 (2.40/2.88) for BMI 35–39.9 and 3.56 (3.12/4.04) for BMI 40–49.9 kg/m^2. Hazard ratios for cancer death were 1.34 (1.27/1.42), 1.47 (1.34/1.61) and 1.70 (1.48/1.96) in the respective BMI categories. In the European EPIC study significant relative risks were present only for circulatory causes of death in males and females in class I obesity (RR 1.62 (1.38/1.90) and RR 1.31 (1.07/1.61), respectively) and for circulatory cause of death in those with a BMI ≥35 in males and females (RR 2.70 (2.13/3.42) and RR 2.27 (1.78/2.90), respectively), followed by death due to neoplastic disease only in women (RR 1.38 (1.14/1.68)) [21].

1.4.2 Population Attributable Fraction

The population attributable risk of overweight or obesity is an estimate of the percentage of premature death or occurrence of a disease in the cohort that would not have occurred if all persons had been of normal weight at the same age. Excess weight accounted for approximately 7.7% of all premature deaths among men and 11.7% among women [32]. It accounted for 18.1% of premature deaths among non-smoking men and 18.7% among non-smoking women [32].

Cardiovascular mortality accounted for 37% of adult deaths in the USA in 2004 [27]; 13% of total CVD mortality was associated with obesity (BMI >30). Cancer accounted for 24% of total deaths in the USA [27]. Flegal et al. found no to little association of BMI categories to excess all-cancer mortality [27]. When they divided cancers into lung cancer (29% of death of all cancers), obesity-associated cancers (32% of all cancer deaths) and other cancers (40% of cancer deaths) it appeared that obesity was significantly associated with 11% of death from cancers considered to be obesity related. Calle et al. estimated that 4.3% of all cancer deaths in men and 14.3% of all cancer deaths in women were associated with obesity in the large Cancer Prevention Study [8]. The WHO emphasized that 44% of the diabetes burden, 23% of the ischaemic heart disease burden and 7–41% of certain cancer burdens are attributable to overweight and obesity [2]. In Europe about 80% of cases of type 2 diabetes, 35% of ischaemic heart disease and 55% of hypertensive disease among adults are attributable to overweight and obesity [4].

1.4.3 Current Developments

There are currently both negative and positive developments. Oldhansky et al. reported a potential decline in life expectancy in the USA in the twenty-first century [34]. They calculated that the life expectancy at birth would be higher in white men with obesity grade I (BMI >30) by 0.33 years and in white men with obesity grade II (BMI >35) by 0.93 years, if subjects would decrease to a BMI of 24. The years gained would be 0.30 and 0.81 years, respectively, for white females; 0.30 and 1.08 years, respectively, for black males; and 0.21 and 0.73 years, respectively, for black females. But the current negative effect of obesity of 1/3 to 3/4 of a year life shortening could rise to 2–5 years as the prevalence of obesity among adults, and especially among children, is increasing and obese children will carry and express obesity-related risks for more years of their lifetime than previous generations.

On the other hand, a recent analysis in three Danish cohorts (the Copenhagen City Heart study 1976–1978 (n = 13,704) and 1991–1994 (n = 9482), and the Copenhagen General Populations Study 2003–2013 (n = 97,362)) discovered that the BMI associated with the lowest mortality increased from 23.7 in 1976–1978 to 24.6 in 1991–1994 to 27.0 in 2003–2013, thus an increase by 3.3 BMI units over three decades [35]. The corresponding BMIs for cardiovascular disease mortality

were 23.2, 24.0 and 26.4 and the BMIs for other mortalities 24.1, 26.8 and 27.8. Analysis of BMI categories against the normal BMI category of 18.5–25 showed decreased risks of all-cause mortality from 1.04 in 1976–1978 and 0.97 in 1991–1994 to 0.86 in the 2003–2013 cohort. The adjusted hazard ratio for all-cause mortality for a BMI of 30 or greater against BMI 18.5–25 changed from 1.31 in 1976–1978 to 1.13 in 1991–1994 and to 0.99 in 2003–2012. The researches provided a potential explanation for the secular trend. They suggested that the improvement of treatment of cardiovascular risk factors or complicating disease has reduced mortality in all weight classes but that these effects may have been greater with subjects at higher BMI levels where hypertension, diabetes and dyslipidaemia place individuals more at risk. Decreased smoking and increased physical activity may also have improved the general health of the population.

In certain circumstances overweight and moderate obesity are not associated with increased mortality, a fact known as the obesity paradox. Especially in the intensive care, the obesity paradox has gained increasing interest: here patients with a BMI between 30 and 40 showed an even lower mortality (relative risk 0.83 (0.74/0.92)) compared with normal-weight subjects, suggesting that increased nutritional reserves are advantageous to survive the intensive care [36].

1.5 Comorbidities in General

Obesity is associated with many comorbidities which relate to weight-bearing influences on bones, joints, ligaments and muscles and respiratory function, to metabolic and hormonal disturbances, cumulating in life-threatening diseases or decreased quality of life as presented in the obesity web (Fig. 1.2). Obesity is a major risk factor for type 2 diabetes mellitus (T2DM) with a 10- to 20-fold increased risk in those with a BMI $\geq$35 kg/m^2 [33]. It is also associated with hypertension and cardiovascular disease and in men with hypercholesterolaemia and stroke. Obesity is also predictive of diseases that cause serious morbidity such as osteoarthritis and sleep apnoea. The other major disease group associated with BMI is cancer with a dose-response relationship between the risk of cancer and BMI. Obesity is also a key factor for the metabolic syndrome (MetS) characterised by dyslipidaemia, hyperinsulinaemia, diabetes and hypertension (Table 1.1). Guh et al. tried to assess the importance of 20 comorbidities in a meta-analysis comprising 89 relevant studies from Europe, North America, Australia and New Zealand and they included only prospective cohort studies [37]. This meta-analysis was unique to the many previous systematic reviews and meta-analyses because they recognised the fact that (1) most studies used BMI and abdominal obesity defined by waist circumference might be a better predictor of many cardiovascular diseases and T2DM, and (2) many studies found associations defined per unit change in BMI of per cm change in waist while now BMI and waist were categorised by overweight (BMI 25–29.9 kg/m^2 and waist $\geq$80 cm for females and $\geq$94 cm for males) and by obesity (BMI $\geq$30 kg/m^2 and waist $\geq$88 cm for females and $\geq$102 cm for males). They found evidence for 18 comorbidities but not for sleep apnoea and dyslipidaemia (Table 1.2).

Statistically significant associations were found for the incidence of T2DM; all cancers except oesophageal (female), prostate and pancreas cancer; all cardiovascular diseases (except congestive heart failure); asthma; gallbladder disease; osteoarthritis and chronic back pain (Table 1.2). Overweight and obesity were very strongly associated with diabetes (RR 3.92 (3.10/4.97) and 12.41 (9.03/17.06)), respectively.

Table 1.2 Meta-analysis of comorbidities related to defined criteria of overweight BMI (BMI 25–29.9 kg/m^2) and obesity BMI (BMI ≥30 kg/m^2) and to overweight waist measures (≥80 cm for females and ≥94 cm for males) and obesity waist measures (≥88 cm for females and ≥102 cm for males) [37]. Relative Risks with 95% Confidence Intervals are given

Comorbidity	No. of studies		RR overweight BMI	RR obese BMI	RR overweight waist	RR obese waist
Breast cancer postmenopausal	14	F	1.08 (1.03/1.14)	1.13 (1.05/1.22)	1.13 (1.01/1.07)	1.30 (1.17/1.44)
Endometrial cancer	10	F	1.53 (1.45/1.61)	3.22 (2.91/3.56)	1.15 (1.02/1.30)	1.42 (0.80/2.49)
Ovarian cancer	9	F	1.18 (1.12/1.23)	1.28 (1.20/1.36)	0.61 (0.35/1.08)	1.35 (0.95/1.93)
Colorectal cancer	12	M	1.51 (1.37/1.67)	1.95 (1.59/2.39)	1.88 (1.47/2.41)	2.93 (2.31/3.73)
		F	1.45 (1.30/1.62)	1.66 (1.52/1.81)	1.25 (0.98/1.59)	1.55 (1.27/1.88)
Oesophageal cancer	1	M	1.13 (1.02/1.26)	1.21 (0.97/1.52)		
		F	1.15 (0.97/1.36)	1.20 (0.95/1.53)		
Kidney cancer	5	M	1.40 (1.31/1.49)	1.82 (1.61/2.05)		
		F	1.82 (1.68/1.98)	2.61 (2.39/2.90)		
Pancreatic cancer	6	M	1.28 (0.94/1.75)	2.29 (1.65/3.15)		
		F	1.24 (0.98/1.56)	1.60 (1.17/2.20)		
Prostate cancer	8	M	1.14 (1.00/1.31)	1.05 (0.85/1.30)		
T2DM	9	M	2.40 (2.12/2.72)	6.74 (5.55/8.19)	2.36 (1.76/3.15)	5.67 (4.46/7.20)
		F	3.92 (3.10/4.97)	12.41 (9.03/17.06)	3.40 (2.42/4.78)	11.1 (8.23/14.96)
Hypertension	4	M	1.28 (1.10/1.50)	1.84 (1.51/2.24)		
		F	1.65 (1.24/2.19)	2.42 (1.59/3.67)	1.38 (1.27/1.51)	1.9 (1.77/2.03)
Stroke	7	M	1.23 (1.13/1.34)	1.51 (1.33/1.72)		
		F	1.15 (1.00/1.32)	1.49 (1.27/1.74)		
CAD	11	M	1.29 (1.18/1.41)	1.72 (1.51/1.96)	1.41 (1.16/1.72)	1.81 (1.45/2.25)
		F	1.80 (1.64/1.98)	3.10 (2.81/3.43)	1.85 (1.41/2.36)	2.68 (2.05/3.53)
Congestive heart failure	4	M	1.31 (0.96/1.79)	1.79 (1.24/2.59)		
		F	1.27 (0.68/2.37)	1.78 (1.07/2.95)		
Asthma	4	M	1.20 (1.08/1.33)	1.43 (1.14/1.79)		
		F	1.25 (1.05/1.49)	1.78 (1.36/2.32)		

(continued)

Table 1.2 (continued)

Comorbidity	No. of studies	RR overweight BMI	RR obese BMI	RR overweight waist	RR obese waist
Chronic back pain	1	1.59 (1.34/1.89)	2.81 (2.27/3.48)		
Osteoarthritis	3 M F	2.76 (2.05/3.70) 1.80 (1.75/1.85)	4.20 (2.76/6.41) 1.96 (1.88/2.04)		
Pulmonary embolism	1	1.94 (1.39/2.64)	3.51 (2.61/4.73)		
Gallbladder disease	4 M F	1.09 (0.87/1.37) 1.44 (1.05/1.98)	1.43 (1.04/1.96) 2.32 (1.17/4.57)	1.63 (1.42/1.88)	2.51 (2.16/2.91)

T2DM type 2 diabetes mellitus, *CAD* coronary artery disease, *RR* relative risk, *F* females, *M* males

1.6 Symptoms and Comorbidities More Specifically Related to the Gastrointestinal Tract

Many of the comorbidities associated with obesity rely to the gastrointestinal tract such as gastro-oesophageal reflux disease (GORD) and its complications, gallbladder stones and pancreatitis, colon polyps and colorectal cancer, liver diseases such as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatosis hepatitis (NASH), and gastrointestinal tract cancers. Most of these comorbidities will change favourably by body weight reduction and the way this weight reduction is achieved will not impact them, with GORD presumably being an exception. As GORD and its complications are also the most prevalent diseases, this chapter focuses extensively on GORD and its complications of erosive oesophagitis, Barrett's oesophagus and oesophageal and gastro-oesophageal junction adenocarcinoma. Also, the liver manifestations of obesity with non-alcoholic fatty liver disease (NAFLD) and its progression to non-alcoholic steatohepatitis (NASH) are discussed at length with an eye to increased needs for liver transplantation in the future. The subchapter of gastro-oesophageal tract malignancies will discuss the cancers in a more general perspective as far as these have not been discussed in detail in the preceding paragraphs.

But before discussing the obesity-related gastrointestinal diseases: what is the relationship between GI complaints and BMI?

1.7 Symptoms Related to the Gastrointestinal Tract

The perception of sensations arising from the GI tract may be diminished in obese subjects and thus facilitate overeating. On the other hand, altered food habits, such as skipping meals, binge-eating, periods of excess food intake and periods of food

restriction, may induce changes in GI function and thereby produce upper and lower GI symptoms. Two studies investigated gastrointestinal symptoms by validated questionnaires such as the Gastro-Oesophageal Reflux Questionnaire and the Bowel Disease/Symptom Questionnaire in a large cohort [38, 39] (Table 1.3). In the first cohort, consisting of residents of the Olmsted County ($N = 1963$) with 51% females and with at least 53% of subjects ≥50 years of age, the prevalence of overweight was 42.5% [38]. Obesity was present in 23% and severe obesity in 2% of cases. There was a positive relationship between BMI and frequent vomiting, upper abdominal pain, bloating and diarrhoea. The prevalence of frequent lower abdominal pain, nausea and constipation was increased among obese subjects, without a significant association between the BMI and these symptoms. The second cohort was a much younger group of 980 26-year-old subjects (47.9% females) [39]. Comorbidities and use of medication were unlikely to be a confounder given the young age group. The prevalence of overweight was 30% and that of obesity 12%; severe obesity was not present. Overweight was negatively associated with abdominal pain and constipation (odds ratio (OR) 0.4). Diarrhoea (>3 stools/day, loose stools, urgency) was associated with obesity (OR 1.8) as was abdominal pain combined with nausea and vomiting (OR 2.0). IBS and reflux were not associated with obesity and the waist/hip circumference ratio was not associated with GI symptoms. In these two cohorts, no information was available about the presence of GI lesions or diseases. A cross-sectional survey in Australia in adults yielded similar results on diarrhoea (OR 1.4) and abdominal pain (OR 1.3) [40]. However, a study in US subjects recruited for a study on weight loss medication differed from the previously mentioned three studies in a lesser symptomatology of diarrhoea and abdominal pain (OR 1.04 and 1.03, respectively) [41].

In a representative Swedish population 2122 individuals completed the validated abdominal symptom questionnaire on 27 troublesome GI symptoms [42].

Table 1.3 Studies evaluating gastrointestinal symptoms from questionnaires in patients with obesity; only significant associations are presented

Author and year	Number of patients and country	Adjustment in analysis	Associations of obesity with symptoms: odds ratio with 95% confidence interval
Delgado-Aros'04 [38]	1963, USA	Age, gender, alcohol, smoking, psychosomatism	Diarrhoea OR 2.7 (1.1/6.8) Vomiting OR 6.7 (2.7/26.6) Upper abdominal pain OR 3.7 (1.0/13.3)
Talley'04 [39]	980, New Zealand	Gender	Diarrhoea OR 1.81 (1.12/2.91) Vomiting OR 2.04 (1.12/2.90)
Talley'04 [40]	777, Australia	Age, gender, alcohol, smoking, education	Diarrhoea OR 1.41 (1.14/1.74) Upper abdominal pain OR 1.29 (1.03/1.61)
Levy'05 [41]	983, USA	Age, gender	Diarrhoea OR 1.04 (1.02/1.07) Abdominal pain OR 1.03 (1.00/1.05)

These reports could be coupled to findings on upper GI endoscopy in 1001 of these responders. Their mean age was 53.5 years and 51% were women. Overweight was present in 46% and obesity in 16%. There were significant associations between obesity and symptoms such as gastro-oesophageal reflux, vomiting, nocturnal urgency and diarrhoea (OR varying between 2.0 and 3.1) and epigastric or any abdominal pain, irritable bowel symptoms, retching, incomplete rectal evacuation and any stool urgency (OR between 1.58 and 1.63). Gastric ulcer was present in 1.4% of normal-weight, 1.3% of overweight and 5.6% of obese subjects; for duodenal ulcer these figures were 1.9%, 2.0% and 2.5%, respectively. Oesophagitis was present in 9.3 of normal-weight, 16.7 of overweight and 26.5% of obese subjects. When patients with oesophagitis were excluded from the analysis, only vomiting, diarrhoea and incomplete rectal evacuation remained associated with obesity (OR between 1.7 and 4.0) and the association with gastro-oesophageal reflux symptoms disappeared, meaning that gastro-oesophageal symptoms were largely explained by increased upper GI findings by endoscopy. Adjusting for medication did not alter the association between oesophagitis and BMI. A dose-response curve appeared to be present: the higher the BMI, the higher the gastro-oesophageal symptom score.

Dutta et al. compared 101 morbidly obese patients scheduled for Roux-en-Y gastric bypass with age- and sex-matched 101 non-morbidly obese patients and assessed the presence of symptoms of heartburn, regurgitation, dysphagia, nausea, epigastric fullness, postprandial discomfort, belching and bloating [43]. They also performed upper gastrointestinal endoscopy and biopsies in both groups of patients. Morbidly obese patients suffered more from heartburn (32.6% vs. 18.8%, p 0.02) compared with the control group. Endoscopically, the prevalence of a hiatal hernia ≥2 cm was higher (38.6% vs. 13.8%, $p < 0.001$) and the frequency of gastritis identified by endoscopy and histology was higher (23.7% vs. 11.8%, p 0.02) without differences in *Helicobacter pylori* infection. However, data on the use of NSAIDs, aspirin and steroids were not available. This study suggests different mechanisms involved in the development of upper GI symptoms and disorders in morbidly versus non-morbidly obese patients, which may be relevant for the evaluation of patients referred for bariatric surgery. Impaired visceral sensation, likely to be ascribed to a dysfunction of the autonomic nervous system, might explain the asymptomatic presence of endoscopic lesions [44]. The frequent use of proton pump inhibitors (PPIs) may also be an explanation.

As can be seen from Table 1.3, all studies reported a higher risk of diarrhoea and three studies reported increased vomiting and upper abdominal pain. Symptoms may be attributed to the size of the meal ingested leading to rapid gastric distension and vomiting [32]. Also, the rapid delivery of a meal into the small intestine with an increased osmotic load may explain the complaints. Furthermore, the cytokines and adipokines secreted by the adipose tissue may impact the gastrointestinal motility. As functional complaints have been related to an inflammatory insult to the gastrointestinal tract, obesity may therefore increase the risk of functional complaints by the release of pro-inflammatory cytokines [32].

1.8 Comorbid Diseases Related to the Gastrointestinal Tract

Apart from the relevance of being symptomatic or not, the obesity-associated diseases of the gastrointestinal tract are of clinical importance for both gastroenterologists and (bariatric) surgeons.

1.8.1 Oesophagus and Stomach

1.8.1.1 Gastro-Oesophageal Reflux Disease

Gastro-oesophageal reflux disease is a major problem, with a prevalence of 20% in Western countries. Over the last 20 years an increase by 4% per year was noticed in the Western world parallel to the doubling of the prevalence of obesity in that same period [45]. The parallel rise in GORD and obesity suggests a link between the two. A causal association between obesity and GORD-related disorders is suggested by these parallel secular trends, by consistent significant associations and compatible temporal associations and the suggestive dose-response relation found in many studies and associations found even in the normal range of BMI [46, 47].

Putative Causative Mechanisms

Obese patients often complain of gastro-oesophageal reflux with the main symptoms of heartburn and regurgitation. There are many putative mechanisms precipitating gastro-oesophageal reflux in obese subjects that makes the notion of obesity as a cause of GORD biologically plausible [47–49].

Mechanical Mechanisms

1. Increased intra-abdominal pressure (20–40 mmHg) with increased intragastric pressure and abdomino-thoracic pressure gradient over the cardia due to excess subcutaneous and intra-abdominal adipose tissue, which increases with increasing BMI and waist circumference.
2. Defective barrier function of the cardia or so-called incompetence of the cardia: Several mechanisms may lead to a defective barrier function such as stretching of the phrenico-oesophageal membrane that may adversely affect the lower oesophageal sphincter (LOS) by reducing the abdominal length of the sphincter, and an abnormal diaphragmatic pinch-cock and the presence of a hiatal hernia which facilitates gastro-oesophageal reflux by serving as a reservoir of gastric acid and by separating the LOS from the lengthening effect of the right crus of the diaphragm. Obese are more likely than lean subjects to have a hiatal hernia (40% vs. 12.6%) [48].
3. Impaired LOS function: Reflux mainly occurs when the LOS is either fully relaxed or has a resting tone less than 2 mmHg. Diet may have a role in altering the LOS tone, such as a high-fat diet through effects of cholecystokinin on LOS function. The postprandial LOS tone may be lowered by chocolate and coffee by the presence of xanthines, by mint by the presence of carminatives and by alcohol. Another mechanism might be increased transient LOS relaxations

(TLOSRs), with a high incidence of acid exposure during TLOSRs, which can be induced experimentally by gastric distension, use of an intragastric balloon or ingestion of a large meal [50, 51].

4. Dysmotility: Dysmotility of the oesophagus may impair the clearance of acid from the oesophagus; delayed gastric emptying induced by fatty meals or related to disturbances in glucose metabolism may favour reflux of acid material. Changes in hormones involved in gastric emptying, secondary to obesity, such as leptin, ghrelin and polypeptide Y (PYY), may play a role as well.
5. Intake of medication with influence on LOS pressure and tone such as the intake of exogenous oestrogens.

Humoral Mechanisms

The response of the oesophageal mucosa to the gastro-oesophageal refluxed materials is modified by humoral effects arising from the increased visceral fat. These humoral factors also govern the GORD-related complications such as erosive oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma. Visceral fat secretes pro-inflammatory cytokines like TNF-α, IL-6 and IL-1β. Both IL-6 and TNF-α are overexpressed in oesophagitis and Barrett's oesophagus and may potentially increase the inflammation and hence the malignant transformation [47].

Role of General Adiposity and Visceral Adiposity

There has been a lot of discussion on the role of overweight and whether overweight may influence the tendency for acid reflux in a graded way or whether a threshold value exists above which overweight might be of importance and some authors found no significant correlation between body weight or BMI and abnormal pH measurements [52, 53]. This discussion was fuelled by discrepancies between textbook recommendations and disappointing findings during weight loss in overweight patients [54].

It should, however, be recognised that the ideal study with data on GORD symptoms by validated scale scores, endoscopy to diagnose oesophagitis and presence of a hiatal hernia, manometry and pH measurements in a large number of individuals with both measures of total body fat (BMI) and central fat (waist measures) within a limited time frame does not (yet) exist.

One of the few studies available examined patients referred for GORD symptoms, with negative endoscopy and negative *Helicobacter pylori* (Hp) by manometry and 24-h pH measurements and had data on BMI [49]. This study proved that most but not all of the association between BMI and acid exposure was due to mechanical disturbances as described above. They mimicked their findings by a constricting abdominal belt in healthy volunteers. In a similar study with the new and sensitive technology of intraluminal high-resolution manometry and pH measurements in subjects with intra-abdominal fat and by placing a waist belt, Lee et al. showed that waist belt and intra-abdominal fat caused a partial hiatus hernia and short-segment acid reflux [55].

On the other hand, Anggiansah et al. could only partly confirm the mechanical theory in patients with typical GORD symptoms, assessed by validated questionnaires, by manometry and pH measurements, but in their study data on endoscopy,

H. pylori status and presence of a hiatal hernia were lacking [56]. Oesophageal acid exposure increased with waist and BMI and was also associated with lower LOS pressure (LOSP), reduced abdominal LOS length and peristaltic dysfunction (lower contractile amplitude of the lower oesophagus). BMI correlated negatively with LOSP but not LOS length and waist correlated negatively with both LOS pressure and abdominal length, consistent with the mechanical hypothesis. In multivariate analysis, correction for the manometric findings maintained the significant relation between obesity (BMI and waist) and acid exposure, but also showed an independent effect of oesophageal dysfunction on acid exposure, which is not in agreement with a pure mechanical hypothesis. GORD has been associated with abdominal obesity through increased intra-abdominal pressure, frequent TLOSRs, increased risk of hiatal hernia and oesophageal acid exposure.

In a large cohort study of 728 subjects undergoing oesophagogastroduodenoscopy (OGD) and having visceral (VAT) and subcutaneous adipose tissue (SAT) measurements by computer tomography (CT), 65 (8.9%) had erosive oesophagitis [57]. The patients with erosive oesophagitis were predominantly female. Compared with controls, they had a higher body mass index, metabolic syndrome prevalence, triglyceride levels and blood pressure. On OGD, hiatal hernia was also more prevalent. The mean VAT/SAT ratio was higher in the erosive oesophagitis group than in the non-erosive oesophagitis group (1.30 vs. 0.92). The results of the multivariate logistic regression analysis demonstrated that hiatal hernia, VFA/SFA ratio ≥1.165 and high triglyceride level were independent risk factors for erosive oesophagitis. Hiatal hernia was associated with a 12.9 times increased risk of erosive oesophagitis (OR 12.90 (3.57/46.65)). Similarly, a VFA/SFA ratio ≥1.165 was a significant risk factor for erosive oesophagitis (OR 2.04 (1.18/3.51)). The severity of the oesophagitis was positively correlated with the VFA/SFA ratio and visceral fat volume. The risk of Los Angeles (LA) oesophagitis types LA-A, LA-B and LA-C/LAC-D increased 1.23-fold, 1.27-fold and 1.56-fold, respectively. So, a VFA/SFA ratio ≥1.165 might be a useful indicator for predicting the presence and severity of erosive oesophagitis.

Yet, others performed manometry and/or pH measurements in obese and morbidly obese subjects referred for bariatric surgery and clearly found abnormalities [57, 58]. Comparison of an obese (BMI >30 kg/m^2) with a normal-weight group (BMI <25 kg/m^2) showed a clear dose-response relationship: per unit BMI increase there were 2.76 more acid reflux episodes postprandially and 1.89 more minutes with a pH <4 postprandially [59]. There were 0.8 more episodes of acid reflux per kg weight and 0.85 more acid reflux episodes per cm of waist postprandially. A BMI >30 kg/m^2 was associated with a 2.5-fold increased likelihood of having an abnormal DeMeester score (2.53 (1.18/5.41)). However, when waist circumference was included in the same model, the association between BMI >30 and oesophageal acid exposure became attenuated, indicating that the waist circumference may mediate a large part of the effect of obesity on oesophageal acid exposure. Ayazi et al. examined retrospectively the relationship between BMI, manometry and 24-h pH findings in 1659 symptomatic patients and found that 13% of the variability in the DeMeester composite score of the 24-h pH measurement was explained by variability in BMI [60]. Each

unit increase of BMI was associated with an increased proportion of the total oesophageal exposure time at pH <4 of 0.35% and increased postprandial exposure time at pH <4 of 0.48% and an increased composite score by 1.46 points. The association between BMI and oesophageal acid exposure was stronger during supine periods compared with being upright. Also, overweight and obese compared to normal weight subjects had an increased risk of 1.69 (1.32/2.16) and 2.12 (1.623/2.747) of having a defective LOS, without any influence by age or sex. Even in those without a manometrically assessed hiatal hernia the OR was 2.36 (1.93/2.89).

