OBESITEXT

CHAPTER 14: CLINICAL PROBLEMS CAUSED BY OBESITY

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Clinical Problems Caused by Obesity

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Introduction

Over the past few decades the incidence of obesity has doubled worldwide and current estimates classify more than 1.5 billion adults as overweight and at least 500 million of them as clinically obese, with body mass index (BMI) over 25 kg/m^2 and 30 kg/m^2, respectively [1]. Obesity prevalence rates are steadily rising in the majority of the modern Western societies, as well as in the developing world. Moreover, alarming trends of weight gain are reported for children and adolescents, undermining the present and future health status of the pediatric population [2]. To highlight the related threat to public health, the World Health Organization has declared obesity a global epidemic, also stressing that it remains an under-recognized problem of the public health agenda [3, 4].

Depending on the degree and duration of weight gain, obesity can progressively cause and/or exacerbate a wide spectrum of co-morbidities, including type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, cardiovascular disease (CVD), liver dysfunction, respiratory and musculoskeletal disorders, sub-fertility, psychosocial problems and certain types of cancer (Figure 1). These chronic diseases have been shown to hold strong correlations with BMI and closely follow the prevalence patterns of excessive body weight in all studied populations [5, 6]. Notably, the risk of developing a number of obesity-related co-morbidities rises exponentially with increasing BMI over 30 kg/m^2, which is further associated with a graded increase in the relative risk of premature death, primarily from CVD [3, 6, 7]. In the overweight BMI range (25-30 kg/m^2) the risk of premature mortality is weaker and appears to be influenced mainly by fat distribution (J-curve relationship, Figure 2). Indeed, fat accumulation intra-abdominally and subcutaneously around the abdomen (central, abdominal, visceral, android, upper body or apple-shaped obesity) is associated with higher risk for metabolic and cardiovascular diseases, independent of BMI [8]. Conversely, fat accumulation in the subcutaneous regions of hips, thighs and lower trunk (gluteofemoral, peripheral, gynoid, lower body or pear-shaped obesity) is considered less harmful or even protective against cardiometabolic complications [9].

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It must be noted that individuals of certain ethnic origins, regardless of the country of residence, are more predisposed to central obesity and more vulnerable to developing complications related to adiposity [10, 11]. Studies in South Asian, Japanese and Chinese populations have demonstrated significantly higher risk for insulin resistance, T2DM and CVD compared to matched overweight and obese Caucasians [12, 13]. Accordingly, rigorous cut-off points are being proposed for weight management among these populations, diagnosing obesity with BMI thresholds as low as 25 to 27.5 kg/m^2 and defining central obesity based on ethnicity specific cut-off values of waist circumference [13-15].

In any case, obesity must be recognized as a disease by the treating physician and appropriate weight loss treatments should be offered to obese patients, with or without related co-morbidities [16]. Weight management is crucial and should be promptly suggested even when these individuals are otherwise healthy (e.g. metabolically healthy obese patients) in order to prevent and/or delay the onset of complications. Interestingly, recent advances in treatments of cardiovascular risk factors and acute coronary syndromes are now offering improved cardio-protection options and appear to prolong life expectancy for obese patients. Indeed, current epidemiologic data support the notion that, in developed societies increasing numbers of these patients are expected to live more than previously predicted, despite failing to significantly reduce their excessive body weight [17, 18]. Thus, it becomes evident that, growing and progressively ageing obese populations in Western societies will inevitably continue to develop an increasing burden of obesity-related disease, including complications (e.g. chronic liver disease, respiratory or mobility problems) which were previously under-diagnosed or under-expressed due to earlier mortality (expansion of morbidity) [18, 19]. Subsequently, the economic impact of obesity on health care costs is profound, while the additional indirect costs (e.g. absence from work, reduced productivity and disability benefits) are also substantial. National surveys in the UK reported that, obesity is directly responsible for almost 7% of the overall morbidity and mortality, with a direct cost to the NHS that reaches up to four billion pounds per year, while these figures are still considered to be an underestimate. [20-22].