Some have found an increased risk of GORD in obese women, with the suggestion that humoral factors should also be considered as a mechanism relating obesity to reflux. Two studies from the same group in Sweden reported on oestrogens considered as a mechanism relating obesity to reflux [61, 62]. One study showed a significant association between obesity and oesophagitis in women, which was potentiated by the use of oestrogens (oestrogen-only hormone replacement therapy (HRT)) by postmenopausal women. Oestrogen increases the synthesis of nitric oxide, a vasodilator leading to smooth muscle relaxation that can include the LOS. The second larger study found that overweight men and women had a similar increased risk of GORD symptoms. However, obese women compared to men had an increased risk of GORD symptoms, with a highest risk both in premenopausal women and in postmenopausal women using oestrogen replacement therapy. They also found that a weight gain of 3.5 kg/m^2 was associated with a 2.7-fold (2.3/3.2) increased risk for developing new symptoms. Also, the increased rates of GORD in pregnant patients have been attributed to increased sex hormone levels but may in fact be due to an increased transmitted gastric pressure from the enlarged uterus.

A substantial barrier in GORD studies is the imperfect association between GORD symptoms and acid reflux; people with severe symptoms may have little acid damage and patients with severe damage may have little symptoms. Therefore, Nocon et al. studied the relationship between severity of symptoms and BMI in 6215 patients with clinically assessed GORD [63]. A higher BMI was associated with more severe symptoms especially regurgitation, which were twice as likely in women and men, and heartburn being 50% more likely with more frequent reflux symptoms and oesophagitis. Obese women but not men had increased risk for severe oesophagitis compared to women with normal weight (OR 2.5 (1.53/4.12)) probably due to an increased oestrogen activity.

Meta-Analyses and Cohort Studies

Two meta-analyses, which found positive correlation between obesity and GORD, questioned their outcomes because of the significant degree of heterogeneity [64, 65]. Hampel et al. performed a meta-analysis in 2005. Nine studies examined the relationship between GORD, based on validated questionnaires and/or endoscopic findings, and BMI. Six studies showed a statistically significant association and three studies did not. Adjusted odds ratio for GORD symptoms was 1.43 among overweight and 1.94 for obese persons. Erosive oesophagitis was investigated in seven studies and in six studies, the adjusted odds ratio for erosive oesophagitis was 1.76 (1.156/2.677) for a BMI ≥25 kg/m^2. Seven studies examined total calorie

intake and dietary fibre, fruits and vegetables and found the effect of BMI on GORD-related disorders to be independent of dietary intake. The second meta-analysis by Corley and Kubo decided to stratify the studies by country of origin [65]. An evaluation of all studies did not demonstrate a consistent association between elevated BMI and GORD. Homogeneous results for seven studies from the USA demonstrated a rising prevalence of GORD with increasing BMI with an OR 1.57 (1.36/1.80) for overweight and an OR 2.15 (1.89/2.45) for obesity. The eight studies from Europe were too heterogeneous and the five studies from outside Europe and the USA were very inconsistent.

A large cohort study in 80,110 subjects revealed gastro-oesophageal reflux symptoms in 11% and tried to correlate BMI and abdominal diameter with gender and ethnicity [66]. They found abdominal diameter to be an independent factor for gastro-oesophageal reflux symptoms in whites without a gender difference and much of the observed association between BMI and gastro-oesophageal reflux symptomatology to be mediated through the abdominal diameter. Abdominal diameter adjusted for BMI increased the risk for symptoms in white (OR 1.85 (1.55/2.21)) but not in black and Asian people. In Caucasian but not in Asian people the abdominal diameter was consistently associated with gastro-oesophageal reflux symptoms. The increased risk with no adjustment for BMI was even greater (OR 2.68 (2.33/3.08)) and also the risk of increasing BMI on symptoms was greater in the white. The attributable fractions among white subjects for a BMI ≥25 versus BMI <25 kg/m^2 and an abdominal diameter of ≥18 cm versus <18 cm were 16.5% and 15.1%, respectively, and among blacks these were 11.9% and 6.5%. In Asians these were not significant.

In the Nurses' Health Study an association between GORD and increasing BMI was found which was not influenced by the WHR [46]. This difference is due to the characteristics of the WHR used: a large waist and a large hip have the same ratio as a small waist and a small hip, whereas in the previous study the absolute abdominal diameter and thus a large abdominal size were measured [66].

What Is the Natural History of GORD?

Longitudinal studies are scarce. The only one available with a large number of subjects is the study by Lee et al. in 3669 subjects who underwent frequent endoscopy during the three periods, separated by 528, 392 and 352 days [67]. At the time points 1.2, 14.9 and 17.9% progressed from non-erosive to erosive oesophagitis whereas 42.5, 37.7 and 34.6% regressed from erosive into non-erosive oesophagitis. Being male (RR 4.31 (3.22/5.75)), being a smoker (RR 1.20 (1.03/1.39)) and having the metabolic syndrome (RR 14.75 (1.29/2.38)) independently increased the likelihood of progression from a non-erosive into an erosive oesophagitis and/or lowered the likelihood of disease regression. Short-term use of acid suppression raises the likelihood of disease regression (RR 0.54 (0.39/0.75)).

1.8.1.2 Barrett's Oesophagus

Although, generally speaking, GORD symptoms are equally distributed over ethnic groups and sexes, oesophagitis, Barrett's oesophagus and oesophageal

adenocarcinoma appear to be dominated by white men of Caucasian origin [47]. Men have a twofold higher risk than women and Caucasians have a fivefold higher risk than African-Americans. Barrett's oesophagus is a metaplastic change from the squamous epithelial lining to a specialised columnar epithelial lining, also called specialised intestinal metaplasia (SIM), the key feature of a Barrett's oesophagus and the only known precursor lesion of oesophageal adenocarcinoma. Persons with Barrett's oesophagus have a 30- to 40-fold increased risk of oesophageal adenocarcinoma through the sequence of Barrett's metaplasia → dysplasia → adenocarcinoma but the progression of Barrett's oesophagus to oesophageal adenocarcinoma is low, at a rate of 0.2–3.5% per year. GORD is associated with and probably directly contributes to Barrett's oesophagus. It is not clear whether obesity alone independent of GORD also plays a role. The association between obesity and Barrett is mixed with an increase of Barrett's oesophagus with increasing BMI, increased risk with increasing BMI only in patients with GORD or no association at all with BMI. Abdominal diameter appears to be a risk factor for Barrett independently of BMI and when adjusted for the waist the relationship between BMI and Barrett's oesophagus disappears [47]. However, the most well-known risk factor, i.e. GORD, is not markedly differentially distributed by sex or race. General obesity reflected by the BMI and abdominal obesity reflected by the waist circumference have been consistently associated with the risk of oesophageal adenocarcinoma, but associations between BMI and Barrett's oesophagus have been inconsistent [68]. Abdominal obesity appears to be more consistently related with Barrett's oesophagus. In men no consistent pattern was observed in the association between BMI and Barrett, and in women there was no association present [68]. Barrett cases were more likely to be men, of Caucasian origin, with a longer duration of GORD symptoms, who were more likely to smoke and who were less likely to be infected with *Helicobacter pylori*.

Case-Control Studies and BMI and Waist

A case-control study in veterans showed that, after correction for age and race, a 2.5 times increased risk of Barrett's oesophagus was present both in overweight and obesity and that for each 5 kg increase in body weight or for each 5-point increase in BMI the risk for Barrett was increased by 10% and 35%, respectively [69].

Several studies have demonstrated that obesity may play a role in Barrett's oesophagus beyond the promotion of gastro-oesophageal reflux and that it is the abdominal fat distribution that may play a crucial role in the risk of developing a Barrett's oesophagus independent of BMI.

In a large case-control study in the Kaiser Permanente Northern Carolina population, patients with a Barrett's oesophagus ($n = 320$) were matched to subjects with GORD without a Barrett ($n = 312$) and to population controls ($n = 317$) [70]. There was a general association between Barrett's oesophagus and a larger abdominal circumference (waist >80 vs. <80 cm, OR 2.24 (1.21/4.15)), independent of BMI. The increased risk was only evident at >80 cm, suggesting a possible risk plateau. Also, a dose-response was apparent with increased risks at higher waist circumferences. There was no substantial difference in risk for short-segment versus

long-segment Barrett. There was no association between Barrett and BMI. Abdominal waist was also associated with the severity of GORD with increasing risk of severe weekly symptoms (OR 1.86 (1.03/3.38) per 10 cm increased circumference). Adjustment for GORD attenuated the association between Barrett and waist from 2.24 (1.21/4.15) to 1.78 (0.86/3.66), which is to be expected when abdominal obesity → GORD → Barrett. So, waist but not BMI had a modest independent association with Barrett's oesophagus.

Increase in girth may increase the intra-abdominal pressure causing reflux, but may also alter GI motility because of metabolic products from the fat mass, and the plateau effect of the waist circumference may signify that at least a certain albeit modest amount of intra-abdominal fat is necessary.

Jacobson et al. discovered 261 cases of Barrett in 15,861 nurses of the Nurses' Health Study [71]. Only being obese (BMI ≥30 kg/m^2), but not being overweight, increased the risk (OR 1.52 (1.02/2.28)) and controlling for frequent GORD symptoms did not alter the observed risks for Barrett, but the association between obesity and Barrett was no longer significant, suggesting that obesity may play a role in Barrett's metaplasia beyond the promotion of GORD. However, waist, WHR and height were not associated with Barrett's oesophagus.

Smith et al. found in a population-based study with 167 cases of Barrett's oesophagus and 261 matched controls that obese people with self-reported symptoms of acid reflux had a markedly higher risk of Barrett (OR 34.4 (6.3/188)) than obese people without reflux (OR 0.7 (0.2/2.4)) or only reflux reporting normal-weight people (OR 9.3 (1.4/62.2)) suggesting that obesity plays a further role in the development of Barrett's oesophagus over and above its role in promoting acid reflux [72].

The strongest available data to date comes from the BEACON consortium with pooled individual participant data from 4 case-control studies including 1102 cases and 1400 controls with also having the possibility to include a sufficient number of females [68]. Waist circumference increased the risk of Barrett's oesophagus both in women and in men, independent of BMI, with a 125% (OR 2.24 (1.08/4.65)) and 275% (OR 3.75 (1.47/9.56)) increased risk for men and women, respectively. There was no association between BMI and risk of Barrett's oesophagus and the association between waist and Barrett strengthened after adjustment for BMI. There was a strong dose-effect association with increased risk by larger waist circumferences whether corrected for gastro-oesophageal reflux symptoms or not. However, the WHR was not associated with a risk in both women and men. Men, particularly of the white race, tend to accumulate more central/visceral fat compared with women. Also the NHANES study showed abdominal obesity to be more common among men and white individuals than among women and other racial/ethnic subgroups [73]. So the greater prevalence of abdominal obesity in men may at least in part explain the observed sex disparities in the incidence of Barrett's oesophagus.

Meta-Analyses

A meta-analysis by Cook et al. tried to solve the issue whether adiposity (BMI) mediates its effect on Barrett's oesophagus independently of GORD [74]. Ten studies were retrieved comparing the BMI of Barrett's and GORD patients and the

general population. When comparing Barrett's oesophagus with GORD patients, the pooled estimate was not significant (0.99 (0.97/1.01) per kg/m^2), with no statistically significant point estimates for men and women separately. The pooled estimate comparing Barrett with the general population was statistically significant (1.02 per kg/m^2 (1.01/1.04)) with no difference between males and females. The meta-analysis concluded that increasing BMI did not present an increased risk of Barrett's oesophagus above what would have been expected from GORD alone. The previously mentioned meta-analysis by Hampel et al. suggested that increasing adiposity is a risk factor for the development of Barrett's oesophagus [64]. The meta-analysis by Cook et al. concluded that the increased risk of GORD, caused by increasing BMI, underlies this association [74]. Once GORD occurs there is no additional effect of BMI on its progression to Barrett's oesophagus. Both meta-analysis could not explain the large male-to-female sex ratio of Barrett 's oesophagus and oesophageal adenocarcinoma and the predominance in Caucasians: men are approximately twice as likely as women to develop Barrett's oesophagus and 5–8 times more likely to develop oesophageal adenocarcinoma.

Sometimes, discrepant findings between studies can be explained [75]. The meta-analysis by Cook found a significant association between BMI and Barrett when considering the general population as controls, an effect that disappeared when GORD controls were used [74]. Jacobson's Nurses' Health Study showed that in women the effects of obesity on Barrett are mediated at least in part by mechanisms other than GORD [71]. Whereas in the latter study controls had an endoscopy and did not have a Barrett's oesophagus, in the Cook's meta-analysis controls did not have an endoscopy and were therefore not known as to have a Barrett's oesophagus or not. Also, the different outcomes between studies concerning the importance of the fat distribution can be explained. Corley et al. reported in their case-control study that both waist and WHR were associated with Barrett's oesophagus, independently of the BMI [70]. Jacobson et al. failed to find an association of Barrett with central adiposity defined by increased WHR in women [71]. When using the WHR it should be realised that a large waist and a large hip have the same ratio as a small waist and a small hip. But also when using the waist circumference no association was found. This may be due to the fact that not all adipose tissues behave the same and that it is the metabolically more active visceral adipose tissue (VAT) and not subcutaneous adipose tissue (SAT) that is associated with Barrett's oesophagus.

By measuring the VAT and SAT by computer tomography at the level of the intervertebral disc between L4 and L5, it was found that in women visceral fat constitutes a much smaller fraction of the abdominal fat (and thus the waist circumference) when compared with men [76]. Likewise, 1 cm increase in waist circumference corresponds to a smaller increase in VAT in women. So, BMI is a significant risk factor for Barrett's oesophagus but VAT is an even stronger and independent risk factor [77–79].

The Visceral Fat Pathway

So, apart from general adiposity, the visceral fat accumulation is at least, if not more, important. The humoral role of the visceral fat has attracted great attention.

Overweight and obese men tend to have more centralised fat while women have more fat in their subcutaneous tissue [48, 73, 76–79]. This may explain why measures of fat distribution appear more strongly associated with Barrett's oesophagus than BMI in predominantly male populations, while BMI may be more important in women. Visceral fat is associated with particular metabolic compounds and a different balance of adipose-related hormones including insulin-like growth factor-1 (IGF-1), TNF-α, IL-6 and adipokines (leptin, adiponectin), many of which are linked to carcinogenesis and with processes of healing and injury to gastrointestinal mucosa and have been implicated in the pathogenesis of Barrett's oesophagus [25, 26, 48]. Visceral obesity is also associated with insulin resistance and metabolic syndrome, and this metabolic dysregulation in itself is associated with Barrett's oesophagus and several cancers.

Visceral Fat Measurements

El Serag et al. performed a CT study in 173 Barrett cases, 343 colonoscopy controls and 172 endoscopy controls, who also all underwent an upper endoscopy [79]. As abdominal fat is comprised of two functionally distinct types of fat: visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT); both fat masses were measured, supposing that on the one hand subcutaneous fat may contribute to the mechanical effect of abdominal fat but is metabolically inert, and on the other visceral fat exerts a mechanical effect on stomach and oesophagus but also secretes multiple pro-inflammatory cytokines and is associated with insulin resistance [79]. Visceral fat but not subcutaneous fat was associated with an increased risk of Barrett's oesophagus; the association was partly explained by the presence of GORD symptoms but was also present in people without symptoms. These important findings point towards humoral mechanisms of obesity-related increased risk of Barrett's oesophagus. Patients with Barrett's were more than twice likely to be in the highest VAT:SAT ratio (OR 2.42 (1.51/3.88)). After adjustment for age, sex, race, *H. pylori* status, smoking, NSAID use and alcohol use, the odds ratio was attenuated, with age and sex being the most attenuating factors. The association was stronger in males (adjusted OR 2.12 (1.15/3.90)) and when a long ≥3 cm Barrett's segment was present (OR 3.42 (1.627/7.01)). With respect to the reported association of Barrett's oesophagus with male gender and Caucasian descent, the analyses were repeated in male Caucasians. The unadjusted association between Barrett's oesophagus and VAT:SAT ratio was similar as in the whole group but now the associations persisted after adjustment for age, NSAIDs, Hp status, smoking and alcohol use (OR 2.27 (1.09/4.72)) as well as after the additional adjustment for GORD and PPI use. VAT and VAT:SAT ratio were associated with both presence and duration of GORD. The fat distribution in male and Caucasian tends to be more abdominal than truncal. Increased obesity may disproportionally increase GORD in white subjects and in males.

Subcutaneous Fat Measurements

Another way to address the fat distribution is to consider a possible protective effect of gluteofemoral (peripherally deposited) fat in oesophagitis and Barrett's

oesophagus [80]. Gluteofemoral obesity protects against T2DM and cardiovascular disease and is positively associated with insulin sensitivity and adiponectin levels. Abdominal obesity was measured by waist circumference and gluteofemoral obesity by hip circumference and also the WHR was taken into account. Waist circumference was positively associated with erosive oesophagitis and Barrett's oesophagus, which became stronger after correction for the hip circumference. The hip circumference was negatively associated. It is difficult to explain the protective role of gluteofemoral fat on a mechanistic basis and it has no role in acid reflux. It may be that gluteofemoral obesity may serve as sink for storing fat in a manner that avoids the inflammatory and other humoral effects of the fat, otherwise stored in the visceral compartment.

Metabolic Syndrome

Apart from a more detailed analysis of humoral factors secreted by the visceral fat also the function of visceral fat and its role in the metabolic syndrome (MetS) can be studied as done by Ryan et al. [81]. One hundred and two patients with Barrett's and specialised intestinal metaplasia were investigated. Of these patients, 46% had the metabolic syndrome, 78% were overweight and 6% had central obesity (waist >80 cm for women and >98 cm for men). When comparing long-segment versus short-segment Barrett's oesophagus patients with a long-segment Barrett had more often MetS in 60%, associated with hyperinsulinaemia and elevated levels of IL-6, and central obesity in 92% compared with short-segment Barrett in 23.8% and 62%, respectively. Long-segment Barrett had a 11 cm greater waist circumference. The MetS was associated with elevated C-reactive protein (CRP) and leptin levels and a tendency of decreased adiponectin levels. Both MetS and waist circumference were independent risk factors for long-segment Barrett (OR 4.23 (1.07/18.6) and OR 5.6 (1.01/1.18), respectively), suggesting that MetS and the pro-inflammatory state may induce progression of the length of Barrett's oesophagus.

Secreted Adipokines

Visceral fat, also named the largest endocrine organ in humans, secretes many adipokines, cytokines and chemokines. The role of adipokines, leptin and adiponectin, has been investigated in patients with Barrett's oesophagus and oesophageal adenocarcinoma [25, 26, 48].

Leptin

Leptin has a role in appetite regulation and energy homeostasis and is also known for its effects on angiogenesis, wound healing, tissue repair, fertility, immune function, renal and lung functions, and cancer [26]. Leptin attached to leptin receptors can inhibit apoptosis, and increase proliferation. It is cytoprotective for the GI mucosa but can also induce neoplastic cell proliferation. Leptin is primarily produced by adipocytes but also secreted by chief cells in the gastric mucosa. Leptin receptor expression was seen in the chief and parietal cells of the gastric fundus and

in superficial and basal layers of the oesophagus. Leptin levels are high in obesity but do not suppress hunger and appetite by leptin resistance, analogous to the effects of high insulin levels and insulin resistance. Francois et al. hypothesized that leptin of gastric origin may participate in the maintenance of normal (non-inflamed) oesophageal mucosa or the more acid-resistant Barrett's epithelium and examined tissue biopsies for leptin levels and leptin receptors in *H. pylori*-negative persons [82]. Barrett patients had significantly higher fundic leptin levels suggesting that the combination of refluxed acid and high leptin could predispose to mucosal proliferation, which depending on the host context may result in repair of oesophageal inflammation or progression of Barrett's oesophagus. For every twofold increase in fundic leptin the odds of having a Barrett's oesophagus was 3.4 (1.5/7.6) times higher when compared with having a normal oesophagus. Kendall et al. investigated levels of serum leptin in Barrett's oesophagus [83]. Their findings in a pilot study (67 controls; 51 Barrett) were confirmed in a large validation study (306 Barrett, 309 controls). In female controls and female Barrett patients serum leptin levels were 2–3 times higher than in males. Serum leptin levels correlated with BMI both in controls and Barrett patients. In men, serum leptin levels increased with increasing BMI and were higher in Barrett than in controls. The risk of a Barrett's oesophagus was highest in men among those in the highest quartile of serum leptin with a significant threefold increased risk of Barrett (OR 3.3 (1.7/6.6)) and this persisted after further adjustment for symptoms of gastro-oesophageal reflux (OR 2.4 (1.1/5.2)). There was a modest age-adjusted risk of Barrett with increasing BMI in males (BMI ≥30 kg/m^2: 1.7 (1.0/3.1)) but not in females and correction for gastro-oesophageal symptoms attenuated the risk. So, in men a proportion of the effect of obesity in the risk of Barrett was likely thought to be via non-reflux pathways including leptin. In women the risk of Barrett decreased with increased leptin levels and was not related to increasing values of BMI and correction for gastro-oesophageal symptoms attenuated the risk. So, men and women behaved quite differently. In women, the peripheral adipocytes secrete more leptin than the omental adipocytes, whereas in men the leptin secretion is similar at both sites. Women with central obesity would have lower serum leptin levels than peripherally obese women of the same BMI, implying that serum leptin would be negatively associated with central obesity and this would explain the negative association of leptin and Barrett's oesophagus in women. Adiponectin levels were not different between Barrett's and controls.

Adiponectin

Another player might be adiponectin which is secreted by adipose tissue [25, 26, 48, 84, 85]. Specific receptors are found in oesophageal mucosa such as AdipoR1 and R2. Adiponectin is an insulin sensitizer and has cardioprotective and immunomodulating actions. Being an anti-inflammatory agent, adiponectin is involved in the regulation of inflammation and suppresses carcinogenesis: it suppresses growth factors, stimulates apoptosis and suppresses cell proliferation. Adiponectin levels are

low in obesity and lower in obese men than in women and low adiponectin levels have been linked to carcinogenesis in colon, gastric, prostate, breast and uterus cancer. Adiponectin has three multimeric forms: low molecular weight (LMW, trimers), middle molecular weight (MMW, hexamers) and high molecular weight (HMW, octadecamers) [84, 85]. These multimeric forms have opposite actions in inflammation: HMW induces the secretion of pro-inflammatory cytokines (IL-6) whereas LMW is anti-inflammatory, suppressing lipopolysaccharide (LPS)-induced release of IL-6 and stimulating the secretion of anti-inflammatory IL-10. In a case-control study Rubenstein et al. compared total adiponectin and different molecular weight adiponectin levels in 112 Barrett patients and in 199 controls [85]. No association of total adiponectin with Barrett's oesophagus was found, but high LMW adiponectin levels and a high LMW/total adiponectin ratio were associated with a decreased risk of Barrett's oesophagus, and the effect was stronger in women than in men. Confounding effects by insulin, glucose and insulin sensitivity were excluded. They hypothesised that normal circulating levels of LMW adiponectin are sufficient to suppress the inflammatory response to GORD and guide the healing of the mucosa towards regeneration of squamous mucosa. LMW suppresses the local expression of IL-6 in the oesophageal mucosa and IL-6 expression has been shown to be increased in Barrett's oesophagus. In the presence of low LMW levels the response to GORD might be directed towards a more exuberant oesophagitis or towards metaplasia in the intestinal epithelium. Unfortunately, IL-6 was not measured and other factors like diet, physical activity and *H. pylori* status were not taken into account.

Both Leptin and Adiponectin

Thompson et al. studied both leptin and adiponectin in men and women in 177 subjects with newly diagnosed Barrett's oesophagus compared with 177 controls [86]. In the whole group both adipokines were predictors of the risk of Barrett's oesophagus independently of each other. In women, those in the highest tertile of BMI and waist had the greatest risk (OR 4.6 (1.9/11.6) and OR 5.1 (2.0/13.0), respectively) for Barrett's metaplasia than those on the lowest tertile. Adjustment for leptin and adiponectin attenuated the risk by 52% and 42%, respectively. In men, those in the highest tertile of WHR were at greatest risk (OR 2.8 (1.3/5.9)) but adjustment for leptin and adiponectin did not attenuate these associations. Taking women and men as a group together, those in the highest tertile of BMI, waist and WHR had increased risks of developing a Barrett's oesophagus (OR 2.3 (1.3/4.1), OR 2.8 (1.6/4.8) and OR 2.4 (1.4/4.2), respectively). Adjustments for both leptin and adiponectin attenuated these with 38%, 17% and 36%, respectively. They concluded that both leptin and adiponectin were significant predictors of Barrett's oesophagus in women and men combined, independent of each other. The associations between adipokine levels and Barrett's risk were the strongest for women. Furthermore, the association between Barrett's risk and obesity was attenuated but not eliminated when adjustments were made for both cytokines by 24–52% in females and by 17–38% in combined male-female models. So, apparently leptin and adiponectin partially account for the relationship between obesity and Barrett's oesophagus.

1.8.1.3 Oesophageal Adenocarcinoma and Gastro-Oesophageal Junction/Gastric Cardia Adenocarcinoma

In the last decades the incidence of oesophageal and gastric adenocarcinoma has increased rapidly with a strong predominance in white Caucasian men, comprising 65% of all cases [48, 87]. Oesophageal adenocarcinoma is fivefold higher in Caucasians than in African-Americans and sixfold higher in men than in women [88]. In some countries the incidence has risen by 500–650% over the last three decades and oesophageal adenocarcinoma now accounts for 50% of all oesophageal cancers in the West [87]. The incidence of oesophageal squamous cell cancer has been stable or is slightly decreasing by 3.6% per year in all ethnic groups and distal gastric cancer is decreasing [48]. Heredity seems to play a role, although the aetiology is mainly non-genetic. Barrett's oesophagus, GORD and obesity are known risk factors and medications that lower the LOS might contribute to the risk through the mechanism of gastro-oesophageal reflux [89]. Polednak et al. used results from published meta-analyses and large cohort studies and reported a steadily increasing impact of obesity on trends in oesophageal adenocarcinoma incidence rates, from 21% in 1976–1980 to approximately 36% in 2001–2004 to 40% in 2007 [90].

Dietary changes with reduced intake of fruits and vegetables with low intake of antioxidants and cereal fibres may contribute; the role of tobacco is probably limited and alcohol consumption is not a risk factor. Heavy alcohol consumption (≥7 drinks/day) was not associated with increased risk of oesophageal and gastric adenocarcinoma in 11 studies and 1800 cases in the BEACON consortium in contrast to the almost ten times increased risk for oesophageal squamous cell carcinoma [91]. Modest consumption (<1 drink per day) had a 37% and 22% decreased risk of oesophageal and gastric cardia carcinoma, respectively. The presence of *H. pylori* with a 50–80% reduced risk was assumed to be related to atrophic gastritis and the use of NSAIDs and selective COX-2 inhibitors, by reducing tumour growth, may be protective. Reasons for this increasing incidence in oesophageal adenocarcinoma include increased obesity rates, with epidemiological evidence linking obesity with up to 40% of cases, increased prevalence of reflux symptoms and Barrett's oesophagus incidence rates and decreasing prevalence of *H. pylori* infection.

Obesity may be an independent risk factor for oesophageal adenocarcinoma by the mechanism of obesity → GORD→ Barrett's oesophagus → adenocarcinoma and it has been postulated that the effects of increased total body fat mass are largely manifested early in the pathogenesis of oesophageal adenocarcinoma, that is, in the development of specialised intestinal metaplasia (SIM), a characteristic feature of Barrett's oesophagus [48]. Later in the pathogenesis, visceral obesity may be more important, by adipokine-induced accelerated rates of cell division and proliferation with progression of Barrett's oesophagus through dysplasia in oesophageal adenocarcinoma. Critically reviewing each of these steps raises many questions [88, 92]. The first question is whether BMI increases the risk of cancer through increasing the chance of GORD. In general the association between both is not very strong and all ethnicities and both sexes commonly have GORD but the risk of cancer is markedly higher in white Caucasian men. Previous studies have demonstrated that both obesity and GORD are independent risk factors. Moreover,

patients with GORD treated with PPI should be at lesser risk which is not the case. The second question is whether BMI increases the risk of Barrett's oesophagus independently of GORD; however, BMI on its own is not a strong risk factor for Barrett's oesophagus. The third question is whether BMI in itself increases the risk of progression of a Barrett's oesophagus to adenocarcinoma independently from GORD and again the answer is negative. Both increased total fat mass (mechanic part) and increased abdominal/visceral fat mass (humoral part) may be required for the development of erosive oesophageal damage, the development of Barrett's oesophagus and its malignant progression to oesophageal adenocarcinoma. With all these reflections in mind, one should realise that only 42% of men and 46% of women with oesophageal adenocarcinoma have a history of weekly reflux symptoms and only 22% have previously diagnosed GORD [93]. Moreover, Barrett's oesophagus is only apparent in 31% of patients. Similarly findings for gastric cardia cancer are 29% having a history of reflux symptoms and only 12% having a Barrett [93].

One explanation for the gender and ethnic specificity of oesophageal adenocarcinoma is the fact that for the same BMI, Caucasians and men tend to have more visceral fat [48, 73, 76–80]. Men of all ages and postmenopausal women tend to deposit fat predominantly intra-abdominally whereas premenopausal females tend to deposit fat subcutaneously. This difference may explain the gender and age disparities in incidence and outcome of some cancers such as oesophageal adenocarcinoma.

The negative association between *H. pylori* infection and oesophageal adenocarcinoma may be due to two different factors: (1) the chronic infection by *H. pylori* and the resultant gastric atrophy with diminished acid production, thereby decreasing gastro-oesophageal acid reflux, and (2) the decreased ghrelin secretion by X/A-like endocrine cells in the fundus of the stomach, protecting against obesity by decreasing hunger and appetite, and protecting against GORD by decreasing acid production. Martel et al. investigated both *H. pylori* infection and ghrelin levels and contrary to the original hypothesis they found that high rather than low serum ghrelin levels were associated with protection against oesophageal adenocarcinoma but only among overweight subjects (BMI $\geq$25 kg/m^2) and the lower risk did not change after correction for BMI and *H. pylori* presence (0.18 (0.04/0.78)) and after full correction, including also correction for smoking and education [26, 94]. Also, the strong protective action of *H. pylori* on cancer risk was not modified by ghrelin, and effects of both *H. pylori* and ghrelin were independent. Ghrelin has been shown to stimulate upper GI motility and to accelerate gastric emptying by effects on the vagal nerve and the myenteric plexus, thereby potentially diminishing oesophageal acid exposure and the risk of oesophageal adenocarcinoma, and also possesses profound anti-inflammatory effects with inhibition of TNF-α and inhibition of activation of NF-κB, thus diminishing the consequences of chronic gastric reflux with chronic inflammation and the development of oesophageal adenocarcinoma [26, 94]. For clinical practice it is important to know that obese patients usually have low levels of ghrelin and are therefore presumably less protected.

Meta-Analyses

Several meta-analyses tried to quantify the risk of oesophageal adenocarcinoma and gastric cardia adenocarcinoma. In Hampel's meta-analysis of nine studies there appeared to be a dose-response relationship with an OR of 1.52 at BMI 25–30 kg/m^2 and 2.78 at BMI ≥30 kg/m^2 [64]. Concerning the gastric cardia adenocarcinoma the adjusted OR was 1.68 for BMI ≥25 kg/m^2. Kubo and Corley had similar results in 14 studies [95]. A BMI ≥25 kg/m^2 was associated with an increased oesophageal adenocarcinoma in men (OR 2.2) and women (OR 2.0), and higher BMIs had higher cancer risks both in men and women: the ORs were for men with overweight 1.8 and with obesity 2.4; for females these ORs were, respectively, OR 1.5 and OR 2.1. There was a trend towards a stronger association in men compared with women. Associations with gastric cardia adenocarcinoma were heterogeneous, but after stratification by study location only a weak association (OR 1.5 for male and female and overweight and obese combined) between gastric cardia cancer and BMI was found in studies from the USA and Europe but not in studies from China.

Recent Cohort and Case-Control Studies

An article by Ryan et al. updated the meta-analysis of 2006 by Kubo and Corley with articles between 2005 and 2010 [48]. Twelve articles were retrieved, four from the USA and Canada, six from Europe and two from Australia [96–107]. As can be seen from Table 1.4 risks of oesophageal adenocarcinoma were at least 2.3 times higher and were as high as 5.3, 6.1 and 11.3 times higher compared with the BMI reference values in the different continents. In the study by Corley et al. also the anteroposterior diameter was taken into consideration [97]. The risk of oesophageal adenocarcinoma was 4.67 (1.14/20.11) when the diameter was equal or greater than 25 cm, suggesting that intra-abdominal fat increases the risk independently of BMI. Ryan compared the highest versus the lowest quartile of BMI and found a dose-dependent relationship between BMI and oesophageal adenocarcinoma for males (OR 4.3(2.3/7.9)); for the lower oesophagus the risk was the highest of all reported risks (OR 11.3 (3.5/36.4)); for the gastro-oesophageal junction the risk of adenocarcinoma was 3.4 (1.4/8.7) [100]. In the Netherlands Cohort Study on Diet and Cancer a dose-response curve was found for overweight and obesity in both oesophageal and gastric cardia adenocarcinoma [103]. Each 1 kg/m^2 increment during adulthood increased the risk of adenocarcinoma of the oesophagus by 14% and a weight gain of BMI ≥8 kg/m^2 had a 3.4 times higher risk than those with 0–3.9 kg/m^2 change. In this population 30.2% of oesophageal and 21.8% of gastric adenocarcinoma could be attributed to overweight and obesity. The European Prospective Investigation into Cancer and Nutrition (EPIC) study found that BMI, waist and WHR were all positively associated with oesophageal adenocarcinoma [105]. In an Australian study the risk increased by 46% for every 10 cm increase in waist [106]. Whiteman et al. also investigated morbidly obese subjects with a BMI ≥40 kg/m^2 [107]. Risk increased from OR 1.4 when being overweight to OR 3.3 in subjects with BMI ≥30 and to 7.0 in subjects with a BMI ≥40 kg/m^2. Adjustment for gastro-oesophageal reflux and other factors modestly attenuated this risk. Risk associated with obesity was significantly higher (almost twice as high) for men than for women and for those aged

<50 years (OR 7.5) versus those aged ≥50 years (OR 2.2). Obese people with frequent reflux had significantly higher risks (OR 16.5 (8.9/30.6)) than obese without reflux (OR 2.2 (1.1/4.3)) or normal weight with reflux (OR 5.6 (2.8/11.3)) consistent with a synergistic action between these factors. Risks of combined exposure were threefold higher than expected assuming a synergistic interaction between obesity and reflux. Similar findings were seen for gastro-oesophageal junctional adenocarcinoma but of smaller magnitude. The prevalence of *H. pylori* in this study was 6.3–8.5% and had no impact on the risk estimates. Their data suggested that patients with obesity and frequent reflux symptoms are especially at risk of adenocarcinoma.

Two more recent studies dating back to 2012 are also included in Table 1.4. The pooled analysis of individual participant data by the international Barrett and Esophageal Adenocarcinoma Consortium (BEACON) included 1997 oesophageal adenocarcinomas, 1900 oesophagogastric junction adenocarcinomas and 11,159

Table 1.4 Recent studies investigating the risk of oesophageal adenocarcinoma in obese subjects

Author and year	Design	Country	Cases/ controls	BMI reference	BMI	Results OR (95% CI)
USA and Canada						
Veugelers'06 [96]	CC	Canada	57/102	<25	>30	4.67 (1.27/17.9)
Corley'08 [97]	CC	USA	94/206,974	18.5–24.9	≥30	3.17 (1.43/7.04)
Abnet'08 [98]	Cohort	USA	371/480,475	18.5– <25.0	>35	2.27 (1.44/3.59)
Figueroa'09 [99]	CC	USA	122/695	<25	>30	5.32 (2.75/10.29)
Europe						
Ryan'06 [100]	CC	Ireland	760/893	<22	>30	11.3 (3.5/36.4)
Samanic'06 [101]	Cohort	Sweden	82/362,552	<24.9	>30	2.7 (1.33/5.55)
Reeves'07 [102]	Cohort	UK	$150/1.2 \times 10^6$	22.5–24.9	≥30	2.54 (1.89/3.41)
Merry 07 [103]	Cohort	The Netherlands	293/4452	<24.9	>30	3.96 (2.27/6.88)
Anderson'07 [104]	CC	Ireland	227/260	<25	>28.1	2.69 (1.62/4.46)
Steffen'09 [105]	Cohort	Germany	198/346,554	<20.5	>30	2.8 (1.4/5.9)
Australia						
MacInnis'06 [106]	Cohort	Australia	30/41,295	<25	>30	3.7 (1.1/12.4)
Whiteman'08 [107]	CC	Australia	793/1580	18.5–24.9	>40	6.1 (2.7/13.6)
Most recent studies						
Hoyo'12 [87]	Cohort and CC	USA, EU, Australia	1997/11,159	<25	≥40	4.76 (2.96/7.66)
Doherty'12 [92]	Cohort	USA	253/218,854	18.5- < 25.0	≥35	2.11 (1.09/4.09)

BMI Body mass index, *OR* odds ratio, *95% CI* 95% confidence interval, *CC* case-control, *UK* United Kingdom, *EU* Europe

controls in 12 epidemiological studies (eight North America, three Europe and one Australia) [87]. Compared with BMI <25, a BMI 25–29.9 increased the risk by 54%; a BMI 30–34.9 gave a twofold increased risk (OR 2.39) and a BMI 35–39.9 gave a risk of 2.79. A BMI ≥40 kg/m^2 increased almost fivefold the risk (OR 4.76). For gastro-oesophageal junctional cancer these OR were smaller and were 1.28, 2.08, 2.36 and 3.07, respectively. Analysis testing for synergism or departure from additivity showed a synergism between BMI and GORD symptoms with respect to the oesophageal adenocarcinoma risk. The excess risk attributable to the synergistic interaction of BMI and GORD was 64% versus the non-interaction group. This observation of a synergetic effect of BMI and GORD on the cancer risk supports the idea of at least two pathways: a direct mechanical and an indirect metabolic one.

In the National Institutes of Health–American Association of Retired Persons (NIH-AARP) Diet and Health study 253 cases of oesophageal adenocarcinoma, 191 cases of gastric cardia adenocarcinoma and 125 cases of gastric non-cardia adenocarcinoma were documented [92]. In oesophageal adenocarcinoma weight, BMI, waist, hip and WHR were positively associated with the risk, with an HR between 1.81 and 2.28. For gastric cardia adenocarcinoma BMI and waist displayed an increasing risk of a HR 3.67 and HR 2.22, respectively. No consistent associations were found for gastric non-cardia adenocarcinoma.

1.8.1.4 Gastric Cancer

A meta-analysis studied the relationship between gastric cancer and overweight and obesity and identified ten studies involving 9492 gastric cancers in a population of almost 3.1 million individuals [108]. Overweight (BMI ≥25 kg/m^2) was associated with an increased gastric cancer risk (OR 1.22 (1.06/1.41)) with a small dose-response relationship: overweight (BMI 25–29.9) was associated with a 21% higher gastric cancer risk and obesity with a 36% higher risk. A stratified analysis showed a BMI ≥25 kg/m^2 to be associated with increased risks of gastric cardia cancer (OR 1.55 (1.31/1.84)), with overweight being at excess risk of 40% and obesity being over two times at risk. Overweight non-Asians had a 24% higher gastric cancer risk.

1.8.1.5 Implications for Clinical Practice

What does this imply for the gastroenterologist and for the surgeon? The degree of overweight and the visceral distribution of fat are involved in the aetiology of GORD, and GORD complications. Especially the obese with large waist circumference and severe symptoms of GORD is at risk for GORD complications. For daily practice this means taking a careful history with measurement of weight, height and waist circumference and a diagnostic workup in the presence of symptoms, with not only an endoscopy, sometimes supplied with manometry or 24-h pH measurements, but also an analysis of components of the metabolic syndrome. This is needed to estimate to what extent the obese subject is at risk of GORD complications. This should be followed by adequate treatment of symptoms with emphasis on attempts to lose weight which automatically will also result in a decreased mass of actively

secreting visceral fat. Seven studies evaluated the effect of a lifestyle or diet intervention: two studies on very-low-calorie diet (VLCD), one on a low-calorie diet (LCD), one on a low-carb diet and three used combined lifestyle; three of the studies used an intragastric balloon [109]. Disappointingly, three of the studies were negative as to the improvement in GORD. In contrast, Roux-en-Y gastric bypass had a beneficial effect on GORD in all studies, although most of the studies evaluated only symptoms by questionnaires and did not perform 24-h pH measurements, manometry or endoscopy. The studies on restrictive surgery were inconsistent. Moreover, the efficacy of proton pump inhibitors and H_2 receptors antagonists has been reported to be less favourable in obese patients.

One should always bear in mind that symptoms may not be present or may disappear when the oesophagus adapts to the acid exposure by changing into a Barrett's oesophagus. When it comes to bariatric surgery, the intervention with the smallest risk of GORD and GORD complications should be chosen. At present, the discussion will centre around the two possibilities of a gastric sleeve or a gastric bypass. At the one side, procedures that enhance the risk of GORD should be denied to patients having already a Barrett's oesophagus present and thus would favour a gastric bypass over a gastric sleeve. On the other, when severe dysplasia or cancer develops in a Barrett's oesophagus, a gastric sleeve resection may enable the construction of a gastric tube.

1.8.2 Gallbladder and Pancreas

1.8.2.1 Gallbladder

Gallbladder Stones

Obesity is a risk factor for the formation of cholesterol gallstones and exposes patients to increased risk of gallstone-related complications. Rapid weight loss is also a risk factor for gallstone formation in obese patients, making the risks especially high in those who go through prominent cycles of gaining and losing weight [33, 110, 111]. Gallstone disease is one of the most prevalent and costly digestive diseases in Western countries with a prevalence of 10–15% in adults [112]. According to the third National Health and Nutrition Examination Survey (NHANES III) about 6.3 million of men and 14.2 million of women aged 20–74 in the USA might suffer from gallbladder disease [113].

Depending on the chemical composition, gallstones are often classified as pure cholesterol, pure pigment and mixed stones. In developed countries, cholesterol gallstones account for about 75% of stones [114–117]. For cholesterol gallstones, the textbooks always mention the 5F's which are still valid: at risk are Females, Fat people, Fair (in this context meaning prosperous) subjects, Fertile women and 40–50 years of age, with endogenous oestrogens, oral oestrogens and contraceptives being involved, as well as conditions leading to gallbladder stasis. Ethnics and genetics also play a role: the Pima Indians of Arizona display the highest prevalence

rate of cholesterol gallstones in the world (about 80% in women by age 25–30), together with a high prevalence of both obesity and type 2 diabetes mellitus, thus combining the most provoking factors [118].

Obesity as such is associated with a higher risk of gallbladder stones linearly increasing over the BMI range compared with a BMI of 22 kg/m^2 with a factor of 1.7 at a BMI of 25, a factor of 3.7–6.0 at a BMI 30–35 and of 7.4 at a BMI >45 kg/m^2 [119, 120]. In males, risks are lower and more related to the central/visceral distribution of adipose tissue. In the Health Professional Study focusing on men, being 40–55 years of age at inclusion and followed for up to 10 years, a 2.5-fold increased risk of developing gallstones was found [121]. Besides obesity per se, the metabolic syndrome has a marked influence on cholesterol gallstones in men [122]. Many obesity-associated factors contribute to the risk of gallstone formation such as the diet, physical inactivity, metabolic syndrome, dyslipidaemia, insulin resistance and gallbladder stasis [110, 116, 117, 123]. Also, the treatment may contribute to the risks: the rapid weight loss as seen with very low calorie diets and with bariatric surgery, i.e., >1.5 kg/week, but also treatment with orlistat, a lipase inhibitor [124, 125]. The risks increase with weight cycling: with greater risks the greater the weight fluctuations and the greater its frequency of occurrence [33, 110, 111].

Gallstones and Complications

Increased BMI is also a risk factor for symptomatic gallstone disease and other complications of gallstone disease such as acute cholecystitis, choledocholithiasis, cholestatic jaundice, acute cholangitis and acute pancreatitis [124, 126]. In women, 30–55 years of age at inclusion in the Nurses' Health Study and followed for up to 18 years, increasing BMI was associated with a threefold increased risk of gallstones [120]. A dramatic increase was observed in the incidence of symptomatic gallstones with a need of cholecystectomy, or newly diagnosed symptomatic gallstones. The incidence of symptomatic gallstones increased from approximately 0.25% per year of follow-up in women with a BMI <24 kg/m^2 to more than 2% per year of follow-up in women with a BMI above 45 kg/m^2.

The presence of gallstones in the gallbladder is associated with the increased prevalence of gallbladder cancer [127]. Overall, the estimated prevalence of gallbladder cancer is 0.5–3%. Gallbladder cancer has a high grade of malignancy and is diagnosed late: it is a rare but often lethal complication of gallstones.

Pathophysiology of Gallstone Formation in Obesity

Central to the formation of gallbladder stones in obesity are the following:

1. Increased cholesterol synthesis and secretion by the liver [114–117]: The amount of cholesterol synthesised by the liver is linearly related to body fat (i.e. about 20 mg of additional cholesterol is synthesised daily for each kg of extra body fat). Because of insulin resistance, hyperinsulinaemia and dyslipidaemia, the liver secretes more cholesterol in the bile with an increased propensity to cholesterol-rich stones.

2. Supersaturated bile: Supersaturated bile is characterised by excess cholesterol relative to bile salts and phospholipids allowing solid cholesterol monohydrate crystals to aggregate and grow in the gallbladder [116, 128]. Gallbladder bile was supersaturated with cholesterol in all obese patients [129]. Also, increased cholesterol pronucleating factors such as gallbladder mucin and biliary calcium were present [129, 130].
3. Gallbladder-emptying disturbances: Reduced gallbladder emptying and gallbladder stasis are often a feature of obese subjects [131]. It might be related to their eating pattern with a prolonged period of fasting because of skipping breakfast and might act as a contributing factor for the aggregation of solid cholesterol crystals and stone growth. Mathus-Vliegen et al. showed that obese subjects with the largest fasting gallbladders had the largest residual and least emptying gallbladders and scored the highest in every aspect of body size, composition and fat distribution, and also had the highest insulin levels [132]. Body weight and fasting insulin levels explained 35.2% of the variance in fasting volume, lean body mass and insulin explained 28.1% of the residual volume and waist circumference explained 23.6% of the ejection volume.
4. Rapid and substantial weight loss after a very-low-calorie diet or bariatric surgery, secondary to enhanced mobilisation of cholesterol and thereby increased biliary cholesterol secretion: Also, secondarily a decreased hepatic bile acid pool and reduced hepatic secretion of biliary bile salts may play a role [111, 116, 117, 130, 133, 134]. Orlistat, reducing the fat absorption by 30% by lipase inhibition, might impair gallbladder emptying, thus further predisposing weight-losing obese subjects to gallstone formation [125]. One month of lipase inhibition by orlistat significantly impaired gallbladder motility, which persisted to some extent after 1 year. Therefore, obese subjects with diabetes or hyperlipidaemia, who are more at risk of gallstones, should be followed carefully.

Solid conglomerates of cholesterol monohydrate crystals, mucin gel, calcium bilirubinate and proteins accumulate and are deposited in the gallbladder to form gallstones. Obesity is also likely to act on and to potentiate lithogenic mechanisms by several associated conditions. These include the metabolic syndrome, insulin resistance, diabetes mellitus, autonomic neuropathy, gallbladder stasis, hypertriglyceridaemia, low HDL-cholesterol levels, sedentary lifestyle and the Western high-calorie, high-fat and refined sugar diet [110, 135]. The metabolic syndrome combines a visceral fat distribution with hypertriglyceridaemia, low HDL-cholesterol levels, impaired fasting glucose levels and hypertension and the central feature is insulin resistance and hyperinsulinaemia. These metabolic syndrome criteria have either isolated or combined effects on the process of cholesterol gallstone formation as shown in a cross-sectional study from China [136]. A number of 7570 subjects including 918 gallstone patients were investigated as to the different components of the metabolic syndrome during a physical check-up. Gallstone prevalence increased with the number of the criteria of the metabolic syndrome being present, from a prevalence of about 5% without any criteria to about 25% when all

five criteria were present. This appeared to increase the risk of gallstone disease by four times in both men and women.

1.8.2.2 Pancreas

Acute Pancreatitis

Gallstones (45%) and alcohol (35%) are the most common aetiologies for acute pancreatitis [137]. Other factors are metabolic derangements such as hypertriglyceridaemia (1–4%) and hypercalcaemia (1.5%), drugs (1.3–1.4%), genetic mutations, trauma (blunt or penetrating trauma or post-ERCP (endoscopic retrograde cholangiopancreaticography)), smoking and infections. The aetiology is different according to gender, age and country: in men acute pancreatitis occurs at ages 30–45 due to alcohol, and in females at ages 50–70 due to gallstone disease. In the UK and Germany gallstones prevail as a causal factor whereas in Italy, the USA and Australia one of the major causes is alcohol [138]. The annual incidence ranges from 4.9 to 35 per 100,000 and acute pancreatitis was the leading gastrointestinal cause of hospitalisation in the USA in 2012 [139]. There is an increase in the incidence of acute pancreatitis in the past 40 years, probably due to a greater prevalence of risk factors such as increased alcohol consumption, obesity and diabetes.

Whatever the cause, exposure to toxins, including alcohol and medication; elevated serum triglycerides or calcium levels; overdistension, obstruction and increased permeability of the pancreatic duct; or ischaemia, trauma and viral infections, the final common pathway to clinical pancreatitis involves activation of pancreatic enzymes with autodigestion of the gland and peripancreatic tissues [137, 138, 140–147]. Normally, autodigestion of the pancreas is prevented by storing the proteases (trypsinogen, chymotrypsinogen, proelastase, phospholipase A) in a precursor form and by the synthesis of protease inhibitors. Pancreatitis occurs when premature activation of these enzymes occurs and the balance between activated proteases and protease inhibitors is disrupted. Premature activation and intracellular release of intrinsic enzymes lead to pancreatic acinar cell injury and, when released into the interstitium, to autodigestion of the organ with devastating effects on its function [138]. The activated pancreatic enzymes subsequently enter the bloodstream, resulting in elevated amylase and lipase blood levels, and leak into the peripancreatic tissue producing characteristic fat necrosis and exudation. The local injury is amplified through the induction of a systemic inflammatory response syndrome (SIRS), mediated by the generation and release of cytokines and the recruitment of aggressive inflammatory cells [137, 138, 143–145]. The gut hypothesis of multiple-organ failure (MOF) supposes that failure of the intestinal barrier function and increased intestinal permeability allow macromolecules, bacteria, endotoxins and antigens to pass into the portal circulation, and thus enter into the tissues of mesenteric nodes, liver, spleen and pancreas. This evasion elicits an inflammatory response by stimulating the macrophages and circulating neutrophil granulocytes and by inflammatory cytokines (interleukin-1 (IL-1), IL-2, IL-6 and TNF-α) [144]. These inflammatory mediators may exacerbate the systemic inflammatory response associated with this process, worsening the overall clinical severity of the

pancreatitis and contributing to complications of organ failure and nosocomial infections. The importance of preventing bacterial gut translocation is further stressed since almost 40% of severe acute pancreatitis cases develop infectious complications such as infected necrosis, pancreatic phlegmons and peripancreatic fluid collections [137, 138]. The organisms responsible for the majority of pancreatic infections are typically those found to colonise the gastrointestinal tract.

The severity of acute pancreatitis forms a continuum from a relatively mild, self-limiting illness in 80–85%, which usually resolves spontaneously within days, to a moderately severe disease with transient organ failure and/or local and systemic complication that resolve within 48 h to a fulminant, rapidly progressive and severe disease with persistent organ failure and development of local and systemic complications in 15–20%. The mortality is between 5% and 15% [137, 148]. An Italian study in 1005 patients reported a mortality of 5%, with a low mortality of 1.5% in mild acute pancreatitis and 17% in severe pancreatitis [149]. A systematic review on acute pancreatitis reported an overall mortality of 5%, with a mortality of 3% in interstitial pancreatitis with acute oedema and inflammation of the pancreas and 17% in necrotising pancreatitis with inflammation and pancreatic and peripancreatic necrosis [150]. In patients with necrotising pancreatitis the mortality may be as high as 12% in sterile necrosis, 30% with infected necrosis and 47% with multi-organ dysfunction. Early death is often linked to systemic inflammatory response syndrome (SIRS) and multi-organ dysfunction (MOD); late death is more often associated with infected pancreas necrosis, sepsis and its complications [137, 148, 150–152].

Monitoring the severity of acute pancreatitis by biochemical, radiological and multifactorial scales of several prognostic factors is relevant but none has proven to be perfect and the most ideal prognostic system is still undetermined. Some scores take 48 h to complete such as the Ranson and Imrie/Glasgow scores where for example in the Ranson score five parameters need to be judged at entry and another six after 48 h [153]. Mortality increased with an increasing score and severe pancreatitis was defined by a Ranson score ≥3 with a mortality of 11–15% whereas a score of ≥6 was associated with a 40% mortality and a score of ≥7 with 100% mortality. Although already in 1999 a meta-analysis found the Ranson score to be a poor predictor of severity, it is still widely used [154]. Probably the most widely studied severity scoring system in acute pancreatitis is the APACHE-II score with 12 physiologic measures; a score of ≥8 is associated with a mortality of 11–18% and therefore it is taken as an indication of severe pancreatitis [148, 150]. New severity scores including obesity such as the APACHE-O have been proposed [155]. One point was added for a BMI of 25–30 and two points were added for a BMI >30 kg/m^2.

Meta-Analyses

Four meta-analyses have studied the relationship between obesity and the risk of acute pancreatitis, the severity and its complication [156–159]. No general accepted definitions of acute pancreatitis were proposed until September 1992, when the so-called Atlanta criteria were launched which were revised in 2012 [150, 160]. All four meta-analyses used the Atlanta criteria and the aetiology was mainly biliary

(about 60%) followed by alcohol (about 17%). None of the meta-analysis took into account the distribution of fat and also could not adjust for gallbladder and other obesity-associated diseases.

Martinez et al. updated their 2004 meta-analysis in 2006. Obesity was defined by a BMI ≥30 kg/m^2 [156, 157]. The meta-analysis involved 739 patients. Severe acute pancreatitis, defined by the Atlanta criteria, was 2.9 times more frequent in obese subjects (OR 2.9 (1.8/4.6)). They were also more at risk for systemic complications such as respiratory failure, renal failure and shock (OR 2.3 (1.4/3.8)) and for local complications (OR 3.8 (2.4/6.6)) such as severe necrosis and pancreatic infection with a twice as great risk of mortality (OR 2.1 (1.0/4.8)). This meta-analysis could not answer the question if the relationship between obesity and gallstones is associated with the relationship between obesity and acute pancreatitis.