Obesity and type 2 diabetes mellitus

Diabetes mellitus represents a rather diverse group of metabolic disorders that are characterized by development of hyperglycemia (e.g. type 1 diabetes, type 2 diabetes, gestational diabetes, maturity onset diabetes of the young, drug-induced diabetes, diabetes secondary to pancreatic damage etc). Type 2 diabetes mellitus (T2DM) comprises up to 90% of all diagnosed diabetic cases and is typically associated with presence of various degrees of obesity. Depending on ethnicity, age and gender, 50-90% of T2DM patients exhibit a BMI over 25 kg/m^2, while patients with severe obesity (BMI > 35 kg/m^2) are almost 20 times more likely to develop T2DM than individuals with normal BMI (18.5-24.9 kg/m^2) [23]. Indeed, T2DM is steadily increasing both in developed and developing countries distinctively following the documented prevalence trends of obesity; hence, it is not surprising that, the term "*diabesity"* has been introduced to describe this twin epidemic [24, 25].

Large-scale population studies have shown that obesity constitutes the most important independent risk factor for insulin resistance and T2DM [26-29]. In adults, the relative risk for T2DM starts to increase even at BMI values within the normal weight range, 24 kg/m^2 for men and 22 kg/m^2 for women, while it rises exponentially with increasing BMI in the obese range (>30 kg/m^2) (Figure 3). Thus, morbid obesity is associated with markedly high relative risk for T2DM in both genders, up to 90 and 40 for women and men, respectively [27, 28]. Although visceral adiposity is more prominent in men, obesity appears associated with higher T2DM risk in women compared to men [30, 31]. Notably, impaired glucose homeostasis and T2DM have been linked to X-chromosomal loci [32], however the relative contribution of these loci to the onset of the disease is not fully clarified yet. In the pediatric population, T2DM constitutes a rather recent phenomenon and, even though type 1 diabetes accounts for most of the diabetic cases in young people, obese children and adolescents are now increasingly diagnosed with impaired glucose tolerance and T2DM [33, 34].

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Furthermore, a strong association is documented between central obesity and T2DM, beyond the impact of BMI [8, 35, 36]. Both insulin resistance and hyperinsulinemia correlate positively to visceral fat accumulation which is now regarded as an independent risk factor for T2DM and the hallmark of metabolic syndrome. Accordingly, anthropometric indices of central obesity (e.g. waist circumference and waist-to-height ratio) are utilized to better assess the risk for glucose intolerance and T2DM [37]. The higher cardiometabolic risk of central fat distribution is attributed to a combination of factors, relating mainly to a more deleterious biochemical profile of adipocytes in these fat depots. Visceral adipose tissue is more lipolytic (decreased insulin-mediated inhibition of the hormone-sensitive lipase and increased catecholamine-induced lipolysis) causing a greater flux of free fatty acids (FFA) into the portal circulation with lipotoxic effects, primarily in the liver and skeletal muscle [38, 39]. Additionally, adipocytes in visceral fat depots exhibit increased secretion of pro-inflammatory adipokines (e.g. tumor necrosis factor-α, intrerleukin-6) and decreased secretion of adiponectin, hence, leading to decreased insulin sensitivity and activation of inflammatory pathways in the adipose tissue, liver, and skeletal muscle [40, 41]. Hormonal changes either at the systemic level of various neuroendocrine axes (e.g. hypercortisolemia and dysregulation of the hypothalamic-pituitary-adrenal axis) or at the local level of the visceral adipose tissue (e.g. increased conversion of cortisone to cortisol via type 1 11β-hydroxysteroid dehydrogenase, 11β-HSD1, in fat depots) may also contribute to adverse metabolic consequences of central obesity [42-44].

Insulin resistance in obese patients stimulates insulin secretion and leads to chronic compensatory hyperinsulinemia which in turn may promote further weight gain. On the other hand, it is interesting that acute and short-term increases of circulating insulin levels can even reduce liver fat accumulation, at least in mice [45]. This concept may contribute to the documented beneficial effects of dietary protein and certain insoluble cereal fibers which induce a short term surge in insulin secretion [46, 47]. Indeed, both dietary protein and cereal fiber intake are associated with beneficial effects on body fat distribution in the long-term [48-51]. However, in chronic hyperinsulinemia a vicious cycle is formed, where fat accumulation causes generalized insulin resistance (insulin resistance in adipose tissue, liver and skeletal muscle) combined with increased insulin secretion and *vice versa*. Decreased insulin sensitivity in adipose tissue is crucial for initiating and fuelling this

vicious cycle [52]. Normally, insulin-mediated inhibition of the hormone-sensitive lipase in adipocytes decreases FFA release from fat depots, leading to lower FFA plasma concentrations, inhibition of hepatic glucose production and increased muscle glucose uptake. However, in T2DM uninhibited lipolysis in insulin-resistant adipocytes causes persistently increased circulating FFA levels which in turn lead to reduced peripheral glucose utilization, increased hepatic glucose production and decreased insulin sensitivity in the liver and skeletal muscle [53, 54]. Thus, adipocytes play a crucial role in the overall regulation of glycemia in T2DM, although the adipose tissue glucose uptake is less than 5% of the total glucose disposal [52].

In the liver insulin regulates the hepatic glucose production rate by activating enzymes which induce glycogenesis and suppressing enzymes involved in gluconeogenesis. Hepatic insulin resistance can be defined as the failure of insulin to adequately suppress hepatic glucose production and is associated with fasting hyperglycemia in T2DM [55]. It must be noted that, the lipogenic actions of insulin do not appear to be compromised in insulin-resistant states, as will be further discussed in the following section of this chapter about obesity and fatty liver. Under normal fasting conditions circulating levels of insulin are low and fasting hepatic glucose production matches the basal glucose utilization (equal gluconeogenesis and glycogenolysis rates). In T2DM, fasting glucose production in the liver is increased due to hepatic insulin resistance despite compensatory hyperinsulinemia [52]. Notably, the absolute amount of hepatic glucose production is moderately increased in T2DM patients compared to that in healthy controls, but is inadequately suppressed relative to the raised concentrations of glucose and insulin [56]. This increased fasting hepatic glucose production exhibits a linear correlation with the degree of fasting hyperglycemia and is caused primarily by accelerated glucose synthesis through the gluconeogenic pathway [57]. On the other hand, insulin resistance in skeletal muscle fuels postprandial hyperglycemia in T2DM, since skeletal muscles are responsible for most of the glucose disposal after meals. Decreased insulin sensitivity in skeletal muscles of T2DM patients causes impaired insulin-stimulated glucose uptake which is both reduced and delayed [58]. This postprandial under-utilization of glucose by skeletal muscles is superimposed on increased hepatic glucose production rates, thus, regulating the magnitude and duration of postprandial hyperglycemia.

Although necessary, insulin resistance alone is not sufficient for T2DM development, since the pancreas has the capacity to adapt by accordingly increasing both beta-cell mass and insulin secretion. Due to these compensatory mechanisms, normoglycemia can be maintained despite reduced insulin sensitivity in the periphery. Thus, inadequate insulin secretion is a crucial component of T2DM pathophysiology [52]. Obesity contributes to beta-cell decompensation and impaired insulin secretion through the related insulin resistant state and various glucotoxic and lipotoxic effects on the pancreas. Lipotoxicity can cause beta-cell dysfunction depending on the degree of FFA exposure and on the underlying genetic predisposition for T2DM. *In vitro*, prolonged exposure of beta-cells to high FFA concentrations increases FFA oxidation and causes accumulation of intracellular metabolites (e.g. citrate and ceramide) which impair glucose-stimulated insulin secretion and promote apoptosis [52, 59]. Clinical studies confirmed that, sustained high FFA plasma levels can impair insulin secretion in predisposed individuals (family history of T2DM) [60], while, on the contrary, pharmacological inhibition of lipolysis in non-diabetic individuals with strong family history of T2DM can improve insulin secretion [61]. Similarly, glucotoxicity can impair beta-cell function depending on the duration and degree of hyperglycemia. *In vitro*, prolonged beta-cell exposure to high glucose concentrations causes glucose desensitization, impairs insulin gene transcription and induces apoptosis. [52]. Clinical studies also reported that reduced beta-cell sensitivity to glucose plays a predominant role in patients with impaired glucose tolerance [62, 63].

It must be emphasized that the insulin resistant state in obesity and related acquired beta-cell defects can be, at least partially, restored with weight loss and tight glycemic control. Indeed, several studies have reported that even modest weight loss is important for T2DM prevention, significantly reducing the risk and delaying the onset of the disease [64-70].