Hong et al. retrieved 14 studies: five studies evaluated BMI as a risk factor (N = 1571) and nine evaluated obesity as a prognostic marker for acute pancreatitis (N = 1365) [158]. Although the heterogeneity was high, obese patients when compared with normal-weight subjects had a 34% increased risk of acute pancreatitis. There was an increased risk of severe acute pancreatitis (summary relative risk (SRR) 1.82 (1.44/2.30)), an increased risk of systemic (SRR 1.71 (1.147/2.50)) and local complications (SSR 2.32 (1.79/3.00)) and an increased mortality (2.21 (1.28/3.83)), all without significant heterogeneity.

Wang et al. decided to study the impact of overweight besides that of obesity [159]. In eight studies including 939 patients the risks of severe pancreatitis (OR 2.48 (1.34/4.60)), local complications (OR 2.58 (1.20/5.57)) and mortality (OR 3.81 (1.22/11.83)) but not for systemic complications were increased in overweight patients. The poor prognosis for obese patients was again confirmed: in seven studies involving 786 obese patients obesity was associated with severe acute pancreatitis (OR 3.36 (2.35/4.81)). Complications were studied in four studies (n = 567). Both local (OR 6.23 (3.90/9.94)) and systemic (OR 2.95 (1.85/4.69)) complications were increased in the obese. The seven studies that looked at mortality (n = 889) found obesity to be related with significant mortality (OR 3.31 (1.96/5.60)). So, not only obesity but also overweight are additional prognostic factors of severity, local complications and mortality in acute pancreatitis.

Why Are the Obese at Risk of Acute Pancreatitis and Local and Systemic Complications?

Obesity is associated with several factors associated with the development of acute pancreatitis, such as gallstones, use of alcohol, smoking and high serum levels of triglycerides. There are two theories explaining the initiation of pancreatitis in gallstones: either obstruction at the ampulla due to an impacted stone or oedema as a result of the passage of a stone or reflux of bile into the pancreatic duct during transient obstruction by a stone at the ampulla [137, 141, 148]. Alcohol may increase the synthesis of digestive and lysosomal enzymes responsible for the development of acute pancreatitis by the pancreatic acini, making them oversensitive to the action of cholecystokinin [161, 162]. Smoking is an independent risk factor but the mechanism remains unclear [163]. Hypertriglyceridaemia occurs in the setting of obesity,

diabetes and use of medications such as β-blockers, but the pathogenesis of pancreatitis in this condition is unexplained.

Besides the obese having several factors predisposing them to acute pancreatitis, there are obesity-related peculiarities that make them at risk for an adverse outcome [156–158]. Patients with obesity have a large visceral fat mass and increased accumulations of peripancreatic fat. The risk of infection is associated with the amount of pancreatic necrosis. They also have hyperinsulinaemia and thereby changes in their microcirculation which are predisposing to ischaemia. The excess visceral adipose tissue contributes to and accelerates the inflammatory cascade as adipose tissue is an important source of pro-inflammatory cytokines. The inflammatory condition of obesity may thus enhance the systemic inflammatory response syndrome (SIRS) and multi-organ dysfunction (MOD) in acute pancreatitis. Obese have a restricted movement of chest wall and diaphragm and a reduced inspiratory capacity, leading to hypoxia and respiratory failure. The ischaemia and hypoxia result in deficient tissue oxygenation, which may aggravate the consequences of the excessive inflammatory response with multi-organ failure and death [156–158].

Pancreatic Cancer

There is a strong role for obesity and diabetes in the risk of pancreatic cancer. At least ten prospective trials have reported an elevated risk of pancreatic cancer when those with a BMI ≥30 kg/m^2 were compared with those with a normal weight (BMI <25 kg/m^2). The risks varied from 1.2 to 3.0 [164]. A meta-analysis of 14 studies showed a 19% increased risk when comparing a BMI of 30 with that of BMI 22 (RR 1.19 (1.10/1.29)) [165].

The problem of the association between pancreatic cancer and type 2 diabetes is the obvious reverse causality: patients may develop type 2 diabetes as a result of their disease. Also, type 2 diabetes is often present in overweight and obese people and correction for the presence of overweight is lacking in most of the studies. A meta-analysis of 20 studies by Everhart et al. estimated that long-standing diabetes, for more than 5 years, increased the risk of pancreatic cancer twofold (RR 2.0 (1.2/3.2)) [166]. A more recent meta-analysis of 50 studies by Huxley et al. found a slightly weaker association compared with non-diabetics; the risk was 50% higher both when diabetes existed for 5–9 or 10 years and longer (RR 1.5 (1.3/1.8) and RR 1.5 (1.2/2.0), respectively) [167].

Four studies examined the role of elevated glucose levels in the risk of pancreatic cancer [168–171]. Two studies, the Chicago Heart Association Detection Project and the Whitehall study, looked at glucoses after a glucose tolerance test (GTT) and found a 2.4 times (especially in men) and a 4 times increased risk of pancreatic cancer, respectively, in those with elevated versus normal post-GTT glucose levels [168, 169]. The Korean Cancer Prevention Study followed patients with diabetes for 10 years and found a 70% increased risk of pancreas cancer [170]. In the Alpha Tocopherol Beta Carotene (ATBC) study a twofold increase in risk was observed for those with glucose ≥7 versus <7 mmol/L and a similarly increased risk in those with insulin in the highest versus the lowest quartile [171]. So there were

statistically significant dose-response associations between glucose levels and pancreatic cancer. Apart from insulin there may be a role for insulin-like growth factor-1 (IGF-1) and oxidative stress.

The role of the diet composition with respect to carbohydrates, glucose and glycaemic index is debated. The relationship between carbohydrate intake, glycaemic index and glycaemic load and pancreatic cancer is inconsistent [164]. The role of added sugar, refined sugar and fructose has been examined in different studies showing a 2- to 3-fold increased risk with added sugar, a 2-fold increased risk with the intake of refined sugar and a 2.3-fold increased risk for ≥2 sweetened soda servings per day and a non-significant risk for fructose from high-fructose syrup [172–175].

1.8.2.3 Implications for Clinical Practice

As obese patients are at risk of gallstone development and of severe pancreatitis and cholangitis when duct obstruction occurs, all measures should be taken to diminish at least the risks. Besides a gradual weight loss when they attempt to lose weight, they should be advised to have a normal three-meal eating pattern without skipping breakfast and without having long periods of fasting. Advices of not drinking alcohol and not smoking should be given. When weight losses exceed the limit of safe weight loss of <1.5 kg/week, ursodeoxycholic acid should be recommended. As a preventive measure attention to the fat content of the diet should be given, which should at least contain 10 g of fats (which is often not the case with very-low-calorie diets). The prophylactic use of 600 mg ursochol for 6 months following gastric bypass has been shown to reduce the incidence of gallstones to 2% in the treatment group compared to 32% in the placebo group [176]. Six months' daily intake resulted in prolonged absence of gallstone formation as at 24 months the differences were still present [177]. This is important as gallstone formation is correlated with the rate of weight loss and bile cholesterol normalises when the weight stabilises, usually after 24 months, and stones may disappear spontaneously. More importantly, the effectiveness of ursodeoxycholic acid prophylaxis has been confirmed by a meta-analysis [178].

1.8.3 Rectocolon

Colorectal cancer is, after lung cancer, breast cancer in women and prostate cancer in men, the fourth most incident cancer and the third leading cause of cancer-related death [179, 180]. The cumulative lifetime risk of developing colorectal cancer in the general population is 5%. As there is a distinct precursor in the form of an adenoma with the well-known adenoma-carcinoma sequence, a screening programme for colon cancer either by examination of stools or by sigmoidoscopy or colonoscopy, with removal of adenomas when present, has been instituted in many countries and has come to fruition with a favourable cost-benefit balance. The adenoma carcinoma sequence is a multistep, multipath and multifocal process with progression of normal mucosa to small polyps and later larger ones that change from advanced

adenomas with advanced histology to invasive cancer. The advanced adenomas, defined by size ≥1 cm, villous component and/or high-grade dysplasia, are adenomas that more likely progress to colorectal cancer.

Known risk factors for colorectal cancer (CRC) are the presence of colon polyps, age, menopausal status, family history of CRC, genetic alterations such as in familial adenomatous polyposis (FAP) and the Lynch syndrome, and inflammatory bowel disease [179]. The rapid rise of colon cancer in several populations previously considered at low risk for colon cancer, the incidence changes in migrant populations and the 20-fold difference in incidence between high- and low-risk areas suggest environmental factors as aetiological agents [181]. Obesity has been proposed as a risk factor for CRC and more for colon than for rectum cancer and the association is weaker for women than for men. The risk is increased in younger and premenopausal women compared to older and postmenopausal women. In Europe 11% of the CRC cases are attributed to overweight and obesity [180]. Other factors like the distribution of adipose tissue, oestrogen levels, physical activity and diet also influence the risk of colorectal cancer. Dietary factors include the consumption of red meat and processed meat, low consumption of fruits and vegetables, low-fibre diet and foods low in calcium and folate.

1.8.3.1 Colorectal Adenoma

Obesity doubles the risk of development of colon adenomas and weight gain is also associated with an increased risk [179]. The risk appears higher in men than in women. The obesity risk is increased further by the abdominal, visceral distribution of fat which is reflected in an increased waist circumference or in increased visceral adipose tissue (VAT) as measured by computer tomography (CT) at the level of L4–L5. For instance, patients with adenomas had on average 1.5 times the VAT area compared with subjects without adenomas and increased VAT area was also associated with the number, size and aggressive histology of adenomas and advanced adenomas [164, 181]. VAT was not associated with recurrence of adenomas, suggesting that visceral adiposity promotes growth rather than increasing the occurrence.

Patients with diabetes are also at increased risk for colon adenoma, especially those who are obese [164]. In the Nurses' Health Study an increased risk for adenomas was found (RR 1.63) in the highest quartile of C-peptide levels when controlling for BMI and exercise [164]. In the Veteran Study, advanced adenomas were found in 2903 older and male veteran patients [182]. Obese patients had a greater prevalence of advanced adenomas when compared with overweight and normal-weight patients (28% vs. 23% and 24%). The risk of advanced adenoma by obesity was 1.01 (1.0/1.02) and there was a corresponding 1% increase in the frequency of finding an advanced adenoma per unit increase of BMI above 30. The findings were controlled for NSAID use, statin use, age and family history of CRC without changing the association. Controlling for NSAID use is important as they block cyclooxygenase (COX) enzymes and nuclear factor-kappa B (NF-κB) and thus prevent angiogenesis and have a pro-apoptotic effect on colonocytes. Statins in rodents have been shown to reduce the CRC risk by 47%.

In a case-control study 2244 age- and sex-matched Korean subjects (1122 with and 1122 without adenomas) underwent an abdominal CT with measurement of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), colonoscopy, and were also investigated for the 5 different components of the metabolic syndrome (MetS) adapted for use in Asian populations and for insulin resistance by the HOMA-IR index [183]. The prevalence of smoking, hypertension and MetS and a family history of CRC were higher in the adenoma group than in the normal control group. In addition BMI, SAT and VAT areas, waist circumference, insulin and triglycerides were higher and HDL cholesterol levels lower in the adenoma group. Mean HOMA was also higher in the adenoma group. In univariate analysis the presence of the MetS (OR 1.55 (1.27/1.90)) appeared to be a risk factor and when analysing the five components of the MetS after correction for NSAID aspirin and positive family history, increased waist (OR 1.66 (1.38/1.99)) and elevated triglycerides (OR 1.53 (1.25/1.89)) were found to be the most prominent MetS components that were significantly associated with colon adenoma. These two factors of the MS were considered to be closely related to visceral obesity but they were lost in the multivariate analysis when also VAT was included, meaning that VAT more sensitively predicts the presence of colorectal adenoma. In multivariate analysis VAT was independently associated with the risk of colorectal adenoma (OR 3.09 (2.19/4.36) for the highest quintile versus the lowest quintile) and there appeared to be a dose-dependent relationship: for a 10 cm^2 increase in VAT area the risk of colorectal adenoma increased by 9%. VAT but not SAT was found to be related to the number of polyps, maximum polyp size and advanced adenoma.

Two recent studies urged the need to look at the colon in patients with non-alcoholic fatty liver disease (NAFLD) [184, 185]. Hwang et al. investigated 2917 participants by colonoscopy, ultrasound and liver tests; they found a prevalence of 41.5% of NAFLD in patients with adenomatous polyps and of 30.2% in the control group [184]. Wong et al. recruited subjects of 40–70 years referred for colonoscopic screening from two study cohorts: one cohort from the community, who had their liver fat estimated by proton magnetic resonance spectroscopy (^{1}H-MRS), and the other cohort from patients with biopsy-proven NAFLD [185]. Patients with NAFLD had a higher prevalence of adenomas (34.7% vs. 21.5%) and advanced adenomas (18.6% vs. 5.5%) than healthy controls. Moreover, 46.4% of adenomas in NAFLD and 44.7% of the advanced adenomas were right-sided lesions. In the group of biopsy-proven NAFLD, patients with inflammation, i.e. patients with non-alcoholic steatohepatitis (NASH), had a higher adenoma rate (51.0% vs. 25.6%) and advanced adenoma (34.7% vs. 14%) than non-NASH NAFLD patients. After adjustment, NASH was associated with an about five times higher risk of adenoma (OR 4.89 (2.04/11.7)) and advanced adenoma (OR 5.34 (1.92/14.84)) rate compared with simple steatosis. Patients with simple steatosis were similar to control subjects in adenoma and advanced adenoma rates. So, NASH was associated with a high prevalence of adenomas and advanced adenomas and these were mainly located in the right colon, needing a total colonoscopy procedure. NAFLD patients are characterised by a profound insulin resistance, with high insulin and IGF-1 levels and low adiponectin levels, and a pro-inflammatory state [185].

Meta-Analyses

A significant increased risk of colorectal polyps was found in patients with obesity and with abdominal obesity. Lee et al. included 25 studies in their meta-analysis and found a pooled odds ratio for obesity and abdominal obesity of 1.43 (1.23/1.67) in 22 studies and 1.42 (1.30/1.56) in 12 studies, respectively [186]. In a subgroup meta-analysis the risk was present for both men and women, for Asian and non-Asian countries and for distal and total colorectum, and the risk was highest for advanced polyps (OR 2.16 (1.49/3.14)). Also a dose-response relationship was present with risks increasing from 1.19 in the lowest category of BMI to 1.40 in the middle and 1.69 in the highest BMI category. They suggested that the strong positive association of abdominal adiposity with large and advanced polyps supported the hypothesis of the role of hyperinsulinaemia, in which insulin and insulin-like growth factor-1 (IGF-1) are the molecules mediating the progression of small to advanced polyps. The growth and progression by the effects of insulin and IGF-1 seem stronger in advanced than in less advanced polyps. In an extensive and comprehensive review Bardou et al. summarised their findings on four meta-analysis on colorectal adenoma [180, 186–189] (Table 1.5). All meta-analyses showed a small but significant association with similar trends over sexes, races, countries, site in the colon other than rectum, etc. The most recent meta-analysis by Okabayashi found a dose relationship with BMI 25–30 of 1.21 and BMI ≥30 of 1.32 when compared with a BMI <25 kg/m^2 [188]. Ben et al. looked at the dose-response per 5 unit increase in the BMI (Table 1.5) [188, 189].

1.8.3.2 Colorectal Carcinoma

Several large studies and also different meta-analyses have found a consistent positive association of obesity defined as a BMI ≥30 kg/m^2 and colon cancer in men and women. Bardou et al. summarised the findings of 5 meta-analyses and found a moderately increased risk of 1.5–2-fold (Table 1.6) [37, 180, 190–193]. The association was weaker for women than for men. This was also true for the waist circumference and the WHR. Most studies showed that the associations of waist circumference and WHR with colon cancer were stronger than for BMI and the associations remained when they corrected for BMI but attenuated when they corrected for waist circumference and WHR, indicating the strongest influence of abdominal obesity [191]. Most of the studies report a lower but significant association of rectum cancer with BMI in males; in females this association is inconsistent and also the relationship of rectum cancer with waist and WHR is unclear or absent (Table 1.6).

There seems also to be an ethnic difference as findings of the USA and Europe are in the same direction and with a somewhat higher risk estimate in the USA concerning the relation between obesity and colon cancer or CRC whereas in Asian countries mainly obese males seem to be affected by colon cancer (Table 1.6). Many of the studies did not take into consideration the effect modification by age and menopausal status which may explain the inconsistent or weak findings among women. The menopausal status was addressed by the Canadian Breast Screening Study which found a weak and insignificant association with

Table 1.5 Published meta-analyses on colorectal adenoma (CRA) with only mentioning of risk ratios that were statistically significant

Author and year	No. of studies/ search period	Reported analysis	Outcomes	Risk ratios (95% CI)
Lee'11 [186]	25 studies/1964–June 2010	Lower class BMI ≥25 and ≥23 in Asians Moderate-class BMI ≥30 and ≥25 in Asians	Men Women Asian countries Western countries Waist Site distal CR Site total CR Large/advanced Small/ non-advanced	1.39 (1.10/1.76) 1.37 (1.08/1.73) 1.88 (1.30/2.71) 1.30 (1.11/1.52) 1.42 (1.30/1.56) 1.46 (1.46/1.72) 1.45 (1.17/1.78) 2.16 (2.16/3.14) 1.51 (1.15/1.99)
Hong'12 [187]	21 studies/up to October 2011	Dose-response per 10 cm increase in waist and 0.1 unit increase in WHR	Waist WHR Men waist Women waist Men WHR Asian waist Non-Asian waist Non-Asian WHR	1.39 (1.24/1.56) 1.22 (1.10/1.36) 1.38 (1.11/1.70) 1.24 (1.00/1.56) 1.34 (1.14/1.58) 1.38 (1.17/1.56) 1.39 (1.20/1.61) 1.26 (1.11/1.43)
Okabayashi'12 [188]	23 studies/1980–August 2011	BMI 25–30 and ≥30 vs. BMI <25	BMI risk CRA Western countries Asian countries	1.24 (1.16/1.33) 1.18 (1.04/1.34) 1.35 (1.27/1.44)
Ben'12 [189]	36 studies/up to July 2011	Dose-response per 5 unit increase in BMI	BMI risk CRA Men Women White USA Europe Asia <10 mm ≥10 mm Non-advanced Advanced	1.19 (1.13/1.26) 1.15 (1.05/1.26) 1.08 (1.02/1.14) 1.12 (1.04/1.21) 1.18 (1.09/1.26) 1.16 (1.06/1.27) 1.29 (1.11/1.51) 1.53 (1.18/1.98) 1.49 (1.16/1.91) 1.36 (1.17/1.58) 1.70 (1.12/2.58)

BMI Body mass index; *WHR* waist/hip ratio; CI confidence interval; CR colorectal

obesity (BMI ≥30 kg/m^2) in the entire cohort (HR 1.08 NS) [194]. Obesity was associated with an approximately twofold risk (HR 1.88 (1.24/2.86)) in women who were premenopausal at inclusion and no altered risk was present among postmenopausal women (with a trend of a small to moderately decreased risk (HR 0.92) for colon cancer). Similar results were found in three older studies with a twofold increased risk in Swedish obese subjects below age 55, in female Seventh Day Adventists, and in obese women in the Nurses' Health Study who were between 34 and 59 at entrance [195–197]. These findings are surprising given that the menopause is associated with a redistribution of fat towards the abdomen [181]. Age is a bias here, as Swedish obese subjects older than 55 years and nurses older than 65 years did not have a higher CRC risk [196, 197]. So, the association

Table 1.6 Published meta-analyses on colorectal cancer (CRC) with only mentioning of risk ratios that were statistically significant

Author and year	No. of studies/ search period	Reported analysis	Outcomes	Risk ratios (95% CI)
Dai'07 [190]	15 studies/up to January 2007	BMI ≥30	Men colon cancer	1.71 (1.33/2.19)
			Men rectal cancer	1.75 (1.17/2.62)
			Men CRC	1.37 (1.21/1.56)
			Waist men colon	1.68 (1.36/2.08)
			Waist women colon	1.48 (1.19/1.84)
			WHR men colon	1.91 (1.46/2.49)
			WHR women colon	1.49 (1.23/1.81)
			WHR men rectum	1.93 (1.19/3.13)
Larsson'07 [191]	31 studies/1966–April 2007	Per 5 unit increase in BMI, per 10 cm increase in waist and per 0.1 unit increase in WHR	Men colon	1.30 (1.25/1.35)
			Women colon	1.12 (1.07/1.18)
			Men rectum	1.12 (1.09/1.16)
			Waist men colon	1.33 (1.19/1.49)
			Waist women colon	1.16 (1.09/1.23)
			Waist men rectum	1.12 (1.03/1.22)
			WHR men colon	1.43 (1.19/1.71)
			WHR women colon	1.20 (1.08/1.33)
			USA men colon	1.39 (1.31/1.48)
			USA women colon	1.17 (1.08/1.25)
			EU men colon	1.27 (1.22/1.32)
			EU women colon	1.04 (1.02/1.07)
			Asia men colon	1.16 (1.05/1.28)
Moghaddam'07 [192]	31 studies/up to April 2007	BMI ≥30	Men CRC	1.46 (1.36/1.56)
			Women CRC	1.15 (1.06/1.24)
Guh'09 [37][a]	12 studies/up to January 2007	BMI ≥30	Men CRC	1.95 (1.59/2.39)
			Women CRC	1.66 (1.52/1.81)
			USA men CRC	1.86 (1.40/2.46)
			USA women CRC	1.47 (1.30/1.66)
			EU men CRC	2.00 (1.40/2.87)
			EU women CRC	1.74 (1.68/1.81)
			Waist men CRC	2.93 (2.31/3.73)
			Waist women CRC	1.55 (1.27/1.88)
Harriss'09 [193]	28 studies/1966–December 2007	Per 5 unit increase in BMI	Men colon	1.24 (1.20/1.28)
			Women colon	1.09 (1.04/1.14)
			Men rectum	1.09 (1.06/1.12)
			USA men colon	1.35 (1.21/1.50)
			USA women colon	1.13 (1.06/1.19)
			EU + A men colon	1.21 (1.18/1.24)
			EU + A women colon	1.04 (1.00/1.07)
			Asian men colon	1.32 (1.20/1.46)

BMI Body mass index, *WHR* waist/hip ratio, *EU* Europe, *EU + A* Europe + Australia; *CI* confidence interval

[a]Data given as incidence risk ratio

between obesity and CRC in premenopausal women may be as strong and as consistent as that in men.

Apart from age and menopausal status physical activity is a confounding factor [181]. A meta-analysis of the association between CRC and physical activity by

Samad et al. could demonstrate a similar decrease in colon cancer (not rectal cancer) risk by increased physical activity both in men and women [198]. Slattery showed that 12–14% of colon cancers can be attributed to lack of involvement in vigorous exercise [199]. Two meta-analysis by the same authors found a decreased risk of colorectal adenoma (OR 0.84 (0.77/0.92)) and colorectal carcinoma (OR 0.76 (0.71/0.82)) with increased physical activity [200, 201]. Adjustment for a confounding factor such as diet (increased red meat and processed meat, low folate and low fibre consumption) did not change the association. Physical inactivity also increases the risk of dying after the diagnosis of colon cancer.

Meta-Analyses

Three of the five meta-analyses as shown in Table 1.6 compared categories of BMI ≥30 kg/m^2 with normal-weight categories. Three of these meta-analyses have also estimated the strength of the association between obesity and CRC and the dose-response relationship: in the meta-analysis of Moghaddam et al. the risk of developing CRC increased by 7% per 2 unit (kg/m^2) increase in BMI and with 4% for each 2 cm increase in waist [192]. In the meta-analysis of Larsson et al. each 5 unit increase in BMI increased the risk by 30% in males and by 12% in females; for each 10 cm increase in waist circumference the risk increased by 33% in men and by 16% in women and for each 0.1 unit increase in WHR the risk increased by 43% in men and by 20% in women [191]. Similarly, Harriss et al. found an increased risk of colon cancer by 24% in males and 9% in females by each 5 kg/m^2 increase in BMI, but only a 9% increased risk in males and no increased risk in females for rectal cancer [193].

1.8.3.3 Pathophysiology of Obesity in Relation to Adenoma and Carcinoma

High BMI, physical inactivity and visceral adiposity are consistent risk factors for colon adenoma and colon cancer [164]. Also patients with type 2 diabetes and metabolic syndrome are at risk. They all have a common feature: hyperinsulinaemia which is a consistent marker of increased colon cancer risk. Also, altered levels of adipokines seem to be of importance. Other biological factors such as bile acids and gut microbiota are still under investigation.

In the pathophysiology of adenoma and carcinoma the role of the visceral fat is predominant by itself or indirectly which is in contrast to gastro-oesophageal reflux disease where also mechanical factors play a role. Colon cancer in men is positively associated with BMI and central adiposity whereas in women these associations are weak or non-existing. Such relationships of rectal cancer are either not investigated and thus unknown, or weak and restricted to men. Visceral fat deposition, reflected in waist circumference measurements or visceral adipose tissue (VAT) measurement by CT, is associated with insulin resistance and higher circulating insulin levels. Especially, hyperinsulinaemia is the critical factor [164, 180, 181]. BMI is strongly correlated with plasma insulin levels. Increased insulin lowers blood levels of insulin-like growth factor-binding proteins (IGFBP-1 and IGFBP-2), resulting in more free and bioactive insulin and IGF-1, which is associated with the risk of CRC in men and women. IGF-1 has a role in the control of normal growth, maintenance of tissue homeostasis, altering the balance between proliferation and apoptosis, and

differentiation, angiogenesis, cell migration, cell adhesion and wound healing. IGF-1 is a procarcinogen that stimulates cell growth and decreases apoptosis. Serum C-peptide is a surrogate test for insulin secretion and many studies found a relation between the highest levels of C-peptide and colon cancer [164, 180, 181]. In the Physicians' Health Study, men with a C-peptide in the highest versus the lowest quintile had a 2.7 times higher risk for CRC after adjustment for BMI and exercise [202]. After controlling for the components of the MetS the risk rose to 3.4. In the Nurses' Health Study both an increased risk of adenomas (RR 1.63) and an increased risk of colorectal carcinoma (RR 1.73) were found in the highest quartile of C-peptide versus the lowest quartile after adjustment for BMI and exercise [203]. Patients with acromegaly have an increased risk of colon cancer because of elevated IGF-1 from excessive growth hormone secretion.

The stronger associations in men may be explained by a more prevalent abdominal obesity. As women tend to accumulate lesser VAT than men with weight gain, this may be an explanation for the gender differences between the risk of cancer and obesity, apart from the role of gonadal hormones. Endogenous oestrogens may be protective and are associated with a lower risk of CRC by inhibiting proliferation and increasing apoptosis [194, 197]. Adipose tissue is the only tissue that expresses oestrogen aromatase and is therefore a primary source of oestrogens by conversion of androgens into oestrogens both in men and women. So, in postmenopausal women extraglandular endogenous oestrogen may counteract the deleterious effects of insulin and IGF-1 and may result in a reduced risk of CRC, which is rather surprising as postmenopausal women behave like men and are more likely to store their fat intra-abdominally [194]. Postmenopausal hormone use has been associated with decreased risk of colon or colorectal cancer in 7 of the 14 studies by Calle et al. [8, 181]. In premenopausal women obesity increases insulin and the contribution of adipose oestrogens is relatively unimportant when compared to that derived from the ovaries [164, 194, 197]. The balance between insulin and IGF-1 and the oestrogens is towards the adverse effects of insulin, thus having a net effect of increasing the risk of CRC. Moreover, adiposity is inversely correlated with testosterone in men but positively associated in women [191]. Androgen deprivation increases adiposity and insulin resistance in men. An obesity-induced reduction of testosterone would be another reason for a higher CRC risk in men.

Physical activity increases insulin sensitivity and reduces plasma insulin levels. It reduced the risk of CRC by 25–50% in physically active individuals [179, 198, 200, 201]. The protection by increased physical activity, related to improved insulin sensitivity, is stronger for colon cancer and absent for rectum cancer [164, 180, 181]. This suggests that colon cancer is more related to insulin resistance and hyperinsulinaemia than rectum cancer. A diet high in refined sugars and low in dietary fibre, linked to colon cancer, also causes hyperinsulinaemia [181].

Metabolic Syndrome

Type 2 diabetes has a 1.43 times increased risk of colon carcinoma and there appears also to be an increased risk for colon adenoma, especially in those who are obese. Hyperglycaemia is associated with increased risk of colon carcinoma. Also,

the presence of the metabolic syndrome increases the risk of colon carcinoma [164, 180]. One study investigated the risk of CRC with increasing number of components of the MetS and found a significantly increased risk of 2.40 and of 2.57 for two and three component versus none [204]. The study by Hu et al. in Taiwan did the same for colorectal adenoma and found a significantly increased risk of 1.61, 2.57 and 3.23 for 3, 4 and 5 components, respectively, of the MetS [205]. Kang et al. [183] measured VAT, SAT and metabolic syndrome components adapted for use in Asian people. In univariate analysis the presence of the MetS (OR 1.55 (1.27/1.90)) is a risk factor and, when analysing the five components of the MS after correction for NSAID, aspirin and positive family history, increased waist and elevated triglycerides were found to be significantly associated with colon adenoma. These two factors of the MetS were lost in the multivariate analysis when also VAT was included. Apparently, VAT predicts more sensitively the presence of colorectal adenoma. VAT has been identified as a risk factor for colorectal adenoma (risk 1.6) and for colorectal cancer with risks varying between 1.9 and 4.0, either independently or via VAT-secreted adipokines [180]. VAT is associated with colorectal adenoma independently of BMI.

Visceral Fat and Adipokines

Omental and subcutaneous fat are metabolically different [206]. The glucose uptake in general, insulin-stimulated glucose uptake and depressed insulin-induced glucose uptake by steroid blockade were greater in omental fat. Also, liposuction of a substantial amount of subcutaneous fat (a mean of 6.3 kg in subjects with normal glucose tolerance and 8.9 kg in type 2 diabetes patients) did not change insulin sensitivity in liver, muscle and adipose tissue; did not change blood levels of glucose, insulin or lipids; and did not result in changes in inflammatory mediators [207]. However, in a pilot study, omentectomy, i.e. removal of visceral fat, together with gastric banding resulted in 2–3 times greater improvements in oral glucose tolerance, insulin sensitivity and fasting plasma glucose and insulin with no differences in blood lipids and these improvements were statistically independent of the loss in body mass index [208].

The relationship between adiposity and insulin sensitivity can be summarised as follows: weight gain increases visceral adipose tissue past a threshold and then the patient passes into a phase of insulin resistance in which the VAT area correlates with C-peptide, insulin and leptin [209].

Insulin is the best established biochemical mediator between obesity and colon cancer. Obesity is also associated with high leptin and low adiponectin levels and both high leptin and low adiponectin levels are related to increased risks of colorectal carcinoma.

Both leptin and adiponectin have an influence on intracellular signal pathways such as the phosphatidylinositol 3-kinase/Akt (PI3K/Akt), mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK), which play an important role in colon carcinogenesis [210]. Leptin is secreted by white adipose tissues and leptin receptors are present in colon tissue. It activates the signal transduction pathways such as Jack kinase, mTOR, AMP-activated protein kinase

(AMPK), ERK and MAPK [180, 209, 210]. High leptin levels are associated with increased colorectal cancer risk and also with more aggressive tumours; it does not initiate tumours but is involved in tumour growth.

Adiponectin is an insulin-sensitising hormone with two known receptors, ADIPOR1 expressed in skeletal muscle and ADIPOR2 expressed in the liver. Also, adiponectin and its receptors are expressed in colonic tissue and adiponectin is inversely associated with colorectal cancer risk [180, 209, 210]. Compared with males in the lowest quintile, men in the highest quintile had a 58% lower risk of colorectal cancer [211]. Two meta-analyses found an inverse association of adiponectin and CRC [212, 213]. One meta-analysis of 13 studies found that per 1 μg/mL higher adiponectin the risk of CRC decreased by 2% [212]. In mice, adiponectin suppresses colonic epithelium proliferation by inhibition of the mTOR pathway and stimulation of the AMP-activated protein kinase pathway, under the condition of a high-fat diet but not a basal diet [84, 214]. A high-fat diet might be able to affect the expression of molecules which link metabolism, inflammation and cancer [214]. Adiponectin counteracts leptin and decreases the PI3K/Akt signal pathway activated by leptin [210, 215]. Adiponectin also modulates genes involved in inflammation and can inhibit inflammatory pathways such as IL-6 and TNF.

1.8.3.4 Implications for Clinical Practice

Current guidelines recommend CRC screening in adults aged 50–70 years. However, it has been demonstrated that males with abdominal obesity and metabolic syndrome might benefit from screening starting at 45 years of age. In the study by Wong et al. males and females aged 40–50 years with biopsy-proven NAFLD, and even more so when inflammation, i.e. NASH, was present, had a higher prevalence of adenomas and advanced adenomas compared with controls, which were in 45% of cases right-sided [184, 185]. The clinical implication might be screening by total colonoscopy at an earlier age than indicated by the guidelines. At least gastroenterologist should be aware of the association.

Apart from being at risk for colorectal cancer while being obese the question is whether obesity influences the outcome after surgery. The outcome might also be related to lifestyle factors associated with obesity such as decreased physical activity and indeed physical inactivity increases the risk of dying after the diagnosis of colon cancer [181]. As to the short-term outcomes for CRC Bardou et al. reviewed the literature on surgery [180]. They retrieved 20 published observational studies and found indications of a significantly longer hospital stay, an increased complication rate, more wound infection and significantly more blood loss. A meta-analysis of 8 studies and a narrative review of 33 studies showed increased conversion rates, operating times and postoperative morbidity [216, 217]. Obesity might be associated with a decreased overall survival in patients with CRC independently of MetS [180].

Bardou et al. also reviewed the response to chemotherapy [180]. Visceral fat and its metabolic hormones promote angiogenesis and thus might predict a less well response to vascular endothelial growth factor (VEGF)-targeted therapy (bevacizumab). They summarised the available literature as follows. When comparing bevacizumab-based regimen with chemotherapy, obese patients with high BMI and

more visceral fat had no response to the former and did well on the latter. High visceral fat was independently associated with time to progress, response and overall survival. These results were confirmed in a study that showed that responders had lower visceral adipose tissue than non-responders. Also in the CAIRO and CAIRO2 studies a high BMI predicted a better survival in the chemotherapy group but not in combined chemotherapy + targeted treatment.

So, to reduce the risk of colorectal cancer, obese patients should lose weight, be more active physically and eat a more healthy food with less meat and more fruits, vegetables, fibre, calcium and folic acid. Although bariatric surgery has resolved or improved many comorbidities and also reduced the mortality risk, there is still some debate about potentially adverse effects. Hull and Lagergren cautioned against the assumption that bariatric surgery will lead to a decreased future incidence rate of CRC [218]. They studied a large cohort of 15,095 patients after bariatric surgery and both restrictive and malabsorptive interventions were included [219]. They found an increased standardised incidence ratio (SIR) of 2.0 (1.48/2.64) for colorectal cancer 10 years after surgery whereas the comparator obese group of 62,016 subjects who had never undergone surgery had a stabile SIR of 1.26 (1.14/1.40). Several factors have to be taken into account: the effect of residual excess weight and a tendency to gain weight postoperatively, but also less desirable consequences of certain operations such as higher intraluminal bile concentrations and changes in microbiota after a gastric bypass, but also the general recommendation to increase the dietary protein postoperatively.

1.8.4 Liver

Non-alcoholic fatty liver disease (NAFLD) encompasses the entire spectrum of fatty liver disease from simple non-alcoholic fatty liver (NAFL) on the one hand to the more complicated non-alcoholic steatohepatitis (NASH), with eventually liver fibrosis/cirrhosis, and hepatocellular carcinoma (HCC) on the other [220, 221]. The natural course and the different stages of the disease with frequencies of evolution are depicted in Fig. 1.5 [222].

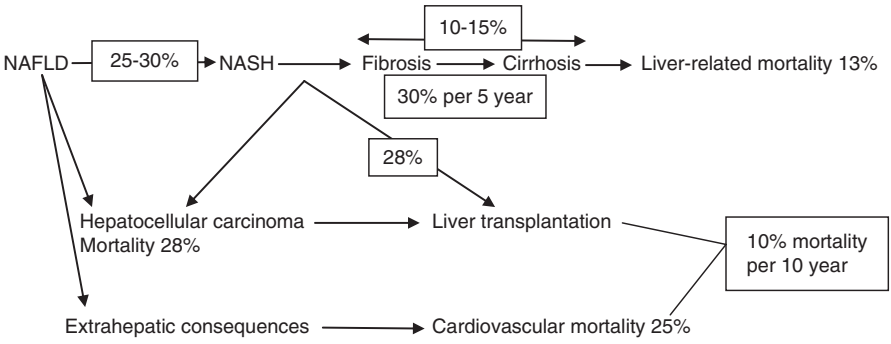

Fig. 1.5 The NAFLD spectrum with rates of prevalence, changeover and mortality

1.8.4.1 Non-alcoholic Fatty Liver Disease

NAFLD is characterised by excessive hepatic fat accumulation, associated with insulin resistance, and is defined by the presence of steatosis in >5% of hepatocytes according to histological analysis, or by a proton density fat fraction, a rough estimation of the volume fraction of fatty material in the liver, >5.6% assessed by proton magnetic resonance spectroscopy (^{1}HMRS) or quantitative fat/water-selective magnetic resonance imaging (MRI) [221].

The diagnosis of NAFLD requires (1) the exclusion of chronic liver diseases associated with fat accumulation such as viral hepatitis, Wilson's disease, lipodystrophy and abetalipoproteinaemia, systemic diseases or certain lipogenic drugs such as amiodarone, corticosteroids and antiretroviral medications and (2) hepatic fat accumulation in the absence of significant alcohol use in the last 2 years, defined as >21 drinks per week in men and >14 drinks per week in women, or a daily alcohol consumption ≥30 g for men and ≥20 g for women [220, 221]. There are also data to suggest that hypothyroidism, hypogonadism, hypopituitarism, sleep apnoea and PCOS, common comorbidities of obesity, further drive NAFLD prevalence and severity independent of obesity [220, 221].

In NAFL simple steatosis is present with an absent to low risk of progression to cirrhosis. The diagnosis of NASH requires the joint presence of steatosis and inflammation with hepatocyte ballooning and lobular inflammation. They may be at risk of progressive disease. The NAFLD Activity Score (NAS) scoring system is a composite score to quantify features of steatohepatitis and to assess treatment response in NASH clinical trials [223]. It is composed of steatosis (0–3), lobular inflammation (0–3) and hepatocyte ballooning (0–2) grades and ranges from 0 to 8. Fibrosis in NASH is staged separately on a scale from 0 to 4 with stages 3–4 considered advanced fibrosis.

NAFLD is tightly associated with insulin resistance, not only in the liver, but also in muscle and adipose tissues, and thus with metabolic risk factors and components of the metabolic syndrome (MetS) and may be considered as the hepatic manifestation of the MetS. The clinical burden of NAFLD being closely related to obesity and other metabolic syndrome risk factors is expected to grow with the bourgeoning epidemics of obesity and diabetes. Moreover, NASH is assumed to be the underlying cause in 30–75% of cryptogenic cirrhosis [224]. NASH-related cirrhosis is the most rapidly rising indication for liver transplantation and by the year 2020 may be the leading cause of liver transplantation.

Patients with NAFLD are mostly asymptomatic and when symptoms are present patients complain of fatigue, malaise and right upper quadrant discomfort. Incidence data are sparse and both incidence and prevalence data of NAFLD vary according to the assessment methods used such as histology, ultrasound, liver aminotransferases or proton magnetic resonance spectroscopy (^{1}H-MRS) or magnetic resonance imaging (MRI). The incidence of NAFLD is 31 and 86 cases per 1000 person-years based on elevated liver enzymes and/or on ultrasound (US), and 34 per 1000 person-years by ^{1}H-MRS, but is also reported as low as 29 cases per 100,000 person-years in a study from the UK [220, 221]. Sherif et al. reviewed the epidemiological data and found a worldwide prevalence of NAFLD between 4 and 46% with a reported

3–5% prevalence of NASH [225]. For Western countries these data are for NAFLD and NASH, 20–40% and 2–3%, respectively. In the USA prevalences of 27–34% and 3–5%, and in Canada 7% and 3%, have been reported for NAFLD and NASH, respectively. So, one can state that in the general population a median prevalence of NAFLDF of 20% is estimated with only a prevalence of NASH between 3% and 5%; the prevalence of NASH-related cirrhosis is not known. They also reviewed the NHANES studies in the USA and found an increased prevalence according to the NHANES study from 5.5% in 1988 to 11% in 2008 and an increased proportion of NAFLD among chronic liver disease from 47% in 1998 to 75% in 2008, attributable to a rise in the prevalence of obesity, insulin resistance and significantly altered dietary habits [222, 225]. Indeed, when considering obese patients and patients with the metabolic syndrome or type 2 diabetes, prevalence was high: the prevalence in obese patients, especially with hyperlipidaemia, is 60–85%, and in diabetic patients it is 30–50%. From the NHANES, the Dallas and the San Antonio study, Sherif et al. also found US Hispanics to be the most disproportionally affected ethnic group with African-American being the least affected, presumably explained by genetic disparities [225].

NAFLD increases with age and is more prevalent in men. Somewhat alarming are the findings in healthy and non-obese young living liver donors, who were reported to have a prevalence of NAFLD varying from 17.9% in Japan to 34% in the USA [225].

The natural course of NAFLD has been studied in two meta-analyses by Vernon et al. and Musso et al. [226, 227]. They show that a minority will progress from simple fatty liver to NASH and also that only NASH is associated with an increased risk of progressive liver disease. In the spectrum of NAFLD only one-third will develop NASH and NASH is the only disease in the NAFLD spectrum that is associated with progression to cirrhosis (9–20% over 5–10 years) and HCC [228]. In a meta-analysis of three population-based and four community-based studies with a follow-up between 7.3 and 24 years, the overall mortality was 57% higher in NAFLD compared with the normal population with a 2.16 times increased cardiovascular mortality but not an increased extrahepatic malignancy mortality [227]. Looking at all deaths 13% of all deaths were related to liver, 28% related to malignancy and 25% of all cases related to ischaemic heart disease. Patients with NASH and a fibrosis score of 3–4 had a 3.3 times higher overall and disease-related mortality. When patients with NASH were compared with patients with NAFL they had an 18% higher mortality, but the liver-related mortality was 5.7 times higher.

A number of factors have been mentioned as potentially leading to the progression of the fatty liver disease such as obesity, type 2 diabetes mellitus (T2DM), age, degree of inflammation, alanine aminotransferase (ALT), aspartate aminotransferase (AST)/ALT ratio, triglycerides, C-peptide, insulin resistance, female sex and hypertension [229]. Also findings at biopsy are important as the degree of inflammation is the strongest and independent predictor of fibrosis progression [230]. Two studies from Sweden demonstrated that the stage of fibrosis was the only independent histological feature on liver biopsy associated with long-term overall mortality and disease-specific mortality [231, 232].

As earlier mentioned, coronary heart disease is the primary cause of morbidity and mortality in patients with NAFLD [233]. There is a strong association between NAFLD and risk of coronary heart disease and cardiac complications such as left ventricle dysfunction, heart valve disease and atrial fibrillation. NAFLD is associated with the metabolic syndrome and therefore with multiple cardiac risk factors such as abdominal obesity, hyperglycaemia, insulin resistance, atherogenic dyslipidaemia, hypertension, ectopic fat accumulation and an altered adipocyte-related hormonal and cytokine profile which results in the development of a pro-inflammatory and pro-atherogenic milieu.

Recent studies have challenged the dogma that NAFL is not progressive. Singh et al. studied the progression of the disease in a meta-analysis of six studies in 133 NAFLD patients and of seven studies in 116 NASH patients [234]. The pooled data from six studies with 133 patients with simple steatosis with over 2146 person-years of follow-up showed that 52 (39.1%) patients developed progressive fibrosis and 70 (52.6%) remained stable while 11 patients (8.3%) had improvement of fibrosis. Accordingly, the fibrosis progression rate in patients with simple steatosis and absence of fibrosis at baseline was 0.07 stages, translating into 1 stage of fibrosis progression over 14.3 years. The pooled data of 116 NASH patients found that 40 patients (34.5%) developed progressive fibrosis, 45 (38.8%) remained stable and 31 (26.7%) showed improvement in fibrosis. The annual fibrosis progression rate in NASH without baseline fibrosis was 0.14 stages, translating into 1 stage of progression over an average of 7.1 years. Predictors associated with progression of fibrosis in NASH appeared to be age, inflammation at index biopsy, hypertension and a baseline low AST/ALT ratio. The long-term outcome related to histology was reported by Matteoni in 132 patients over 8 years [235]. Cirrhosis developed in 21–28% of patients with NASH compared to 3% in non-NASH with a liver-related mortality of 11% versus 2%. They updated their cohort with 18.5 years of follow-up and found increased liver-related mortality of 18% in the NASH and 3% in the non-NASH groups [236].

In the Million Women Study with 1.3 million women the admission rates and death rates for liver cirrhosis in a 6-year follow-up period were investigated [237]. Compared with the reference group with a BMI of 22.5–24.9 kg/m^2, those with a BMI of 25–27.4 had a non-significant 5% higher risk and with a BMI of 27.5–29.9 a non-significant 11% higher risk of liver cirrhosis. However, those with a BMI 30–34.9 had a 49% higher risk (RR 1.49 (1.33/1.68)) and those with a BMI 35–39.9 a 77% higher risk (RR 1.77 (1.49/2.10)) and per 5 units of increased BMI the risk of cirrhosis increased by 24% (RR 1.24 (1.19/1.38)). The relative risk did not change according to the amount of alcohol consumed but the absolute risk did. The absolute risk of liver cirrhosis per 1000 women over a period of 5 years was 2.7 (2.1/3.4) and 5.0 (3.8/6.6) in women who reported drinking 150 g or more per week (18 units) with a BMI of 22.5–25.0 and BMI ≥30 kg/m^2, respectively. Also, Hart et al. showed that being overweight or obese and drinking 15 or more units each week had a synergistic effect which amplified the insult to the liver and greatly increased the risk of liver-related morbidity and mortality [238].

Hamaguchi et al. examined the relationship between the metabolic syndrome and NAFLD diagnosed by ultrasound in 4401 Japanese men and women drinking 20 g or less of ethanol each day [239]. On ultrasound at the start, a fatty liver was identified in 18% with a 2.5-fold higher incidence in men than women. Patients with a fatty liver were more likely to be obese and to have the metabolic syndrome. Those who were free of NAFLD diagnosis at the start developed NAFLD in the 1-year interval period in 14% of males and 5% of women; they gained only little body weight, 1.7 and 1.3 kg, respectively. The most important finding was that the presence of the metabolic syndrome carried a 4–11 times higher risk for future NAFLD. Fourteen percent of males and 25% of females showed regression to normal of their initially fatty livers; they lost 2.5 kg and 2.3 kg, respectively, and had less components of the metabolic syndrome. Hamaguchi et al. thus provided strong support for the central role of insulin resistance in the pathophysiology of NAFLD and also showed that weight gain and metabolic syndrome are risk factors for NAFLD. More importantly, NAFLD may be reversible if obesity and certain aspects of the metabolic syndrome are managed effectively, even without normalisation of body weight. In a study from Italy with 304 patients by Marchesini et al., the presence of the metabolic syndrome conferred a higher risk of NASH (OR 3.2 (1.2/8.9)) and a higher risk for advanced fibrosis (OR 3.5 (1.1/11.2)) [240].

1.8.4.2 Hepatocellular Carcinoma

Patients with NASH are also at risk for the development of hepatocellular carcinoma (HCC) and the increased risk for HCC is likely to be limited to those with advanced fibrosis and cirrhosis. Advanced fibrosis remains a strong risk factor for HCC with cumulative incidence rates reported between 2.4 and 12.8% [222]. The recent Surveillance Epidemiology and End Results (SEER) study compared a total of 4929 HCC cases and 14,937 controls without HCC over the years 2004–2009 [241]. Of the HCC cases, 54.9% were related to hepatitis C, 16.4% to alcoholic liver disease, 14.1% to NAFLD and 9.5% to hepatitis B. Across the 6-year period the number of NAFLD-HCC showed a 9% annual increase. NAFLD-HCC patients were older, had shorter survival time, more heart disease and were more likely to die from their primary liver cancer. In multivariate analysis, NAFLD increased the risk of HCC by a factor of 2.6 (OR 2.62 (2.28/3.00)) and increased the 1-year mortality by 21% (OR 1.21 (1.01/1.45)).

Hassan et al. from the MD Anderson Cancer Centre performed a case-control study to evaluate the association between obesity and HCC and they tried to correct for confounding factors such as hepatitis B and C, diabetes, a family history of cancer, smoking and alcohol consumption [242]. Obesity, but not overweight, in early adulthood (in the mid-20–mid-40 years of age) was a significant risk factor for HCC in the total population (OR 2.6 (1.4/4.4)), both in men (OR 2.3 (1.2/4.4)) and in women (OR 3.6 (1.5/8.9)). For each 1 kg/m^2 increase in BMI in early adulthood, hepatocellular carcinoma occurred 3.9 months earlier in life. Obesity had no influence on HCC outcome. Obesity and virus infections had a synergistic interaction, suggesting that obesity, in addition to its own direct effects, may exacerbate the effect of chronic hepatitis. For example, the population attributable risk percentages

were 21% for diabetes, 10% for early adulthood obesity and 11% for the combination. So, 42% of cases of hepatocellular cancer could be explained by obesity and diabetes.

In 2010 the American Diabetes Association and the American Cancer Society concluded that T2DM was convincingly associated with increased risk of cancers such as colorectal, pancreas, liver, breast, endometrial and bladder cancer [243]. Tsilidis et al. in their umbrella review confirmed the robust associations for some of these cancers but not for others [244].

The incidence of HCC has tripled in the USA in the last decades. Due to the falling incidence because of prevention and adequate treatment of viral hepatitis, the increase is consequent to the rising prevalence of obesity and T2DM, the two major risk factors for NAFLD.

Sex and ethnic-specific studies suggested that not adiposity in general but specific fat depots in viscera and liver might be more relevant. In the Multiethnic Cohort Study, overweight was associated with a 50% increased risk (HR 1.50 (1.16/1.95)) and obesity with a 82% increased risk (HR 1.82 (1.31/2.52)) of HCC with an increased risk per 5 kg/m^2 increase in BMI of 1.26 (1.26 (1.12/1.42)) in males and no increased risks in women [245]. There were also ethnic differences with BMI $\geq$30 kg/m^2 and the increased risk per 5 kg/m^2 increase in BMI being strongly associated with HCC with the greatest risk in Japanese, followed by Latinos, whites and native Hawaiians but not in black men. Detailed adiposity measurements showed that Asians and Latinos were likely to accumulate more and blacks less fat in the abdominal visceral compartment, suggesting that studying the association between obesity and HCC should move beyond BMI and should use a measure for fat-specific depots. Similarly, the European Prospective Investigation into Cancer and Nutrition (EPIC) study showed that WHR had the strongest association with HCC and also that in multivariate analysis the association of BMI with HCC disappeared whereas that of WHR remained [246]. A Japanese study determined the visceral fat mass quantitatively by CT and found that visceral fat was an independent risk factor for (recurrent) HCC in patients with suspected NASH [247].

Pathophysiology of Obesity in Relation to NAFLD

The pathophysiology of non-alcoholic fatty liver disease has been discussed in a number of recent review articles and is summarised below [228, 248–251].

The fundamental derangement in NAFLD is insulin resistance. Insulin resistance is also the pathogenic denominator of the metabolic syndrome which includes type 2 diabetes mellitus, essential hypertension, hypertriglyceridaemia, low circulating levels of HDL cholesterol and (visceral) obesity (Table 1.1). Steatosis of the liver may therefore be considered the hepatic manifestation of the metabolic syndrome and is closely associated with diabetes, obesity and hyperlipidaemia. In healthy subjects insulin, secreted by the pancreas and entering the portal circulation, stimulates glycogen synthesis, lipogenesis and lipoprotein synthesis and suppresses gluconeogenesis and glycogenolysis. Insulin resistance may present as whole-body insulin resistance as shown by a 50% reduction in glucose disposal, but also at the tissue level of the hepatocyte, adipocyte and skeletal muscle. Hepatic insulin

resistance is characterised by a reduced suppression of endogenous glucose production via gluconeogenesis and reduced VLDL secretion because of an altered apolipoprotein B synthesis, which normally exports lipids from the liver in a complex of apolipoprotein B, lipids and phospholipids. Insulin resistance in the adipocyte promotes lipolysis and increased free fatty acid flux to the liver, and in skeletal muscle it impairs glucose uptake and disposal. Hyperinsulinaemia is a consequence of target cells, such as liver, adipose tissue and skeletal muscle being resistant to normal concentrations of insulin. As insulin stimulates lipogenic enzymes and portal insulin levels are high, the de novo lipogenesis in the liver is increased, contributing to hepatic fat accumulation. Apart from the increased fatty acid influx from adipocyte lipolysis, the increased de novo lipogenesis and the impaired fatty acid hepatic efflux due to reduced synthesis of apolipoprotein B or reduced secretion of VLDL, excess free fatty acids that can be stored in the liver as triglycerides may come from a reduced hepatic fatty acid oxidation as a result of hyperinsulinaemia and from excess dietary consumption of fat or carbohydrates in the condition of excess caloric intake.

A study by Donelli et al. has demonstrated that in obese NAFLD patients 59% of triglycerides arose from non-esterified fatty acids, 26% from de novo lipogenesis and 15% from the diet [252]. Nielsen et al. found that in lean individuals 5% of the portal vein free fatty acids originated from visceral fat in contrast to a 20% in obese patients [253]. Free fatty acids and their metabolites are highly toxic to the liver and in this way the storage of fatty acids in triglycerides as lipid droplets in the liver has a protective role. Simple steatosis patients with non-alcoholic fatty liver (NAFL) thus may be considered as good fat storers [228]. However, when excessive fatty acids cannot be converted into triglycerides and when excessive fatty acids overload the mitochondrial capacity for fatty acid oxidation, good fat storers may change into bad fat storers [228].