Obesity-related inflammatory and procoagulant state: link to CVD and metabolic syndrome

Obesity as an inflammatory and procoagulant state

Following the recognition of adipocytes as endocrine cells, one focus of research was studying the association between obesity and the development of a chronic low-grade inflammatory state. An impressive body of recent data strongly indicates that weight gain promotes an unconventional, sub-clinical inflammation, mainly due to secretion of a battery of pro-inflammatory factors (e.g. leptin, TNF-α, IL-6, IL-1β) [71, 72]. The pro-inflammatory nature of adipose tissue is heightened in proportion to fat accumulation and exhibits consistent positive correlations with increasing BMI and especially with visceral adiposity [38, 71, 72]. Thus, central obesity appears to trigger and exacerbate an inflammatory cascade that initially evolves within fat depots, but eventually exerts systemic effects, since enhanced adipose tissue secretion of pro-inflammatory adipokines persists for as long as the excess abdominal fat mass is maintained. Indeed, current evidence suggests that this obesity-related activation of inflammatory signaling pathways is linked to major CVD risk factors (e.g. T2DM and atherosclerosis) [73, 74]. Obesity induces multiple constitutional alterations in the micro-environment and cellular content of adipose tissue depots which collectively promote differentiation of pre-adipocytes, insulin resistance and pro-inflammatory responses [71, 72]. A closer look at the underlying molecular interplay unveils a vicious cycle between pre-adipocytes, mature adipocytes and macrophages that reside in adipose tissue of obese patients (Figure 4). Weight gain enhances both lipogenesis and adipogenesis inside fat depots, as well as secretion of pro-inflammatory adipokines and chemokines (e.g. monocyte chemotactic protein-1, MCP-1, and IL-8) into the plasma. In response to such chemotactic stimuli mononuclear cells are recruited from the circulation and transmigrate into adipose tissue depots, increasing the number of resident macrophages [75, 76]. In turn, this growing local population of macrophages secretes cytokines, such as TNF-α, IL-1β and IL-6, which can potentially aggravate the pro-inflammatory and insulin resistant profile of adipocytes; although there is also a body of literature suggesting that IL-6 does not cause insulin resistance [72, 77, 78]. Thus, sustained fat accumulation establishes an unremitting local inflammatory response within the expanding adipose tissue. Progressively this cascade transcends to a chronic low-grade generalized inflammatory state in obesity, mediated by persistent release of pro-inflammatory adipokines of either

adipocyte or macrophage origin [71, 79], with adverse effects on peripheral tissues and organs (e.g. liver, muscles, endothelium). These effects promote hepatic and skeletal muscle insulin resistance, hypertension, atherosclerosis, hypercoagulability and enhanced secretion of acute-phase reactants (e.g. C-reactive protein, fibrinogen haptoglobin) [72, 80].

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The procoagulant state in obesity is further characterized by increased levels of fibrinogen and plasminogen activator inhibitor-1 (PAI-1) which both promote atherogenic processes and increase the risk of CVD [81-84]. Fibrinogen is synthesized by hepatocytes and holds a pivotal role in the coagulation cascade, being a major determinant of plasma viscosity and platelet aggregation. Expression of fibrinogen in the liver is up-regulated by IL-6 during the acute phase reaction and various studies have documented an association between elevated fibrinogen levels and increasing BMI [85]. Notably, fibrinogen has been also shown to predict weight gain in middle-aged adults [86]. PAI-1 regulates the endogenous fibrinolytic system and constitutes the main inhibitor of fibrinolysis by binding and inactivating the tissue plasminogen activator, thus increased PAI-1 activity leads to decreased clearance of clots. Elevated PAI-1 levels have been associated with increasing BMI and visceral adiposity, as well as with metabolic syndrome components [87-90]. Enhanced adipose tissue expression of PAI-1 has been reported in obesity, particularly in visceral adipose tissue, while an inverse relationship was also demonstrated between PAI-1 activity and adiponectin in overweight and obese women [89, 90].

It is interesting to note that a putative integration of adipocytes into the innate immune system, has been suggested, thus linking metabolic and inflammatory signaling pathways. Apart from their documented reciprocal interactions inside adipose tissue depots, particular interest is also focused on inherent similarities between adipocytes and macrophages which are more apparent in obesity [72, 91, 92]. Although these cells clearly belong to distinct lines, they have a common ancestral origin from the mesoderm during early embryogenesis. Mature adipocytes differentiate from pluripotent mesenchymal stem cells that, under certain conditions, become committed to the adipocyte lineage and produce pre-