Progression of NAFLD to NASH is assumed to occur by two or multiple hits. Some, however, do not support the continuum of NAFLD → NASH→ advanced fibrosis → cirrhosis, but consider NAFL and NASH as discrete entities rather than two points on a spectrum, supported by the fact that progression from pure fatty liver to NASH is very rare [228]. The two-hit hypothesis in the progression of NAFLD put forward by Day and James in 1998 has been replaced by the multiple-hit model [228]. The first hit consists of insulin resistance with a resultant hyperinsulinaemia causing an impaired inhibition of adipose tissue lipolysis, an increased efflux of free fatty acids from the adipose tissue to the liver and increased hepatic de novo lipogenesis resulting in a simple fatty liver. Due to the hepatic fat infiltration, the liver may become vulnerable to a series of hits. These hits consist of oxidative injury and stress from reactive oxygen species (ROS), leading to lipid peroxidation, impaired mitochondrial and peroxisome oxidation of fatty acids, endoplasmatic reticulum stress, dysregulated hepatic apoptosis and activation of profibrinogenic cytokines and of hepatic stellate cells, all together resulting in inflammation (steatohepatitis) and fibrosis. Also, the release of adipokines, cytokines and chemokines plays a role: adipokines such as leptin, adiponectin and resistin; acylation-stimulating protein; TNF-α; and IL-6 are associated with insulin resistance and IL

1, TGF-β, VEGF, angiotensinogen and angiotensin II are inflammatory mediators (Figs. 1.3 and 1.4). Furthermore, low levels of adiponectin may predispose patients to the progressive form of NAFLD or NASH. Adiponectin is produced by omental fat and levels are low in diabetes and metabolic syndrome.

A high-calorie diet, excess (saturated) fats, refined carbohydrates, sugar-sweetened beverages, a high fructose intake and a Western diet have all been associated with weight gain and obesity, and more recently with NAFLD [220, 221]. Apart from the role of the diet as a source of excess energy and excess fat, the role of carbohydrates and especially simple carbohydrates such as fructose, sucrose, glucose and high-fructose corn syrup (HFCS) should be discussed. Carbohydrates can stimulate lipogenesis via carbohydrate response element-binding proteins, converting excess glucose to fatty acids. Fructose, present in HFCS, fruit juices and sucrose (glucose:fructose 1:1), has attracted much attention especially in the USA, where fat was substituted by carbohydrates during the low-fat lobby and sweetened soda contained fair amounts of HFCS. In the USA, HFCS is the most common consumed sugar.

Several properties make fructose a particularly lipogenic carbohydrate [254]. The liver is exposed to much higher fructose concentrations as compared to other tissues because fructose is absorbed from the intestine and delivered to the liver via the portal vein. In contrast, long-chain fatty acids are absorbed from the intestine as chylomicron particles and enter the systemic circulation via the lymphatic system and the thoracic duct and thus expose liver and peripheral tissue to a similar degree. Furthermore, fructose absorption and metabolism are insulin independent in contrast to glucose absorption. After absorption, carbohydrates are metabolised to acetyl CoA and activate lipogenic transcriptional factors in the liver stimulating every step in the de-novo lipogenesis that converts acetyl CoA into triglycerides [254]. Fructose phosphorylation into fructose-1-phosphate requires ATP, thereby decreasing ATP levels. Decreased ATP levels in the liver may also be the result of decreased mitochondrial ATP production because of the inhibition of β-oxidation by malonyl CoA. The depletion of ATP leads to uric acid production which may promote lipogenesis through the generation of mitochondrial oxidative stress. The suppression of mitochondrial lipid oxidation results in increased production of reactive oxygen species which augment steatosis through insulin-independent pathways [254]. Fructose increases protein levels of enzymes involved in de-novo lipogenesis during its conversion into triglycerides. Fructose promotes stress in the endoplasmatic reticulum resulting in upregulation of de-novo lipogenesis. So, in summary, fructose supports lipogenesis in the presence of insulin resistance and contributes further to insulin resistance.

Fructose has also been implicated in the progression to fibrosis. The major risk factor for development of NAFLD is excess calorie intake mainly derived from high-fat foods and increased intake of sugar-sweetened beverages [220, 221]. Overconsumption of refined sugar is a risk factor for the development of obesity, diabetes and NAFLD and in countries with high intakes of HFCS diabetes is 20% higher compared to countries that do not use HFCS. Chung et al. performed a meta-analysis of 21 intervention studies on the effects of sucrose, fructose, HFCS and

glucose on NAFLD [255]. They found a low level of evidence that a hypercaloric fructose diet (supplemented by pure fructose) increased liver fat and AST in healthy men when compared with the consumption of a weight-maintenance diet. In addition, hypercaloric fructose and glucose had similar effect on liver fat and liver enzymes in healthy adults. There was insufficient evidence to draw a conclusion on the effects of HFCS or sucrose on NAFLD. The apparent association between indexes of liver health and fructose of sucrose intake appeared to be confounded by excessive energy intake and they concluded that the available evidence is not sufficiently robust to draw conclusions regarding the effect of fructose, HFCS or sucrose consumption on NAFLD [221, 255].

The importance of the location of the ectopic fat, i.e. liver versus visceral fat, was demonstrated in a study that used sophisticated methods for total fat and visceral adipose tissue (VAT) measurements (by dual-energy X-ray absorptiometry (DEXA) and MRI), intrahepatic triglyceride content (IHTG by proton magnetic resonance spectroscopy) and kinetic studies (hyperinsulinaemic euglycaemic clamp and VLDL-triglyceride kinetic studies) [256]. Subjects matched for VAT were dissimilar in IHTG, and subjects matched for IHTG differed in VAT. Subjects with higher IHTG content and matched on VAT had 41%, 13% and 36% lower insulin sensitivity in liver, adipose tissue and muscle, respectively, whereas VLDL-triglyceride secretion from mainly non-systemic fatty acids was almost double. Patients with high IHTG had twofold greater insulin and 50% lower adiponectin levels. No differences were found in insulin sensitivity and VLDL secretion when subjects with different VAT masses but matched for IHTG levels were examined. So, the relationship between VAT and metabolic disease is because of the relationship between VAT and IHTG and therefore the level of intrahepatic triglycerides is a better marker of metabolic derangements than visceral adiposity.

Pathophysiology of Obesity in Relation to Hepatocellular Carcinoma

Many studies have supported a key role of obesity in the risk of hepatocellular carcinoma and accumulating evidence exists that type 2 diabetes mellitus (T2DM) predisposes to a number of cancers [243, 244]. As mentioned above, both obesity and diabetes may contribute to NAFLD and the contribution of NAFLD to the prevalence of HCC has been reported repeatedly. Moreover, inactivity and excess food intake link obesity and NAFLD.

There are both systemic and local factors that contribute to the HCC risk and that may explain the association of obesity, T2DM and metabolic syndrome with HCC and the predominant presence of HCC in males [251]. *Systemic* factors contributing to the HCC risk are hyperinsulinaemia, obesity-related hypoxia, systemic inflammation, systemic effects of cytokines and adipokines, systemic immune dysregulation and systemic effects of the microbiome. High levels of insulin promote cell survival and cell proliferation and the binding of insulin at the insulin receptor activates mitogenic and anti-apoptotic pathways intracellularly. Insulin also suppresses the production of insulin-like growth factor-1-binding proteins which cannot bind sufficiently IGF-1 and cannot inhibit its mitogenic, anti-apoptotic and proangiogenic action [251].

Hypoxia of adipose tissue contributes to insulin resistance and to elevated pro-inflammatory adipokines and cytokines, increased levels of leptin involved in initiation and progression of HCC, and decreased levels of adiponectin that delays hepatocarcinogenesis and antagonises the oncogenic effect of leptin. Also macrophages accumulating in adipose tissue secrete inflammatory cytokines such as TNF-α, IL 6, IL-1β, nitric oxide, leukotrienes and chemokines that attract fibroblasts and other inflammatory cells. Persistent inflammation and persistent reactive oxygen species generation promote DNA damage and HCC [251].

Local factors in the liver contributing to the HCC risk are similar as described in adipose tissue and similar to the progression of NASH with liver cell damage, inflammatory infiltrates, pro-inflammatory signalling and insulin resistance, generation of reactive oxygen species that interfere with endoplasmatic reticulum and mitochondrial function, and release of TNF-α and IL-6, which promote proliferation and malignant progression [251].

1.8.4.3 Implications for Clinical Practice

In NAFLD/NASH, strategies should point to metabolic conditions such as obesity, diabetes and metabolic syndrome that favour progressive fibrosis. However, prevention is the key and advices to change the food consumption and increase physical exercise should be given to all patients. Related to potential mechanisms of hepatotoxicity are foods high in energy density with large portion sizes, high in fat and saturated fat, high in refined carbohydrate, high-fructose corn syrup (HFCS) and caramel colouring (cola soft drinks rich in advanced glycation end products that can promote insulin resistance and inflammation), low in fibre, low in antioxidants, high in red meat, high in industrially produced trans fatty acids, and promoting free fatty acid overload in the liver and local inflammation [220, 221, 223, 249, 251, 257–259].

Advices derived from this knowledge are a reduced calorie diet, reduction in saturated fatty acids along with an increase in MUFA and ω-3 PUFA, consumption of low glycaemic index carbohydrates, a reduced consumption of simple sugars especially in sweetened beverages, a higher intake of fruit and vegetables and a higher intake of fibre. Also adherence to a Mediterranean diet may be useful but scientific evidence to recommend specific diets is currently lacking [251, 257, 258].

Regular exercise reduces the risk of T2DM, insulin resistance, hypertension, dyslipidaemia, impaired fasting glucose and metabolic syndrome, all of which are factors involved in the pathogenesis of NAFLD. Exercise also has immunostimulatory effects, reduces systemic inflammation and decreases the activity of the mTOR system, thereby reducing HCC risk. Physical activity should be at least 30 min of moderate-intensity physical activity on most, and preferably all days of the week, or vigorous-intensity physical activity ≥3 times a week for ≥20 min each time.

What is the evidence for these lifestyle interventions by diet and physical exercise and how much weight should be lost? Promrat et al. randomised 21 patients with NASH to an intervention group which received a diet between 1000 and 1500 kcal/day with 25% of total energy from fat and ten patients to the control group, which received basal nutrition education [260]. The goal was a 7–10% weight reduction and the primary endpoint was improvement in NAFLD activity

score (NAS) after 48 weeks. The intervention group lost 9.3% of total bodyweight versus 0.2% in the control arm with a significantly higher proportion of histological improvement in 72% versus 30%, respectively. Those with ≥7% weight loss showed improvements in steatosis, lobular inflammation and NAFLD activity score, but a weight loss of at least 10% was required to improve fibrosis and portal hypertension. Evidence for the substantial effects of moderate weight losses followed in larger studies. Villar-Gomez et al. evaluated 293 patients with biopsy-proven NASH after 52 weeks of lifestyle intervention consisting of a low-fat calorie-reduced diet (750 kcal less per day) and walking 200 min/week [261]. Paired biopsies were present in 261 patients. Among the entire cohort a weight loss was obtained of 4.6 kg, NASH resolution occurred in 25%, NAS reduction in 47% and fibrosis regression in 19%. The degree of weight loss was independently associated with improvements in all NASH-related histology features. Those who obtained a weight loss ≥5% (30% of subjects) had NASH resolution in 58%, a 2-point reduction in NAS score in 82%. Of those who achieved a ≥10% weight reduction (11% of subjects), 90% experienced a resolution of NASH and 100% a reduction in NASH and 45% a regression of fibrosis. Harrison et al. had similar findings: a ≥5% weight loss resulted in a significant improvement of insulin sensitivity and steatosis and those with a ≥9% weight loss improved in steatosis, inflammation and hepatocyte ballooning and NAS [262].

So all studies agreed that a minimum of 9–10% weight loss is needed to achieve NASH improvement and fibrosis regression.

Keating et al. reviewed 16 studies on exercise in a meta-analysis [263]. There was a significant pooled effect size for the comparison between exercise therapy and controls, even in the absence of significant weight loss. A recent systematic review of 23 studies on lifestyle interventions showed that diet or physical activity consistently reduced liver fat and improved glucose control and insulin sensitivity [264].

Important in this context is the rate of weight loss. Weight loss should be moderate and gradual (<1.6 kg/week) as a rapid reduction in body weight may decrease hepatic fat content but can induce hepatic inflammation and exacerbate NASH and thus worsening of liver disease. Ketosis may be deleterious for patients with NAFLD. Data on the upper limit of weight loss came from a study by Andersen et al. who provided a 400 kcal formula diet to 41 morbidly obese subjects [265]. They showed improvement of steatosis and improvement in liver biochemistry but 24% developed slight portal inflammation and portal fibrosis but none of the patients who lost less than 1.6 kg/week developed fibrosis.

Another important point for clinical practice is the recognition that all components of the metabolic syndrome correlate with liver fat content, independently of BMI. So, the presence of the metabolic syndrome in any given patient should lead to an evaluation of the risk of NAFLD, and vice versa the presence of NAFLD should lead to an assessment of all components of the metabolic syndrome [220]. Patients with steatosis or steatosis with non-specific inflammation are on the one end of the spectrum and are not candidates for pharmacological treatment that specifically targets the liver condition [230]. On the other end are patients with the progressive form of NAFLD (i.e. NASH), particularly when associated with

advanced fibrosis. At-risk patients (age > 50 years, type 2 diabetes mellitus or metabolic syndrome) should be identified because of its prognostic implications. Treatment for the prevention of liver-related comorbidities should be focused on patients with NASH and particularly those with a fibrosis stage ≥2 [220]. For the many therapeutic options and the many medications in phase II and III studies the reader is referred to superb and very recent overviews and meta-analysis [223, 230, 249, 259, 266, 267] and the two recent guidelines from the USA in 2012 [220] and from Europe in 2016 [221].

1.8.5 Gastrointestinal Cancers

Mechanisms explaining the association between obesity and gastrointestinal cancers include hormonal effects of adipose tissue, insulin resistance, inflammation, effects on predisposing conditions such as GORD, Barrett's oesophagus, gallbladder disease, colorectal adenomas and effects through the immune system [48]. In obesity, endogenous hormones such as sex steroids, insulin and IGF-1 are increased and are important in the control of growth, differentiation and metabolism of cells [268]. Patients with diabetes type 2, which often accompanies overweight and obesity, have increased rates of cancer [243, 244]. Obesity is a state of low-grade chronic systemic inflammation characterised by pro-inflammatory cytokines produced by adipocytes and chronic inflammation is an important factor in the initiation and promotion of cancer cells. Obesity is also associated with enhanced oxidative stress by local ischaemia and through the inflammatory process. The World Cancer Research Fund and the American Institute for Cancer Research estimated in 2007 that a large percentage of cancers are attributable to obesity: 28% of gallbladder cancers, 35% of pancreatic, 16% of colorectal, 17% of breast and 49% of endometrial cancers, and 28% of kidney and 35% of oesophageal cancers [269]. Calle et al. estimated that in the USA obesity is responsible for up to 14% and 20% of all cancer deaths in males and females, respectively, signifying that 90,000 annual deaths are avoidable if BMI was kept below 25 [8]. In Europe, it is estimated that 36,000 cancer cases could be avoided by halving the prevalence of overweight and obesity [270].

Several large cohort studies and meta-analyses have examined cancer incidence and cancer mortality for all obesity-related cancers.

1.8.5.1 Cohort Studies

A large cohort study by Calle et al. followed more than 900,000 US adults free of cancer at enrolment in 1982 in the Cancer Prevention Study II, with an average age at that time of 57 years, over 16 years [8]. Death due to cancer was related to the BMI measured between 1982 and 1988. Of the 900,053 included persons 57,145 died (6.3%) of whom 16,962 (30%, one-third) being non-smokers. A BMI above the reference BMI (18.5–24.9 kg/m^2) was associated with cancer of the oesophagus,

colon and rectum, liver, gallbladder, pancreas and kidney; the same was true for death due to non-Hodgkin's lymphoma and multiple myeloma. Significant trends for an association with higher BMI were present for gastric and prostate cancer in men and breast, uterus, cervix and ovary cancer in women. An inverse association was observed between BMI and lung cancer in male and females.

The highest relative death rate was for uterine cancer in females with a BMI ≥40 kg/m^2 with a RR 6.25; in males the highest relative death rate was for liver cancer (RR 4.52). There was, however, no clear documentation of presence or absence of liver disease in affected individuals. Also, no information about impaired glucose tolerance or NAFLD was present. At a BMI ≥40 kg/m^2 the cancer death rates were 52% higher in men and 62% higher in women when compared with normal-weight subjects and went even up to 88% in non-smoking women with a BMI ≥40 kg/m^2. The risks according to the BMI classes for gastrointestinal cancer are visible in Table 1.7 and in Fig. 1.6 for males and Fig. 1.7 for females. The population attributable fraction of death of all cancers varied between 4.2% in the population of men and 14.2% among male non-smokers and in women between 14.3% and 19.8%. So the avoidable proportion of cancers was as high as 14% for males and 20% for females, signifying that 90,000 cancer deaths could have been avoided when BMI had remained 25.0 throughout life [8].

The critics concerning this landmark study touched upon the fact that comparison was made with weight 16 years ago and the people could have gained 1–2 units BMI over the 16-year period of the study and 10% of people have an increased BMI by 5 units over less than 10 years. This was addressed in the Northern Sweden Health and Disease Cohort (1985–2003) which consisted of 35,362 women and 33,424 men with weights and heights measured and repeated at 10-year intervals [271]. After 10 years of follow-up >70% preserved their initial BMI classification in the quartiles; on average women gained about 1.8 BMI units and men about 1.4 BMI units and the annual increase in BMI was 0.1 BMI units among men and 0.06 BMI units among women. Obese women had a 36% higher cancer incidence than normal-weight women while overweight women had a risk largely similar to that of normal-weight women [271]. Obese women had a 2.0 times higher risk of colorectal cancer and 2.25 times higher risk of colon cancer. In men there was no association of BMI with total cancer risk. Obese men were 1.77 times at risk of developing colon cancer. In women up to 7% of cancer were attributable to overweight and obesity, with a larger attribution on endometrium (30%), ovarian (22%), colon (20%) and colorectal (16%) which could have been avoided by keeping BMI in the normal range [271].

A cohort study by Reeves et al. and a meta-analysis by Reneman et al. investigated the effect of an increase in BMI by 5 or 10 BMI units [102, 272]. Reeves et al. investigated 1.2 million women in the Million Women breast cancer screening study, with an age of 55.9 years at recruitment and recruited over the years 1996–2001 [102]. The reference BMI group had a BMI 22.5–24.9 kg/m^2 and the trend in risk per 10 units BMI was taken as this was equivalent to the difference in median

Table 1.7 Relative risks (with 95% confidence intervals in brackets) for cancer death according to BMI classes of overweight (BMI 25–29.9), class I (BMI 30–34.9), class II (BMI 35–39.9) and class III of obesity (BMI ≥40 kg/m²) [8]

	BMI 25–29.9	BMI 30–34.9	BMI 35–39.9	BMI ≥40	*p* for trend
Males *N* = 404,576					
All cancers	0.97 (0.94/0.99)	1.09 (1.05/1.14)	1.23 (1.11/1.34)	1.52 (1.13/2.05)	0.001
Oesophagus	1.15 (0.99/1.32)	1.28 (1.00/1.63)	1.63 (0.95/2.80)		0.008
Stomach	1.01 (0.88/1.16)	1.20 (0.94/1.52)	1.94 (1.21/3.13)		0.03
Colorectal	1.20 (1.12/1.30)	1.47 (1.30/1.66)	1.84 (1.39/2.41)		<0.001
Liver	1.13 (0.94/1.34)	1.90 (1.46/2.47)	4.52 (2.94/6.54)		<0.001
Gallbladder	1.34 (0.97/1.84)	1.76 (1.06/2.94)			0.02
Pancreas	1.13 (1.03/1.25)	1.41 (1.19/1.66)	1.49 (0.99/2.22)		<0.001
Non-smoking males *N* = 107,030					
All cancers	1.11 (1.05/1.18)	1.38 (1.24/1.52)	1.31 (1.01/1.70)		<0.001
Oesophagus	1.76 (1.08/2.86)	1.91 (0.92/3.96)			0.04
Pancreas	1.24 (1.01/1.54)	1.34 (0.92/1.95)	2.61 (1.27/5.35)		0.005
Females *N* = 495,477					
All cancers	1.08 (1.05/1.11)	1.23 (1.18/1.29)	1.32 (1.20/1.44)	1.62 (1.40/1.87)	<0.001
Oesophagus	1.20 (0.86/1.66)	1.39 (0.86/2.25)			NS
Stomach	0.89 (0.72/1.09)	1.30 (0.97/1.74)	1.08 (0.61/1.89)		NS
Colorectal	1.10 (1.01/1.19)	1.33 (1.17/1.51)	1.36 (1.06/1.74)	1.46 (0.94/2.24)	<0.001
Liver	1.02 (0.80/1.31)	1.40 (0.97/2.00)	1.68 (0.93/3.05)		0.04
Gallbladder	1.12 (0.86/1.47)	2.13 (1.56/2.90)			<0.001
Pancreas	1.11 (1.00/1.24)	1.28 (1.07/1.52)	1.41 (1.01/1.99)	2.76 (1.74/4.36)	<0.001
Non-smoking females *N* = 276,564					
All cancers	1.14 (1.09/1.18)	1.33 (1.25/1.41)	1.40 (1.25/1.58)	1.88 (1.56/2.27)	<0.001
Oesophagus	1.49 (0.85/2.59)	2.64 (1.36/5.12)			0.004

BMI among obese women and the reference category. They found that an increased BMI was associated with increased risk of cancer for 10 of the 17 examined cancer types. More specifically, the risk of adenocarcinoma of the oesophagus was 2.38 times higher per 10 kg/m² increase in BMI, followed by CRC in premenopausal women (1.61 (1.05/2.48)) and pancreatic cancer (1.24 (1.03/1.48)) (Table 1.8). Postmenopausal women were not at increased risk (0.99 (0.88/1.12)), a finding strengthened by findings by Terry et al. who also showed different risks in premenopausal obese (RR 1.88 (1.24/2.86)) and postmenopausal obese (0.73 (0.48/1.10)) women [194, 197].

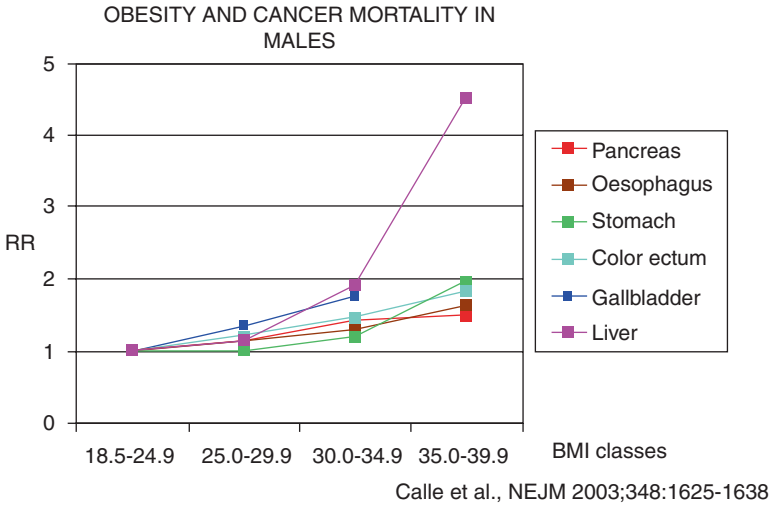

Fig. 1.6 The risks according to the BMI classes for gastrointestinal cancer for males

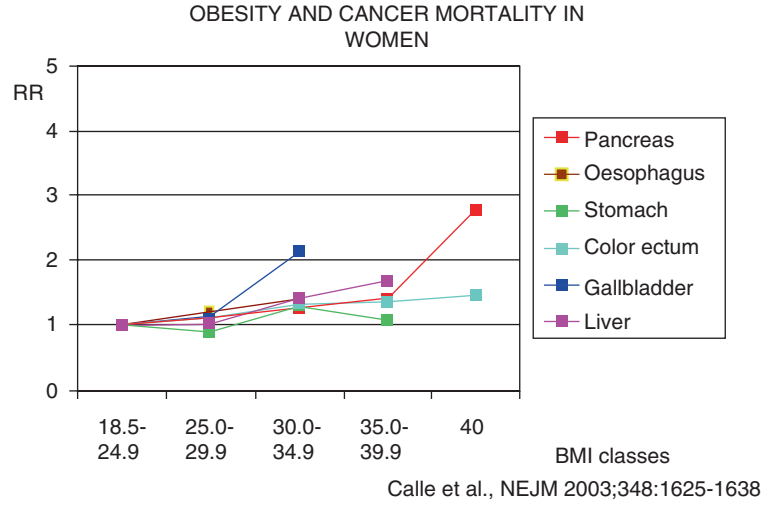

Fig. 1.7 The risks according to the BMI classes for gastrointestinal cancer for females

1.8.5.2 Meta-Analyses

Bergstrom et al. examined the prevalence of six cancer sites (colon, endometrium, prostate, kidney, gallbladder and postmenopausal breast cancer) and the proportion of these six cancers attributable to overweight (BMI 25–29.9 kg/m^2) and obesity (BMI ≥30 kg/m^2) in the European union [270]. Overweight (BMI >25 kg/m^2) was slightly more prevalent in southern countries (61% for men and 52% for women) compared with the northern countries (59% for men and 47% for women). Obesity was more prevalent in women and overweight more in men. Excess body weight

Table 1.8 Relative risk (with 95% confidence interval) associated with a 5 kg/m^2 increase in BMI or a 10 kg/m^2 increase in BMI in the Million Women Cohort Study [102, 272]

Cancer type	RR per 5 kg/m^2 males	*p*-Value	RR per 5 kg/m^2 females	*p*-Value	RR per 10 kg/m^2 females
Oesophagus adenocarcinoma	1.52 (1.33/1.74)	<0.001	1.51 (1.31/1.74)	<0.001	2.38 (1.59/3.56)
Colon cancer	1.24 (1.20/1.28)	<0.001	1.09 (1.05/1.13)	<0.001	1.00 (0.92/1.08)
Liver cancer	1.24 (0.95/1.62)	NS	1.07 (0.55/2.08)	NS	
Rectum cancer	1.09 (1.06/1.12)	<0.001	1.02 (1.00/1.05)	NS	1.00 (0.92/1.08)
Gallbladder cancer	1.09 (0.99/1.21)	NS	1.59 (1.02/2.47)	0.04	
Pancreas cancer	1.07 (0.93/1.23)	NS	1.12 (1.02/1.22)	0.01	1.24 (1.03/1.48)
Stomach cancer	0.97 (0.88/1.06)	NS	1.04 (0.90/1.20))	NS	0.90 (0.72/1.13)
Oesophagus squamous cell cancer	0.71 (0.60/0.85)	<0.001	0.57 (0.47/0.69)	<0.001	0.26 (0.18/0.38)
All cancers					1.12 (1.09/1.14)

accounted for 5% of all cancers in Europe, 3% for men and 6% for women, corresponding to 27,000 cases in males and 45,000 cases in females. So, more than 70,000 of the 3.5 million new cases of cancer each year in the European union are attributable to overweight (34,800 cases) and to obesity (37,000). This is likely to be an underestimation as only six cancers, for which there is existing evidence to suggest a link between obesity and cancer, were examined in Bergstrom's study. The attributable proportion varied by gender and country: for males the attributable proportion varied between 2.1% for Greece and 4.9% for Germany, and for women between 3.9% for Denmark and 8.8% for Spain.