adipocytes. Notably, pre-adipocytes are reported to have the ability to differentiate into macrophages and to function as macrophage-like cells, developing phagocytic activity against microorganisms [93, 94]. Furthermore, analysis of the adipocyte gene expression profile in obesity revealed striking resemblances to that of macrophages, with adipocytes expressing specific cytokine genes (e.g. IL-6, TNF-α) which were typically associated to macrophages [95, 96]. Finally, both pre-adipocytes and adipocytes express Toll-like receptors (TLRs) which are cardinal regulators of innate and adaptive immune responses and, interestingly, have been proven to undergo direct activation by fatty acids [97]. This advocates a suspected role of the adipose tissue as an immune organ, with potential implications for treatment of obesity-related complications. Identifying common initial inflammatory mechanisms could lead to therapeutic interventions that may inhibit at an early stage the adipose-initiated inflammatory cascade, and, thus, prevent clinical complications (e.g. modulation of IκB kinase, IKKβ, and nuclear factor-κB, NF-κB, activity, which are pivotal signaling mediators that trigger intracellular inflammatory pathways).

All the aforementioned findings support the notion that obesity-related pro-inflammatory pathways mediate deleterious cardiometabolic effects which can lead to clinical manifestations of the metabolic syndrome.

Metabolic syndrome: Definitions and quest for a single set of diagnostic criteria.

Over two decades ago, Reaven proposed the term "Syndrome X" to describe a constellation of diseases, including obesity, T2DM, dyslipidemia and hypertension which exhibit a marked tendency to cluster together, revolving around insulin resistance [98]. All these metabolic disorders are established independent risk factors for cardiovascular complications and, indeed, their coexistence correlates with high CVD morbidity and mortality, an association that also aptly led to the description of the syndrome as the "deadly quartet" [99]. Since then, the term "Metabolic Syndrome" has been adopted to better illustrate this clustering of cardiometabolic risk factors, opening new vistas for the study of their interrelationships [100]. Data regarding the prevalence of the syndrome, based on large US, European and Australian cohorts, suggest that it affects over a quarter of the adult population in Western societies, conferring a five-fold increase in T2DM risk and twice greater relative risk for

CVD [101, 102]. Several prominent medical bodies, such as the World Health Organization (WHO), the European Group for the Study of Insulin Resistance (EGIR), and the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) have proposed different metabolic syndrome definitions in order to help identify individuals at high risk for T2DM and CVD in clinical practice (Figure 5) [103-105]. These definitions applied diagnostic criteria that varied significantly, limiting comparability between studies and creating some confusion regarding their use by clinicians. In order to address the need for widely accepted criteria that could be easily applied in different ethnic populations, in 2005 the International Diabetes Federation (IDF) issued a consensus statement introducing a worldwide metabolic syndrome definition based on assessment of simple anthropometric and plasma measurements (waist circumference, blood pressure and plasma levels of triglycerides, high-density lipoprotein cholesterol and fasting glucose) (Figure 5). [106]. According to this consensus, central obesity becomes the hallmark of the metabolic syndrome and is a prerequisite for its diagnosis. To ensure applicability in various ethnic groups, central obesity diagnosis in the IDF definition relies on waist circumference measurements that put into practice a set of ethnic-specific cut-off values. Thus, an approach was adopted to take into account the fact that individuals of specific ethnic origin (e.g. South Asians), regardless of their country of residence, are more predisposed to central obesity and more susceptible to complications of visceral adiposity [10-15]. Overall, the IDF consensus represents a targeted effort to offer a metabolic syndrome definition set on criteria that are friendly to routine clinical practice and could be uniformly applied in different settings and patient groups. Moreover, the adopted rationale proceeds to embody a growing body of evidence which highlights the crucial role of central obesity in metabolic syndrome pathophysiology.

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Notably, the published IDF consensus statement included a recommended “Platinum standard” list of additional criteria to be included in epidemiological and other research studies regarding the metabolic syndrome [106, 107]. Assessment of multiple metabolic parameters was proposed, including markers of adipocyte function (leptin, adiponectin), inflammatory markers (C-reactive protein, TNF-α, IL-6),

and coagulation markers (PAI-1, fibrinogen), together with evaluation of fat distribution (visceral adiposity, liver fat), and precise measurements of insulin resistance, endothelial dysfunction, atherogenic dyslipidemia and urinary albumin. Research into metabolic syndrome pathogenesis incorporating these complementary variables is expected to advance our understanding of underlying pathogenetic pathways and help identify even more precise criteria for the clinical diagnostic process.