Of the 19 studies related to colon cancer six were used in the meta-analysis. Per unit increase in BMI the risk increased by 3% (RR 1.03 (1.02/1.04)). Overweight attributed to a 15% increase and obesity to a 33% increase in risk. The average proportion attributable to excess body weight was 11% with a number of 11,000 new cases per year. For gallbladder cancer, six epidemiological studies were found with conflicting data. Only two studies could be used and assessed a risk of 1.06 (1.00/1.12)) per unit BMI increase. Overweight attributed to a 34% and obesity to a 78% increase in risk. Twenty-four percent of gallbladder cancers could be attributed to excess body weight amounting to 6000 new cases/year. The highest attributable proportions were found for endometrium (39%), kidney (25% in both sexes) and gallbladder (25% in men and 24% in women). More important is the absolute number of cases and then the highest attributable number of cases were attributable to colon cancer (21,500 annual cases) followed by endometrium (14,000 cases) and breast (12,800). In Europe, an estimated 36,000 cases could have been avoided by halving the prevalence of overweight and obesity.

In a meta-analysis of 221 data sets by Reneman et al., the incidence of 20 most common cancers were studied per 5 unit increase in BMI, corresponding to a 15 kg weight gain in males and 13 kg in females with an average BMI at baseline of 23 kg/m^2 [272] (Table 1.8). In men, a 5-point increase in BMI was

strongly associated with an increased risk of oesophageal adenocarcinoma and colon cancer, and in women with gallbladder and oesophageal adenocarcinoma. Weaker positive associations (RR < 1.20) were discovered between increased BMI and rectal cancer in men and pancreas and colon cancer in women. The associations for colon cancer were stronger in men than in women. The associations did not differ in studies from Europe, North America and Australia and the Asia Pacific group.

Guh et al. considered overweight and obesity not only as defined by BMI criteria, but also as defined by waist circumference in their meta-analysis [37]. As can be seen in Table 1.2, relative risks in men were higher for colorectal cancer and gallbladder cancer when overweight waist and obese waist were compared by their respective BMIs. For women this was not the case as far as colorectal cancer was concerned.

1.8.5.3 Implications for Clinical Practice

It is evident that keeping the body weight at a level below BMI 25 kg/m^2 can reduce substantially the burden of cancer and also that weight stability, even when it is in the overweight range, is preferable over weight gain. An at least 50% greater risk was only observed in people with a BMI ≥35 kg/m^2. In males with a BMI 30–34.9 kg/m^2 the RR for cancer death was greater than 50% in liver, gallbladder and non-Hodgkin's lymphoma; in women this was true for cancer of the gallbladder, breast, uterus and kidneys. Evidence for a reduction in cancer risk by attempts of weight loss by lifestyle measures is lacking. The only available evidence in a prospective, controlled trial comes from the Swedish Obesity Subjects (SOS) study [273]. The SOS study involved 2010 obese subjects who underwent gastric bypass in 13%, gastric banding in 19% and vertical banded gastroplasty in 68%. They were compared with 2037 contemporaneously matched obese controls who received usual care. Over 10 years there was a significantly different mean weight reduction of 19.9 kg in the bariatric group versus a weight gain of 1.3 kg in controls. The risk of incident cancers was reduced by 33% in the whole group (HR 0.67 (0.53/0.85)) but there was clearly a gender-treatment interaction: in women the incidence was significantly lower (HR 0.58 (0.44/0.77)) but there was no effect of surgery in men. With respect to the above-mentioned attributable fractions by overweight and obesity and the impressive reduction when excess weight was halved or wiped out, the adage remains: prevention is the key!

References

1. NCD (Non-Communicable Disease) Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. Lancet. 2016;387:1377–96.
2. WHO: fact sheetno.311; updated June 2016. www.who.int/mediacentre/factsheets/fs311/en/. Accessed May 2017.
3. WHO: fact sheet no 311; updated June 2016. www.who.int/dg/speeches/2016/obesity-diabetes-disaster/en/. Accessed May 2017.

4. Frühbeck G, Toplak H, Woodward E, Yumuk V, Maislos M, Oppert J-M. Obesity: the gateway to ill health—an EASO position statement on a rising public health, clinical and scientific challenge in Europe. Obes Facts. 2013;6:117–20.
5. Fried M, Yumuk V, Oppert J-M, Scopinaro N, Torres AJ, Weiner R, et al. Interdisciplinary European guidelines on metabolic and bariatric surgery. Obes Facts. 2013;6:449–68.
6. Aune D, Sen A, Prasad M, Norat T, Janszky I, Tonstad S, et al. BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. BMJ. 2016;353:i2156.
7. NCD (Non-Communicable Disease) Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. Lancet. 2016;387:1513–30.
8. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003;348:1625–38.
9. Mathus-Vliegen EMH, Romijn JA, Belachew M, Greve JW. Morbid obesity. Gastrointestinal aspects/surgical aspects. In: van Lanschot JJB, Gouma DJ, Jansen PLM, Jones EA, Pinedo HM, Schouten WR, et al. (eds). Integrated medical and surgical gastroenterology. Houten, The Netherlands; Bohn Stafleu Van Loghum, 2004: 124-145.
10. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363:157–63.
11. Chandalia M, Lin P, Seenivasan T, Livingston EH, Snell PG, Grundy SM, Abate N. Insulin resistance and body fat distribution in south Asian men compared to Caucasian men. PLoS One. 2007;2:e812.
12. Chitturi S, Farrell GC, Hashimoto E, Saibara T, Lau GKK, Sollano JD, et al. Non-alcoholic fatty liver disease in the Asia–Pacific region: definitions and overview of proposed guidelines. J Gastroenterol Hepatol. 2007;22:778–87.
13. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new worldwide definition. A consensus statement from the international diabetes federation. Diabet Med. 2006;23:469–80.
14. Tan C-E, Ma S, Wai D, Chew S-K, Tai E-S. Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? Diabetes Care. 2004;27:1182–6.
15. Heymsfield SB, Cefalu WT. Does body mass index adequately convey a patient's mortality risk? JAMA. 2013;309:87–8.
16. Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering. Arch Intern Med. 2008;168:1617–24.
17. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions? Ann Intern Med. 2013;159:758–69.
18. Hill JO, Wyatt HR. The myth of healthy obesity. Ann Intern Med. 2013;159:789–90.
19. Ferrannini E, Natali A, Bell P, Cavallo-Perin P, Lalic N, Mingrone G. Insulin resistance and hypersecretion in obesity. J Clin Invest. 1997;100:1166–73.
20. Stefan N, Kantartzis K, Machann J, Schick F, Thamer C, Rittig K, et al. Identification and characterisation of metabolically benign obesity in humans. Arch Intern Med. 2008;168:1609–16.
21. Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, et al. General and abdominal adiposity and risk of death in Europe. N Engl J Med. 2008;359:2105–20.
22. Virtanen KA, Lidell ME, Orava J, Heglind M, Westergren R, Tiemi T, et al. Functional brown adipose tissue in healthy adults. N Engl J Med. 2009;360:1518–25.
23. Blondin DP, Labbe SM, Tingelstad HC, Noll C, Kunach M, Phoenix S, et al. Increased brown adipose tissue oxidative capacity in cold-acclimated humans. J Clin Endocrinol Metab. 2014;99(3):E438–46.
24. Van der Lans AA, Hoeks J, Brans B, Vijgen GH, Visser MG, Vosselman MJ, et al. Cold acclimation recruits human brown fat and increases nonshivering thermogenesis. J Clin Investig. 2013;123:3395–403.
25. Juge-Aubry CE, Henrichot E, Meier CA. Adipose tissue a regulator of inflammation. Best Pract Res Clin Endocrinol Metab. 2005;19:547–66.

26. Wozniak SE, Gee LL, Wachtel MS, Frezza EE. Adipose tissue: the new endocrine organ? A review article. Dig Dis Sci. 2009;54:1847–56.
27. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. JAMA. 2007;298:2028–37.
28. Prospective Studies Collaboration. Body mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009;373:1083–96.
29. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med. 2010; 363:2211–9.
30. Peeters A, Barendregt JJ, Willekens F, Mackenbach JP, Al Mamun A, Bonneux L. Obesity in adulthood and its consequences for life expectancy: a life-table analysis. Ann Intern Med. 2003;138:24–32.
31. Flegal K, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories. JAMA. 2013;309:71–82.
32. Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med. 2006;355:763–78.
33. Moayyedi P. The epidemiology of obesity and gastrointestinal and other disease: an overview. Dig Dis Sci. 2008;53:2293–9.
34. Oldhansky SJ, Passaro DJ, Hershow RC, Layden J, Carnes BA, Brody J, et al. A potential decline in life expectancy in the United Sates in the twenty-first century. N Engl J Med. 2005;352:1138–45.
35. Afzal S, Tybjaerg-Hansen A, Jensen GB, Nordestgaard BG. Change in body mass index associated with lowest mortality in Denmark, 1976–2013. JAMA. 2016;315:1989–96.
36. Akinussi ME, Pineda LA, El-Sohl AA. Effect of obesity on intensive care morbidity and mortality: a meta-analysis. Crit Care Med. 2008;36:151–8.
37. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham L, Anis AH. The incidence of comorbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health. 2006;9:88.
38. Delgado-Aros S, Locke GR III, Camilleri M, Talley NJ, Fett S, Zinsmeister AR, et al. Obesity is associated with increased risk of gastrointestinal symptoms: a population-based study. Am J Gastroenterol. 2004;99:1801–6.
39. Talley NJ, Howel S, Poulton R. Obesity and chronic gastrointestinal symptoms in young adults: a birth cohort study. Am J Gastroenterol. 2004;99:1807–14.
40. Talley NJ, Quan C, Jones MP, Horowitz M. Association of upper and lower gastrointestinal tract symptoms with body mass index in an Australian cohort. Neurogastroenterol Motil. 2004;16:413–9.
41. Levy RL, Linde JA, Feld KA, Crowell MD, Jeffery RW. The association of gastrointestinal symptoms with weight, diet, and exercise in weight-loss program participants. Clin Gastroenterol Hepatol. 2005;3:992–6.
42. Aro P, Ronkainen J, Talley NJ, Storskrubb T, Bolling-Sternevald E, Agreus L. Body mass index and chronic unexplained gastrointestinal symptoms: an adult endoscopic population based study. Gut. 2005;54:1377–83.
43. Dutta SK, Arora M, Kireet A, Bashandy H, Gandsas A. Upper gastrointestinal symptoms and associated disorders in morbidly obese patients: a prospective study. Dig Dis Sci. 2009;54:1243–6.
44. Carabotti M, Avallone M, Cereatti F, Paganini A, Greco F, Scirocco A, et al. Usefulness of upper gastrointestinal symptoms as a driver to prescribe gastroscopy in obese patients candidate to bariatric surgery. A prospective study. Obes Surg. 2016;26:1075–80.
45. El-Serag HB. Time trends of gastroesophageal reflux disease: a systematic review. Clin Gastroenterol Hepatol. 2007;5:17–26.
46. Jacobson BC, Somers SC, Fuchs CS, Kelly CP, Camargo CA Jr. Body-mass index and symptoms of gastroesophageal reflux in women. N Engl J Med. 2006;354:2340–8.
47. El-Serag H. Role of obesity in GORD-related disorders. Gut. 2008;57:281–4.

48. Ryan AM, Duong M, Healy L, Ryan SA, Parekh N, Reynolds JV, et al. Obesity, metabolic syndrome and esophageal adenocarcinoma: epidemiology, etiology and new targets. Cancer Epidemiol. 2011;356:309–19.
49. Derakhshan MH, Robertson EV, Fletcher J, Jones G-R, Lee YY, Wirz AA, et al. Mechanisms of association between BMI and dysfunction of the gastro-oesophageal barrier in patients with normal endoscopy. Gut. 2012;61:337–43.
50. Hirsch DP, Mathus-Vliegen EM, Holloway RH, Fakry N, D'Amato M, Boeckxstaens GE. Role of CCK(A) receptors in postprandial lower esophageal sphincter function in morbidly obese subjects. Dig Dis Sci. 2002;47:2531–7.
51. Hirsch DP, Mathus-Vliegen EM, Dagli U, Tytgat GN, Boeckxstaens GE. Effect of prolonged gastric distension on lower esophageal sphincter function and gastroesophageal reflux. Am J Gastroenterol. 2003;98:1696–704.
52. Lundell L, Ruth M, Sandbergh N, Bove-Nielsen M. Does massive obesity promote abnormal gastroesophageal reflux? Dig Dis Sci. 1995;40:1632–5.
53. Lagergren J, Bergström R, Nyren O. No relation between body mass and gastro-oesophageal reflux symptoms in a Swedish population based study. Gut. 2000;47:26–9.
54. Kjellin A, Ramel S, Rossner S, Thor K. Gastroesophageal reflux in obese patients is not reduced by weight loss. Scand J Gastroenterol. 1996;31:1047–51.
55. Lee YY, Wirz AA, Whiting JGH, Robertson EV, Smith D, Weir A, et al. Waist belt and central obesity cause partial hiatus hernia and short-segment acid reflux in asymptomatic volunteers. Gut. 2014;63:1053–60.
56. Anggiansah R, Sweis R, Anggiansah A, Wong T, Cooper D, Fox M. The effects of obesity on oesophageal function, acid exposure and the symptoms of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2013;37:555–63.
57. Ze EY, Kim BJ, Kang H, Kim JG. Abdominal visceral to subcutaneous adipose tissue ratio is associated with increased risk of erosive esophagitis. Dig Dis Sci. 2017;62:1265–71.
58. Fisher BL, Pennathur A, Mutnick JLM, Little AG. Obesity correlates with gastroesophageal reflux. Dig Dis Sci. 1999;44:2290–4.
59. El-Serag HB, Ergun GA, Pandolfino J, Fitzgerald S, Tran T, Kramer JR. Obesity increases oesophageal acid exposure. Gut. 2007;56:749–55.
60. Ayazi S, Hagen JA, Chan LS, DeMeester SR, Lin MW, Ayazi A, et al. Obesity and gastroesophageal reflux: quantifying the association between body mass index, esophageal acid exposure, and lower esophageal sphincter status in a large series of patients with reflux symptoms. J Gastrointest Surg. 2009;13:1440–7.
61. Nilsson M, Lundegardh G, Carling L, Ye W, Lagergren J. Body mass and reflux oesophagitis: an oestrogen-dependent association? Scand J Gastroenterol. 2002;37:626–30.
62. Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Obesity and estrogen as risk factors for gastroesophageal reflux symptoms. JAMA. 2003;290:66–72.
63. Nocon M, Labenz J, Jaspersen D, Meyer-Sabellek W, Stolte M, Lind T, et al. Association of body mass index with heartburn, regurgitation and esophagitis: results of the progression of Gastroesophageal reflux disease study. J Gastroenterol Hepatol. 2007;22:1728–31.
64. Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. Ann Intern Med. 2005;143:199–211.
65. Corley DA, Kubo A. Body mass index and gastroesophageal reflux disease: a systematic review and meta-analysis. Am J Gastroenterol. 2006;108:2619–28.
66. Corley DA, Kubo A, Zhao W. Abdominal obesity, ethnicity and gastro-oesophageal reflux symptoms. Gut. 2007;56:756–62.
67. Lee Y-C, Yen AM, Tai JJ, Chang SH, Lin JT, Chiu HM, et al. The effect of metabolic risk factors on the natural course of gastro-oesophageal reflux disease. Gut. 2009;58:174–81.
68. Kubo A, Cook MB, Shaheen NJ, Vaughan TL, Whiteman DC, Murray L, et al. Sex-specific associations between body mass index, waist circumference and the risk of Barrett's oesophagus: a pooled analysis from the international BEACON consortium. Gut. 2013;62:1684–91.

69. Stein DJ, El-Serag HB, Kuczynski J, Kramer JR, Sampliner RE. The association of body mass index with Barrett's esophagus. Aliment Pharmacol Ther. 2005;22:1005–10.
70. Corley DA, Kubo A, Levin TR, Block G, Habel L, Zhao W, et al. Abdominal obesity and body mass index as risk factors for Barrett's esophagus. Gastroenterology. 2007;133:34–41.
71. Jacobson BC, Chan AT, Giovannucci EL, Fuchs CS. Body mass index and Barrett's oesophagus in women. Gut. 2009;58:1460–6.
72. Smith KJ, O'Brien SM, Smithers BM, Gotley DC, Webb PM, Green AC, et al. Interaction among smoking, obesity, and symptoms of acid reflux in Barrett's esophagus. Cancer Epidemiol Prev. 2005;14:2481–6.
73. Ford ES, Li C, Zhao G, Tsai J. Trends in obesity and abdominal obesity among adults in the United States from 1999–2008. Int J Obes. 2012;7:e48528.
74. Cook MB, Greenwood DC, Hardie LJ, Wild CP, Forman D. A systematic review and meta-analysis of the risk of increasing adiposity on Barrett's esophagus. Am J Gastroenterol. 2008;103:292–300.
75. Abrams JA. Obesity and Barrett's oesophagus: more than just reflux. Gut. 2009;58:1437–8.
76. Pou KM, Massaro JM, Hoffmann U, Lieb K, Vasan RS, O'Donnell CJ, et al. Patterns of abdominal fat distribution: the Framingham heart study. Diabetes Care. 2009;32:481–5.
77. El-Serag HB, Graham DY, Satia JA, Rabeneck L. Obesity is an independent risk factor for GERD symptoms and erosive gastritis. Am J Gastroenterol. 2005;100:1243–50.
78. Akiyama T, Yoneda M, Imamori M, Iida H, Endo H, Hosono K, et al. Visceral obesity and the risk of Barrett's oesophagus in Japanese patients with non-alcoholic liver disease. BMC Gastroenterol. 2009;9:56.
79. El-Serag HB, Hashmi A, Garcia J, Richardson P, Alsarraj A, Fitzgerald S, et al. Visceral abdominal obesity measured by CT scan is associated with an increased risk of Barrett's oesophagus: a case-control study. Gut. 2014;63:220–9.
80. Rubenstein JH, Morgenstern H, Chey WD, Murray J, Scheiman JM, Schoenfeld P, et al. Protective role of gluteofemoral obesity in erosive oesophagitis and Barrett's oesophagus. Gut. 2014;63:230–5.
81. Ryan AM, Healy LA, Power DG, Byrne M, Murphy S, Byrne PJ, et al. Barrett oesophagus. Prevalence of central adiposity, metabolic syndrome, and a proinflammatory state. Ann Surg. 2008;247:909–15.
82. Francois F, Roper J, Goodman AJ, Pei Z, Ghumman M, Mourad M, et al. The association of gastric leptin with oesophageal inflammation and metaplasia. Gut. 2008;57:16–24.
83. Kendall BJ, Macdonald GA, Hayward NK, Prins JB, Brown I, Walker N, et al. Leptin and the risk of Barrett's oesophagus. Gut. 2008;57:448–54.
84. Tilg H, Kaser A. Adiponectin and JNK: metabolic inflammatory pathways affecting gastrointestinal carcinogenesis. Gut. 2009;58:1576–7.
85. Rubenstein JH, Kao JY, Madanick RD, Zhang M, Spacek MB, Donovan JL, et al. Association of adiponectin multimers with Barrett's oesophagus. Gut. 2009;58:1583–9.
86. Thompson OM, Beresford SAA, Kirk EA, Bronner MP, Vaughan TL. Serum leptin and adiponectin levels and risk of Barrett's esophagus and intestinal metaplasia of the gastroesophageal junction. Obesity. 2010;18:2204–11.
87. Hoyo C, Cook MB, Kamangar F, Freedman ND, Whiteman DC, Bernstein L, et al. Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the International BEACON Consortium. Int J Epidemiol. 2012;41:1706–18.
88. Corley DA. Obesity and the rising incidence of oesophageal and gastric adenocarcinoma: what is the link? Gut. 2007;56:1493–4.
89. Lagergren J. Adenocarcinoma of oesophagus: what exactly is the size of the problem and who is at risk? Gut. 2005;54(Suppl I):i1–5.
90. Polednak AP. Estimating the number of US incident cancers attributable to obesity and the impact on temporal trends in incidence rates for obesity-related cancers. Cancer Detect Prev. 2008;32:190–9.

91. Freedman ND, Murray LJ, Kamangar F, Abnet CC, Cook MB, Nyren O, et al. Alcohol intake and risk of oesophageal adenocarcinoma: a pooled analysis from the BEACON consortium. Gut. 2011;60:1029–37.
92. O'Doherty MG, Freedman ND, Hollenbeck AR, Schatzkin A, Abnet CC. A prospective cohort study of obesity and risk of oesophageal and gastric adenocarcinoma in the NIH-AARP Diet and Health Study. Gut. 2012;61:1261–8.
93. Robertson EV, Derakhshan MH, Wirz AA, Lee YY, Seenan JP, Ballantyne SA, et al. Central obesity in asymptomatic volunteers is associated with increased intrasphincteric acid reflux and lengthening of the cardiac mucosa. Gastroenterology. 2013;145:730–9.
94. Martel de C, Haggerty TD, Corley DA, Vogelman JH, Orentreich N, Parsonnet J. Serum ghrelin levels and risk of subsequent adenocarcinoma of the esophagus. Am J Gastroenterol. 2007;102:1166–72.
95. Kubo A, Corley DA. Body mass index and adenocarcinomas of the esophagus or gastric cardia: a systematic review and meta-analysis. Cancer Epidemiol Biomark Prev. 2006;15:872–8.
96. Veugelers PJ, Porter GA, Guernsey DL, Casson AC. Obesity and lifestyle risk factors for gastroesophageal reflux disease, Barrett esophagus ad esophageal adenocarcinoma. Dis Esophagus. 2006;19:321–8.
97. Corley DA, Kubo A, Zhao W. Abdominal obesity and the risk of esophageal and gastric cardia carcinoma. Cancer Epidemiol Biomark Prev. 2008;17:352–8.
98. Abnet CC, Freedman ND, Hollenbeck AR, Fraumeni JF Jr, Leitzmann M, Schatzkin A. A prospective study of BMI and risk of oesophageal and gastric adenocarcinoma. Eur J Cancer. 2008;44:465–71.
99. Figueroa JD, Terry MB, Gammon MD, Vaughan TL, Risch HA, Zhang FF, et al. Cigarette smoking, body mass index, gastro-esophageal reflux disease and non-steroidal anti-inflammatory drug use and risk of subtypes of esophageal and gastric cancers by P53 expression. Cancer Causes Control. 2009;20:361–8.
100. Ryan AM, Rowley SP, Fitzgerald AP, Ravi N, Reynolds JV. Adenocarcinoma of the oesophagus and gastric cardia: male preponderance in association with obesity. Eur J Cancer. 2006;42:1151–8.
101. Samanic C, Chow WH, Gridley G, Jarvholm B, Fraumeni JF Jr. Relation of body mass index to cancer risk in 362,552 Swedish men. Cancer Causes Control. 2006;17:901–9.
102. Reeves CK, Pirie K, Beral V, Green J, Spencer E, Bull D. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. BMJ. 2007;335:1134.
103. Merry AH, Schouten LJ, Goldbohm RA, van den Brandt PA. Body mass index, height and risk of adenocarcinoma of the oesophagus and gastric cardia: a prospective cohort study. Gut. 2007;56:1503–11.
104. Anderson LA, Watson RG, Murphy SJ, Johnston BT, Comber H, McGuigan J, et al. Risk factors for Barrett's oesophagus and oesophageal adenocarcinoma: results from the FINBAR study. World J Gastroenterol. 2007;13:1585–94.
105. Steffen A, Schultze MB, Pischon T, Dietrich T, Molina E, Chirlaque MD, et al. Anthropometry and esophageal cancer risk in European prospective investigation into cancer and nutrition. Cancer Epidemiol Biomark Prev. 2009;18:2079–89.
106. MacInnis RJ, English DR, Hopper JL, Giles GG. Body size and composition and the risk of gastric and esophageal adenocarcinoma. Int J Cancer. 2006;118:2628–31.
107. Whiteman DC, Sadeghi S, Pandeya N, Smithers BM, Gotley DC, Bain CJ, et al. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. Gut. 2009;57:173–80.
108. Yang P, Zhou Y, Chen B, Wan H-W, Jia G-Q, Bai H-L, et al. Overweight, obesity and gastric cancer risk: results from a meta-analysis of cohort studies. Eur J Cancer. 2009;45:2867–73.
109. Groot de NL, Burgerhart JS, van de Meeberg PC, de Vries DR, Smout AJPM, Siersema PD. Systematic review: the effects of conservative and surgical treatment for obesity on gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2009;30:1091–102.
110. Bonfrate L, Wang DQ-H, Garruti G, Portincasa P. Obesity and the risk and prognosis of gallstone disease and pancreatitis. Best Pract Res Clin Gastroenterol. 2014;28:623–35.