It must be mentioned that, the waist circumference values in the IDF definition were proposed as initial guidelines, based on available evidence, and, thus, were accepted as neither complete nor definite [13, 106]. Further epidemiological studies are expected to continue to offer additional data which will supplement existing knowledge and help in recommending more accurate cut-off points for various populations (e.g. Sub-Saharan Africans, South and Central Americans, Asian, Eastern Mediterranean and Middle East populations). Indeed, recent studies have suggested cut-off points of over 85 to 90 cm for men and over 80 cm for women in Japan [108, 109]. In China threshold values of over 85 cm and over 80 cm have been proposed in men and women, respectively, while slightly lower values have been suggested in India [110]. Recently, another attempt was made to resolve the remaining differences between metabolic syndrome definitions which resulted into a joint interim statement from the IDF and the American Heart Association/National Heart, Lung, and Blood Institute [15]. In order to harmonize the criteria for metabolic syndrome diagnosis, this statement accepted the previous five criteria of the IDF and ATP-III definitions and agreed that central obesity should not be a prerequisite for diagnosis which instead should be confirmed by the presence of any 3 of the 5 accepted risk factors (Figure 6). In this joint definition central obesity diagnosis is based on population- and country-specific thresholds of waist circumference with a recommendation that the IDF cut-off points should be used for non-Europeans, while either the IDF or the AHA/NHLBI cut-off points can be used for people of European origin until more data are available (Figure 6).

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To date, the IDF metabolic syndrome definition has contributed in setting widely accepted diagnostic criteria and emphasizing the significance of central adiposity, while it can be regarded as an

additional tool in forming and evaluating strategies for diagnosis and treatment [102, 106, 111]. However, there is still ongoing debate and controversy as to whether it adds more value in clinical decision making compared to its individual components and by many it is considered useful mainly as an educational concept [112-119]. Thus, it is important to stress that, in parallel to the risk conferred by a metabolic syndrome diagnosis, additional risk factors, such as age, gender, smoking and low-density lipoprotein cholesterol plasma levels, substantially increase the risk of T2DM and CVD and must be also assessed in clinical practice, as will be further reviewed in the following chapter regarding the metabolic syndrome (chapter 23).

Obesity and non-alcoholic fatty liver disease

The liver is the largest solid organ in adults constituting 2-3% of the body weight and accounting for 25-30% of the total oxygen consumption. Normal hepatic function is essential for preserving metabolic homeostasis and a dynamic crosstalk exists between the liver and adipose tissue in order to regulate carbohydrate, lipid and protein metabolism. Obesity may cause hyperinsulinemia, hyperglycemia and ectopic fat accumulation in the liver which, in turn, can impair hepatic function and lead to a spectrum of abnormalities, ranging from steatosis and elevation of circulating liver enzyme levels to cirrhosis, liver failure and even liver cancer [120-123]. The term non-alcoholic fatty liver disease (NAFLD) is now applied to describe this spectrum of hepatic abnormalities.

The relationship between obesity and liver dysfunction has been noted in the literature since the first half of the past century [124]. Yet, it wasn't until 1980 that the term non-alcoholic steatohepatitis (NASH) was introduced by Ludwig *et al.* to describe findings in 20 patients at the Mayo clinic exhibiting a non-alcohol related liver disease which was histologically similar to alcoholic hepatitis [125]. Hepatocellular steatosis is the hallmark of the disease, defined as a triglyceride content higher than 5-10% of the total liver weight, although the minimum fat content which should be considered pathologic and uniform criteria for its assessment are still debated [126, 127]. This steatosis reflects ectopic fat deposition in the liver, usually starting from the less oxygenated zone of the acinus (zone 3), and is more frequently macrovesicular (one large intracellular fat droplet displacing the nucleus). Microvesicular steatosis may also occur (numerous small intracytoplasmic fat vesicles not displacing the nucleus) and is often underestimated due to limitations of routinely applied staining techniques [128, 129].

NAFLD pathology extends from steatosis to steatohepatitis and fibrosis. Matteoni *et al.* have proposed a histologic classification of NAFLD into four distinct types (Figure 7A) [130]. NASH corresponds to types 3 and 4 of this classification, representing the most severe histologic form of NAFLD. In addition to steatosis, NASH is characterized by various degrees of inflammation, hepatocyte injury and fibrosis which may gradually lead to cirrhosis [131]. It must be noted that, the exact histologic criteria for diagnosing and staging NASH are debated among pathologists and distinction between NASH and alcoholic hepatitis may not be possible at the histological level.

Accordingly, a detailed alcohol consumption history is crucial for differential diagnosis, while various scoring systems for grading and staging of NAFLD have been developed to consistently assess the disease and compare outcomes of therapeutic interventions, such as the proposed NAFLD activity score (NAS) which, however, requires repeated liver biopsies (Figure 7B) [132, 133].

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NAFLD is now recognized as one of the most common causes of chronic liver disease, exhibiting rising prevalence and worldwide distribution which follows the global trends of obesity and T2DM [134, 135]. Data on NAFLD prevalence in the general population vary depending on applied diagnostic criteria, while large-scale population studies are hindered by the fact that the disease can remain asymptomatic for years, may coincide with other chronic liver diseases and requires a liver biopsy for definite diagnosis [136]. Based on current evidence, the estimated overall NAFLD prevalence in several Western countries is approximately 20-30% [137-142], with a corresponding NASH prevalence of 2-3% [143, 144]. Particularly significant are reported data for obese and T2DM cohorts which consistently document a very high incidence of NAFLD, thus, suggesting strong pathogenetic links. Indeed, up to 75% of obese and T2DM patients appear to develop steatosis, while NASH can be diagnosed in 10-20% of these cases [144, 145]. Notably, even higher NAFLD incidence (90-95%) is documented among patients with morbid obesity and manifestations of the metabolic syndrome [145, 146]. NAFLD also exhibits increasing prevalence among the pediatric population (general prevalence of 2.6-10%) in close association with childhood obesity, since up to 80% of obese children are reported to present the disease [147].

Gender differences appear to exist, thus, NAFLD is considered more common in males, although initial data suggested female predominance, peaking during the fourth decade in men and postmenopausally in women (after the fifth decade) [134]. Furthermore, family clustering and significant ethnic variations have been documented, supporting the role of genetic predisposition [141, 148]. Indeed, NAFLD prevalence in India is estimated at 20-30%, despite lower reported obesity rates compared to Western societies [149]. Conversely, African Americans exhibit NAFLD less often than

expected based on their respective incidence of obesity and T2DM; while Hispanic and Asian populations overall tend to be more susceptible to steatosis and NASH [150, 151]. Notably, these ethnicity-related variations coincide with higher predisposition of specific ethnic groups for developing central obesity, insulin resistance and metabolic syndrome complications [10-15].

To date, a limited number of studies have described the natural history of NAFLD. However, it is now clear that NAFLD may lead to severe liver complications (Figure 7). The underlying histologic stage dictates NAFLD prognosis which appears to rely crucially on the presence of fibrosis [152]. It is generally accepted that absence of inflammation and fibrosis is associated with a stable and benign long-term course in approximately 95% of the cases [153]. On the other hand, NASH exhibits an increased risk for developing cirrhosis, liver failure and even hepatocellular carcinoma (HCC), with 3-15% of NASH cases progressing to cirrhosis over 10-20 years [154, 155]. The prognosis is poor once NASH-related cirrhosis is established and 30-40% of these cases will require liver transplantation. Furthermore, HCC appears to develop at an annual rate of 2-5% in NASH patients with cirrhosis (Figure 7) [156, 157]. Indeed, long-term follow-up of patients with biopsy-proven NAFLD (129 patients followed for 13.7 years) has shown that NASH patients had significantly reduced survival due to liver-related and cardiovascular causes [158]. Overall, the age and gender adjusted mortality rate in patients with NAFLD is significantly higher compared to the general population (both for overall and liver-related mortality) [152, 159]. NAFLD severity increases with age, however regression is also possible if effective weight management is applied before the stage of cirrhosis, thus, highlighting the need for prompt and aggressive weight loss treatment. Notably, signs of regression can be misleading since progressing fibrosis may be silent or even associated with normalization of circulating aminotransferases levels and improvement of steatosis and inflammation features particularly in older patients. This often reflects a transition of NASH to cryptogenic cirrhosis which is associated with high HCC risk [160].