111. Tsai CJ, Leitzmann MF, Willett WC, Giovannucci EL. Weight cycling and risk of gallstone in men. Arch Intern Med. 2006;166:2369–74.
112. Shaffer EA. Gallstone disease: epidemiology of gallbladder stone disease. Best Pract Res Clin Gastroenterol. 2006;20:981–96.
113. Everhart JE, Khare M, Hill M, Maurer KR. Prevalence and ethnic differences in gallbladder disease in the United States. Gastroenterology. 1999;117:632–9.
114. Carey MC. Pathogenesis of gallstones. Am J Surg. 1993;165:410–9.
115. Beckingham IJ. Gallstone disease. BMJ. 2001;322:91–4.
116. Portincasa P, Moschetta A, Palasciano G. Cholesterol gallstone disease. Lancet. 2006;368:230–9.
117. Portincasa P, Wang DQ. Intestinal absorption, hepatic synthesis, and biliary secretion of cholesterol: where are we for cholesterol gallstone formation? Hepatology. 2012;55:1313–6.
118. Sampliner RE, Bennett PH, Comess LJ, Rose FA, Burch TA. Gallbladder disease in Pima Indians. Demonstration of high prevalence and early onset by cholecystography. N Engl J Med. 1970;283:1358–64.
119. Maclure KM, Hayes KC, Colditz GA, Stampfer MJ, Speizer FE, Willett WC. Weight, diet, and the risk of symptomatic gallstones in middle-aged women. N Engl J Med. 1989;321:563–9.
120. Stampfer MJ, Maclure KM, Colditz GA, Manson JE, Willett WC. Risk of symptomatic gallstones in women with severe obesity. Am J Clin Nutr. 1992;55:652–8.
121. Sahi T, Paffenbarger RS Jr, Hsieh CC, Lee IM. Body mass index, cigarette smoking, and other characteristics as predictors of self-reported, physician-diagnosed gallbladder disease in male college alumni. Am J Epidemiol. 1998;147:644–51.
122. Tsai CJ, Leitzmann MF, Willett WC, Giovannucci EL. Prospective study of abdominal adiposity and gallstone disease in US men. Am J Clin Nutr. 2004;80:38–44.
123. Mendez-Sanchez N, Chavez-Tapia NC, Motola-Kuba D, Sanchez-Lara K, Ponciano-Rodriguez G, Baptitsa H, et al. Metabolic syndrome as a risk factor for gallstone disease. World J Gastroenterol. 2005;11:1653–7.
124. Johansson K, Sundstrom J, Marcus C, Hemmingsson E, Neovius M. Risk of symptomatic gallstones and cholecystectomy after a very-low-calorie diet or low-calorie diet in a commercial weight loss program: 1-year matched cohort study. Int J Obes. 2014;38:279–84.
125. Mathus-Vliegen EM, van Ierland-van Leeuwen ML, Terpstra A. Lipase inhibition by orlistat: effects on gall-bladder kinetics and cholecystokinin release in obesity. Aliment Pharmacol Ther. 2004;19:601–11.
126. Stender S, Nordestgaard BG, Tybjaerg-Hansen A. Elevated body mass index as a causal gallstone disease: a Mendelian randomization study. Hepatology. 2013;58:2133–41.
127. Misra S, Chaturvedi A, Misra NC, Sharma ID. Carcinoma of the gallbladder. Lancet Oncol. 2003;4:167–76.
128. Mabee TM, Meyer P, DenBesten L, Mason EE. The mechanism of increased gallstone formation in obese human subjects. Surgery. 1976;79:460–8.
129. Freeman JB, Meyer PD, Printen KJ, Mason EE, DenBesten L. Analysis of gallbladder bile in morbid obesity. Am J Surg. 1975;129:163–6.
130. Shiffman ML, Sugerman HJ, Kellum JM, Moore EW. Changes in gallbladder bile composition following gallstone formation and weight reduction. Gastroenterology. 1992;103:214–21.
131. Portincasa P, Di Ciaula A, Palmieri V, Van Berge-Henegouwen GP, Palasciano G. Effects of cholestyramine on gallbladder and gastric emptying in obese and lean subjects. Eur J Clin Investig. 1995;25:746–53.
132. Mathus-Vliegen EM, van Ierland-van Leeuwen ML, Terpstra A. Determinants of gallbladder kinetics in obesity. Dig Dis Sci. 2004;49:9–16.
133. Weinsier RL, Ullmann DO. Gallstone formation and weight loss. Obes Res. 1993;1:51–6.
134. Erlinger S. Gallstones in obesity and weight loss. Eur J Gastroenterol Hepatol. 2000;12:1347–52.
135. Diehl AK. Cholelithiasis and the insulin resistance syndrome. Hepatology. 2000;31:528–30.

136. Chen LY, Qiao QH, Zhang SC, Chen YH, Chao GQ, Fang LZ. Metabolic syndrome and gallstone disease. World J Gastroenterol. 2012;18:4215–20.
137. Forsmark CE, Baillie J. AGA Institute clinical practice and economics committee, AGA Institute governing board. AGA Institute technical review on acute pancreatitis. Gastroenterology. 2007;132:2022–44.
138. Mathus-Vliegen EMH. Facts and fallacies of diets in gastroenterology. Institute Danone. 2010. ISBN 2-930151-28-5.
139. Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, et al. Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology. 2012;143:1179.
140. Niederau C, Nierdeau M, Luthen R, Strohmeyer G, Ferrell LD, Grendel JH. Pancreatic exocrine secretion in acute experimental pancreatitis. Gastroenterology. 1990;99:1120–7.
141. Lerch MM, Saluja AK, Rünzi M, Dawra R, Saluja M, Steer ML. Pancreatic duct obstruction triggers acute necrotizing pancreatitis in the opossum. Gastroenterology. 1993;104:853.
142. Rattner DW. Experimental models of acute pancreatitis and their relevance to human disease. Scand J Gastroenterol. 1996;219(suppl):6.
143. Steer ML. Pathogenesis of acute pancreatitis. Digestion. 1997;58(suppl 1):46.
144. Kingsnorth A. Role of cytokines and their inhibitors in acute pancreatitis. Gut. 1997;40(1):1–4.
145. Purohit V, Russo D, Salin M, Brown R. Mechanisms of alcoholic pancreatitis, introduction and summary of the symposium. Pancreas. 2003;27:281–5.
146. Russell MK. Acute pancreatitis: a review of pathophysiology and nutrition management. Nutr Clin Pract. 2004;19:16–24.
147. Kingsnorth A, O'Reilly D. Acute pancreatitis. BMJ. 2006;332:1072–6.
148. Banks PA, Freeman ML. Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. Am J Gastroenterol. 2006;101:2379.
149. Cavallini G, Frulloni L, Bassi C, Gabbrielli A, Castoldi L, Costamagna G, et al. Prospective multicentre survey on acute pancreatitis in Italy (ProInf-AISP): results on 1005 patients. Dig Liver Dis. 2004;36:205.
150. Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the international symposium on acute pancreatitis. Arch Surg. 1993;128:586.
151. Gloor B, Müller CA, Worni M, Martignoni ME, Uhl W, Büchler MW. Late mortality in patients with severe acute pancreatitis. Br J Surg. 2001;88:975.
152. Mutinga M, Rosenbluth A, Tenner SM, Odze RR, Sica GT, Banks PA. Does mortality occur early or late in acute pancreatitis? Int J Pancreatol. 2000;28:91.
153. Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, Spencer FC. Prognostic signs and the role of operative management in acute pancreatitis. Surg Gynecol Obstet. 1974;139:69.
154. De Bernardinis M, Violi V, Roncoroni L, Boselli AS, Giunta A, Peracchia A. Discriminant power and information content of Ranson's prognostic signs in acute pancreatitis: a meta-analytic study. Crit Care Med. 1999;27:2272.
155. Johnson CD, Toh SK, Campbell MJ. Combination of APACHE-II score and an obesity score (APACHE-O) for the prediction of severe acute pancreatitis. Pancreatology. 2004;4:1.
156. Martinez J, Sanchez-Paya J, Palazon JM, Suazo-Barahona J, Robles-Diaz G, Perez-Mateo M. Is obesity a risk factor in acute pancreatitis? A meta-analysis. Pancreatology. 2004;4:42–8.
157. Martinez J, Johnson CD, Sánchez-Payá J, de Madaria E, Robles-Díaz G, Pérez-Mateo M. Obesity is a definitive risk factor of severity and mortality in acute pancreatitis: an updated meta-analysis. Pancreatology. 2006;6:206.
158. Hong S, Qiwen B, Ying J, Wei A, Chaoyang T. Body mass index and the risk and prognosis of acute pancreatitis: a meta-analysis. Eur J Gastroenterol Hepatol. 2011;23:1136–43.
159. Wang S-Q, Li S-J, Feng Q-X, Feng X-Y, Xu L, Zhao Q-C. Overweight is an additional prognostic factor in acute pancreatitis: a meta-analysis. Pancreatology. 2011;11:92–8.
160. Banks PA, Bollen TI, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62:102.
161. Apte MV, Wilson JS, McCaughan GW, Korsten MA, Haber PS, Norton ID, et al. Ethanol-induced alterations in messenger RNA levels correlate with glandular content of pancreatic enzymes. J Lab Clin Med. 1995;125:634.

162. Tiscornia OM, Celener D, Perec CJ, De Lehmann ES, Cresta M, Dreiling DA. Physiopathogenic basis of alcoholic pancreatitis: the effects of elevated cholinergic tone and increased "pancreon" ecbolic response to CCK-PZ. Mt Sinai J Med. 1983;50:369.
163. Majumder S, Gierisch JM, Bastian LA. The association of smoking and acute pancreatitis: a systematic review and meta-analysis. Pancreas. 2015;44:540.
164. Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. Gastroenterology. 2007;132:2208–25.
165. Berrington de Gonzalez A, Sweetland S, Spencer E. A meta-analysis of obesity and the risk of pancreatic cancer. Br J Cancer. 2003;89:519–23.
166. Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. JAMA. 1995;273:1605–9.
167. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer. 2005;92:2076–83.
168. Gapstur SM, Gann PH, Lowe W, Liu K, Colangelo L, Dyer A. Abnormal glucose metabolism and pancreatic cancer mortality. JAMA. 2000;283:2552–8.
169. Batty GD, Shipley MJ, Marmot M, Smith GD. Diabetes status and post-load plasma glucose concentrations in relation to site-specific cancer mortality: findings from the original Whitehall study. Cancer Causes Control. 2004;15:873–81.
170. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose levels and cancer risk in Korean men and women. JAMA. 2005;293:194–202.
171. Stolzenberg-Solomon RZ, Graubard BI, Chari S, Limburg P, Taylor PR, Virtamo J, et al. Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. JAMA. 2005;294:2872–8.
172. Lyon JL, Slattery ML, Mahoney AW, Robison LM. Dietary intake as a risk factor for cancer of the exocrine pancreas. Cancer Epidemiol Biomark Prev. 1993;2:513–8.
173. Baghurts PA, McMichael AJ, Slavotinek AH, Baghurst KI, Boyle P, Walker AM. A case-conrol study of diet and cancer of the pancreas. Am J Epidemiol. 1991;134:167–79.
174. Schernhammer ES, Hu FB, Giovannucci E, Michaud DS, Colditz GA, Stampfer MJ, et al. Sugar-sweetened soft drink consumption and risk of pancreatic cancer in two prospective cohorts. Cancer Epidemiol Biomark Prev. 2005;14:2098–105.
175. Larsson SC, Bergkvist L, Wolk A. Consumption of sugar and sugar-sweetened foods and the risk of pancreatic cancer in a prospective study. Am J Clin Nutr. 2006;84:1171–6.
176. Sugerman HJ, Brewer WH, Shiffman ML, Brolin RE, Fobi MA, Linner JH, et al. A multicenter, placebo-controlled, randomized, double-blind, prospective trial of prophylactic ursodiol for the prevention of gallstone formation following gastric-bypass-induced rapid weight loss. Am J Surg. 1995;169:91–6.
177. Miller K, Hell E, Lang B, Lengauer E. Gallstone formation prophylaxis after gastric restrictive procedures for weight loss: a randomized double-blind placebo-controlled trial. Ann Surg. 2003;238:697–702.
178. Uy MC, Talingdan-Te MC, Espinosa WZ, Daez ML, Ong JP. Ursodeoxycholic acid in the prevention of gallstone formation after bariatric surgery: a meta-analysis. Obes Surg. 2008 Dec;18(12):1532–8.
179. El-Sherag HB. Obesity and disease of the esophagus and colon. Gastroenterol Clin N Am. 2005;34:63–82.
180. Bardou M, Basrkun AN, Martel M. Obesity and colorectal cancer. Gut. 2013;62:933–47.
181. Frezza EE, Wachtel MS, Chiriva-Internati M. Influence of obesity on the risk of developing colon cancer. Gut. 2005;55:285–91.
182. Siddiqui A, Sahdala HNP, Nazario HE, Mahgoub A, Patel M, Cipher D, et al. Obesity is associated with an increased prevalence of advanced adenomatous polyps in a male veteran population. Dig Dis Sci. 2009;54:1560–4.
183. Kang HW, Kim D, Kim HJ, Kim CH, Kim YS, Park MJ, et al. Visceral obesity and insulin resistance as risk factors for colorectal adenoma: a cross-sectional, case-control study. Am J Gastroenterol. 2010;105:178–87.
184. Hwang ST, Cho YK, Park JH, Kim HJ, Park DI, Sohn CI, et al. Relationship of non-alcoholic fatty liver disease to colorectal adenomatous polyps. J Gastroenterol Hepatol. 2010;25:562–7.

185. Wong VW-S, Wong GL-H, Tsang SW-C, Fan T, Chu WC-W, Woo J, et al. High prevalence of colorectal neoplasm in patients with non-alcoholic steatohepatitis. Gut. 2011;60:829–36.
186. Lee YJ, Myung S-K, Cho BL, Park B-J, Park JH, Ju W, et al. Adiposity and the risk of colorectal adenomatous polyps: a meta-analysis. Cancer Causes Control. 2011;22:1021–35.
187. Hong S, Cai Q, Chen D, Zhu W, Huang W, Li Z. Abdominal obnesity and the risk of colorectal adenoma: a meta-analysis of observational studies. Eur J Cancer Prev. 2012;21:523–31.
188. Okabayashi K, Ashrafian H, Hasegawa H, Yoo JH, Patel VM, Harling L, et al. Body mass index category as a risk factor for colorectal adenoma: a systematic review and meta-analysis. Am J Gastroenterol. 2012;107:1175–85.
189. Ben Q, An W, Jiang Y, Zhan X, Du Y, Cai QC, et al. Body mass index increases risk for colorectal adenomas based on meta-analysis. Gastroenterology. 2012;142:762–72.
190. Dai Z, Xu YC, Niu L. Obesity and colorectal cancer risk: a meta-analysis of cohort studies. World J Gastroenterol. 2007;13:4199–206.
191. Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. Am J Clin Nutr. 2007;86:556–65.
192. Moghaddam AA, Woodward M, Huxley R. Obesity and risk of colorectal cancer: a meta-analysis of 31 studies with 70,000 events. Cancer Epidemiol Biomark Prev. 2007;16:2533–47.
193. Harriss DJ, Atkinson G, George K, Cable NT, Reilly T, Haboubi N, et al. Lifestyle factors and colorectal cancer risk (1): systematic review and meta-analysis of associations with body mass index. Color Dis. 2009;11:547–63.
194. Terry PD, Miller AB, Rohan TE. Obesity and colorectal cancer risk in women. Gut. 2002;51:191–4.
195. Phillips R, Snowdon D. Dietary relationships with fatal colorectal cancer among seventh-day adventists. J Natl Cancer Inst. 1985;74:307–17.
196. Martinez M, Giovannucci E, Spiegelman D, Hunter DJ, Willett WC, Colditz GA. Leisure-time physical activity, body size, and colon cancer in women. J Natl Cancer Inst. 1997;89:948–55.
197. Terry P, Giovannucci E, Bergkvist L, Holmberg L, Wolk A. Body weight and colorectal cancer risk in a cohort of Swedish women: relation varies by age and cancer site. Br J Cancer. 2001;85:346–9.
198. Samad AKA, Taylor RS, Marshall T, Chapman MA. A meta-analysis of the association of physical activity with reduced risk of colorectal cancer. Color Dis. 2005;7:204–13.
199. Slattery ML. Physical activity and colorectal cancer. Sports Med. 2004;34:239–52.
200. Wolin KY, Yan Y, Colditz GA. Physical activity and risk of colon adenoma: a meta-analysis. Br J Cancer. 2011;104:882–5.
201. Wolin KY, Yan Y, Colditz GA, Lee IM. Physical activity and colon cancer prevention: a meta-analysis. Br J Cancer. 2009;100:611–6.
202. Ma J, Giovannucci E, Pollak M, Leavitt A, Tao Y, Gaziano JM, et al. A prospective study of plasma C-peptide and colorectal cancer risk in men. J Natl Cancer Inst. 2004;96:546–53.
203. Wei EK, Ma J, Pollak MN, Rifai N, Fuchs CS, Hankinson SE, et al. A prospective study of C-peptide, insulin-like growth factor-1, insulin-like growth factor binding protein-1, and the risk of colorectal cancer in women. Cancer Epidemiol Biomark Prev. 2005;14:850–5.
204. Stocks T, Lukanova A, Johansson M, Rinaldi S, Palmqvist R, Hallmans G, et al. Components of the metabolic syndrome and colorectal cancer risks: a prospective study. In J Obes (Lod). 2008;32:304–14.
205. Hu NC, Chen JD, Lin YM, Chang JY, Chen YH. Stepwise relationship between components of metabolic syndrome and risk of colorectal adenoma in a Taiwanese population receiving screening colonoscopy. J Formos Med Assoc. 2011;10:100–8.
206. Lundgren M, Buren J, Ruge T, Myrnäs T, Eriksson JW. Glucocorticoids down-regulate glucose uptake capacity and insulin signaling proteins in omental but not subcutaneous human adipocytes. J Clin Endocrinol Metab. 2004;89:2989–97.
207. Klein S, Fontana L, Young VL, Coggan AR, Kilo C, Patterson BW, et al. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. New Engl J Med. 2004;350:2549–57.

208. Thörne A, Lönnqvist F, Apelman J, Hellers G, Arner P. A pilot study of long-term effects of a novel obesity treatment: omentectomy in connection with adjustable gastric banding. Int J Obes. 2002;26:193–9.
209. Freedland ES. The role of a critical visceral adipose tissue threshold (CVATT) in metabolic syndrome: implications for controlling dietary carbohydrates: a review. Nutr Metab. 2004;1:12.
210. Huang X-F. Adiponectin and signal pathways in obesity-induced colon cancer. Gut. 2009;58:1169–70.
211. Kaklamani VG, Wisinski KB, Sadim M, Gulden C, Do A, Offit K, et al. Variants of the adiponectin (ADIPOQ) and adiponectin receptor 1 (ADIPOR1) genes and colorectal cancer risk. JAMA. 2008;300:1523–31.
212. Xu XT, Xu Q, Tong JL, Zhu MM, Huang ML, Ran ZH, et al. Meta-analysis: circulating adiponectin levels and risk of colorectal cancer and adenoma. J Dig Dis. 2011;12:234–44.
213. An W, Bai Y, Deng SX, Gao J, Ben QW, Cai QC, et al. Adiponectin levels in patients with colorectal cancer and adenoma: a meta-analysis. Eur J Cancer Prev. 2012;21:126–33.
214. Fujisawa T, Endo H, Tomimoto A, Sugiyama M, Takahashi H, Saito S, et al. Adiponectin suppresses colorectal carcinogenesis under the high-fat diet condition. Gut. 2008;57:1531–8.
215. Eraslan E, Turkay C, Koktener A, Koca C, Uz B, Bavbek N. Association of visceral fat accumulation and adiponectin levels with colorectal neoplasia. Dig Dis Sci. 2009;54:862–8.
216. Zhou Y, Wu L, Li X, Wu X, Li B. Outcome of laparoscopic colorectal surgery in obese and nonobese patients: a meta-analysis. Surg Endosc. 2012;26:783–9.
217. Makino T, Shukla PJ, Rubino F, Milsom JW. The impact of obesity on perioperative outcomes after laparoscopic colorectal resection. Ann Surg. 2012;255:228–36.
218. Hull M, Lagergren J. Obesity and colorectal cancer. Gut. 2014;63:205.
219. Derogar M, Hull MA, Kant P, Östlund M, Lu Y, Lagergren J. Increased risk of colorectal cancer after obesity surgery. Ann Surg. 2013;258(6):983–8. https://doi.org/10.1097/SLA.0b013e318288463a.
220. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Disease, and American College of Gastroenterology. Gastroenterology. 2012;142:1592–609.
221. EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO). J Hepatol. 2016;64:1388–402.
222. Goh GB-B, McCullough AJ. Natural history of nonalcoholic fatty liver disease. Dig Dis Sci. 2016;61:1226–33.
223. Corey KE, Rinella ME. Medical and surgical treatment options for non-alcoholic steatohepatitis. Dig Dis Sci. 2016;61:1387–97.
224. Anstee QM, McPherson S, Day CP. Uncertainty pages. How big a problem is non-alcoholic fatty liver disease? BMJ. 2011;343:d3897.
225. Sherif ZA, Saeed A, Ghavimi S, Nouraie S-M, Laiyemo AO, Brim H, et al. Global epidemiology of nonalcoholic fatty liver disease and perspectives on US minority populations. Dig Dis Sci. 2016;61:1214–25.
226. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34:274–85.
227. Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann Med. 2011;43:617–49.
228. Yilmaz Y. Review article: is non-alcoholic fatty liver disease a spectrum or are steatosis and non-alcoholic steatohepatitis distinct conditions? Aliment Pharmacol Ther. 2012;36:815–23.
229. Strengel JZ, Harrison SA. Nonalcoholic steatohepatitis: clinical presentation, diagnosis, and treatment. Gastroenterol Hepatol. 2006;6:440–7.

230. Ratziu V. Novel pharmacotherapy options for NASH. Dig Dis Sci. 2016;61:1398–405.
231. Ekstedt M, Hagstrom H, Nasr P, Fredrikson M, Stål P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLS after up to 33 years of follow-up. Hepatology. 2015;61:1547–54.
232. Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with non-alcoholic fatty liver disease. Gastroenterology. 2015;149:389–97.
233. Mantovani A, Ballestri S, Lonardo A, Targher G. Cardiovascular disease and myocardial abnormalities in nonalcoholic fatty liver disease. Dig Dis Sci. 2016;61:1246–67.
234. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in non-alcoholic fatty liver vs non-alcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol. 2015;13:643–54.
235. Matteoni CA, Younossi ZM, Gramlich T, Prokop LJ, Murad MH, Loomba R. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology. 1999;116:1413–9.
236. Rafiq N, Bai C, Fang Y, Srishord M, McCullough A, Gramlich T, et al. Long-term follow-up of patients with nonalcoholic fatty liver. Clin Gastroenterol Hepatol. 2009;7:234–8.
237. Liu B, Balkwill A, Reeves G, Beral V, on behalf of the Million Women Study Coordinators. Body mass index and risk of liver cirrhosis in middle aged UK women: a prospective study. BMJ. 2010;340:c912.
238. Hart CL, Batty GD, Morrison DS, Mitchell RJ, Smith GD. Obesity, overweight and liver disease in the Midspan prospective cohort studies. Int J Obes. 2010;34:1051–9.
239. Hamaguchi M, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Fujii K, et al. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. Ann Intern Med. 2005;143:722–8.
240. Marchesini G, Bugianesi E, Forlaini G, Cerrelli F, Lenzi M, Manini R, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology. 2003;37:917–23.
241. Younossi ZM, Otgonsuren M, Henry L, Venkatesan C, Mishra A, Erario M, et al. Association of Nonalcoholic Fatty Liver Disease (NAFLD) with Hepatocellular Carcinoma (HCC) in the United States from 2004 to 2009. Hepatology. 2015;62:1723–30.
242. Hassan MM, Abdel-Wahab R, Kaseb A, Shalaby A, Phan AT, El-Serag H, et al. Obesity early in adulthood increases risk but does not affect outcomes of hepatocellular carcinoma. Gastroenterologia. 2015;149:119–29.
243. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. Diabetes Care. 2010;33:1674–85.
244. Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JP. Type 2 diabetes and cancer: umbrella review of meta-analysis of observational studies. BMJ. 2015;350:g7607.
245. Setiawan VW, Lim U, Lipworth L, Lu SC, Shepherd J, Ernst T, et al. Sex and ethnic differences in the association of obesity with risk of hepatocellular carcinoma. Clin Gastroenterol Hepatol. 2016;14:309–16.
246. Schlesinger S, Aleksandrova K, Pischon T, Fedirko V, Jenab M, Trepo E, et al. Abdominal obesity, weight gain during adulthood and risk of live rand biliary tract cancer in a European cohort. Int J Cancer. 2013;132:645–57.
247. Ohki T, Tateishi R, Shiina S, Goto E, Sato T, Nakagawa H, et al. Visceral fat accumulation is an independent risk factor for hepatocellular carcinoma recurrence after curative treatment in patients with suspected NASH. Gut. 2009;58:839–44.
248. Parekhi S, Anania FA. Abnormal lipid and glucose metabolism in obesity: implications for non-alcoholic fatty liver disease. Gastroenterology. 2007;132:2191–207.
249. Kopec KL, Burns D. Nonalcoholic fatty liver disease: a review of the spectrum of disease, diagnosis, and therapy. Nutr Clin Pract. 2011;26:565–76.
250. Sattar N, Forrest E, Preiss D. Non-alcoholic fatty liver disease. BMJ. 2014;349:g4596.
251. Reeves HL, Zaki MYW, Day CP. Hepatocellular carcinoma in obesity, type 2 diabetes, and NAFLD. Dig Dis Sci. 2016;61:1234–45.
252. Donelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in live rand secreted via lipoproteins in nonalcoholic fatty liver disease. J Clin Invest. 2005;115:1343–51.

253. Nielsen S, Guo Z, Johnson CM, Hensrud DD, Jensen MD. Splanchnic lipolysis in human obesity. J Clin Invest. 2004;113:1582–8.
254. Softic S, Cohen DE, Kahn CR. Role of dietary fructose and hepatic de novo Lipogenesis in fatty liver disease. Dig Dis Sci. 2016;61:1282–93.
255. Chung M, Ma J, Patel K, Berger S, Lau J, Lichtenstein AH. Fructose, high-fructose corn syrup, sucrose, and non-alcoholic fatty liver disease or indexes of liver health: a systematic review and meta-analysis. Am J Clin Nutr. 2014;100:833–49.
256. Fabbrini E, Magkos F, Mohammed BS, Pietka T, Abumrad NA, Patterson BW, et al. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. PNAS. 2009;106:15430–5.
257. Leclercq IA, Horsmans Y. Nonalcoholic fatty liver disease: the potential role of nutritional management. Curr Opin Clin Nutr Metab Care. 2008;11:766–73.
258. Zelber-Sagi S, Ratziu V, Oren R. Nutrition and physical activity in NAFLD: an overview of the epidemiological evidence. World J Gastroenterol. 2011;17:3377–89.
259. Hannah WN Jr, Harrison SA. Lifestyle and dietary interventions in the management of non-alcoholic fatty liver disease. Dig Dis Sci. 2016;61:1365–74.
260. Promrat K, Kleiner DE, Niemeier HM, Jackvony E, Kearns M, Wands JR, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology. 2010;51:121–9.
261. Villar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduced features of non-alcoholic hepatitis. Gastroenterology. 2015;149:367–78.
262. Harrison SA, Fecht W, Brunnt EM, Neuschwander-Tetri BA. Orlistat for overweight subjects with non-alcoholic steatohepatitis: a randomised prospective trial. Hepatology. 2009;49:80–6.
263. Keating SE, Hackett DA, George J, Johnson NA. Exercise and non-alcoholic fatty liver disease: a systematic review and meta-analysis. J Hepatol. 2012;57:157–66.
264. Thoma C, Day CP, Trenell MI. Lifestyle inteventions for the treatment of non-alcoholic fatty liver disease in adults: a systematic review. J Hepatol. 2012;56:255–66.
265. Andersen T, Gluud C, Franzmann MB, Christoffersen P. Hepatic effects of dietary weight loss in morbidly obese subjects. J Hepatol. 1991;12:224–9.
266. Musso G, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. Diabetologia. 2012;55:885–904.
267. Younossi ZM, Reyes MJ, Mishra A, Mehta R, Henry L. Systematic review with meta-analysis: non-alcoholic steatohepatitis—a case for personalised treatment based on pathogenic targets. Aliment Pharmacol Ther. 2014;39:3–14.
268. McMillan DC, Sattar N, Lean M, McArdle CS. Obesity and cancer. BMJ. 2006;333:1109–11.
269. World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition, physical activity and the prevention of cancer: a global perspective. Washington DC: AICR; 2007.
270. Bergstrom A, Pisani P, Tenet V, Wolk A, Adami HO. Overweight as an avoidable cause of cancer in Europe. Int J Cancer. 2001;91:421–30.
271. Lukanova A, Björ O, Kaaks R, Lenner P, Lindahl B, Hallmans G, et al. Body mass index and cancer: results from the Northern Sweden Health and Disease Cohort. Int J Cancer. 2005. https://doi.org/10.1002/ijc.21354.
272. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371:569–78.
273. Sjöström L, Gummesson A, Sjöström CD, Narbro K, Peltonen M, Wedel H, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. Lancer Oncol. 2009;10:653–62.