NAFLD pathogenesis is strongly linked to obesity and obesity-related insulin resistance [120-123]. Fat accumulation in adipose tissue depots is typically followed by ectopic fat deposition in the liver and skeletal muscle and by insulin resistance in these tissues. Although hepatic insulin resistance can develop independently as a result of increased hepatocyte triglyceride content, current evidence

indicates that this usually follows insulin resistance in adipose tissue. It is now evident that, obesity-related insulin resistance can cause fatty liver, while, *vice versa*; excessive intrahepatic fat accumulation may promote insulin resistance and weight gain [55]. Notably, the lipogenic actions of insulin appear to remain uncompromised in insulin-resistant states, thus, *de novo* fatty acid synthesis is undeterred even in the presence of marked insulin resistance (e.g. hepatic transcription of the gene encoding SREBP-1c remains stimulated by both insulin and glucose, Figure 8). Day *et al.* have proposed a two stage hypothesis to describe the pathogenetic mechanisms leading from obesity to NAFLD ("two-hit" model), with development of steatosis at the initial stage (first "hit") and subsequent progression to hepatic injury, inflammation and fibrosis (second "hit") (Figure 9) [161-163]. Insulin resistance directly facilitates the first "hit" through decreased inhibition of lipolysis in adipocytes as well as decreased inhibition of gluconeogenesis and increased lipogenesis in the liver. Thus, steatosis appears primarily caused by an overall enhanced hepatic influx of circulating FFA which are released by insulin resistant adipocytes. It is important to highlight that, in central obesity visceral fat depots exhibit a higher lipolysis turnover creating an amplified direct supply of FFA to the liver via the portal vein which can account for 20-30% of the total hepatic FFA influx [164].

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Notably, there is also evidence that hepatic accumulation of previously stored body fat and saturated dietary fat may induce hepatic insulin resistance, whereas newly produced fat by the liver and mono- and poly-unsaturated dietary fat is likely to have less deleterious effects, thus suggesting compartmentalisation of fatty acid metabolism in hepatocytes [165]. In the context of hepatic insulin resistance, hyperinsulinemia and hyperglycemia can further increase the intrahepatic triglyceride content due to stimulated *de novo* lipogenesis (DNL), impaired hepatic fatty acid oxidation and decreased VLDL efflux, while dietary fatty acids also contribute to steatosis (Figure 10) [166, 167]. Indeed, it has been shown that of the triacylglycerol accounted for in the liver of NAFLD patients approximately 60% arose from serum FFA, while 26% from DNL and 15% from the diet [167]. A positive correlation is reported between the degree of insulin resistance and steatosis which is

considered to subsequently enhance the liver susceptibility to the second "hit" [163]. This second "hit" causes progression from steatosis to NASH and cirrhosis by inducing hepatocyte injury and formation of fibrotic tissue (Figure 9). Current evidence suggests that this process reflects a diffusion of detrimental effects from adipose tissue depots to the hepatic level [133, 168, 169]. Thus, NASH is regarded to result from a cascade inside the steatotic liver which involves escalating hepatic insulin resistance and lipid peroxidation, in combination with local pro-inflammatory, oxidative stress and endoplasmic reticulum stress responses [163, 164]. In obesity-related insulin resistance these pathways are triggered and continuously fuelled by hyperleptinemia, hypoadiponectinemia and increased circulating concentrations of adipose-derived cytokines, primarily TNF-α and IL-6. Intermittent exposure of the steatotic liver to this adverse adipokine profile increases hepatic insulin resistance and leads to mitochondrial dysfunction, inflammation, cell injury, apoptosis and fibrosis [162, 170, 171]. Hepatocytes are further stimulated to locally secrete pro-inflammatory cytokines and factors (e.g. TNF-α, IL-6, IL-1β). Furthermore, Kupffer and hepatic stellate cells are potently activated, while circulating inflammatory cells are also chemo-attracted and infiltrate the liver [172, 173]. The final outcome of these processes is a chronic and progressive pro-inflammatory state inside the liver which bears striking resemblance to the low-grade inflammation within adipose tissue depots in obesity.

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Research for specific therapeutic interventions regarding NAFLD and NASH is now focused on identifying critical steps of the aforementioned pathogenetic links which could be modulated in order to either prevent steatosis or stop/delay progression to steatohepatitis (e.g. targeting the peroxisome proliferator-activated receptor-γ pathway, oxidative stress responses or the pro-inflammatory IKKβ/NF-κB pathway). It is important to mention that most of the existing evidence on NAFDL pathogenesis is derived from *in vitro* experiments and animal models and results cannot be necessarily extrapolated to other species, including humans. Yet, novel data indicate that at least some of the proposed molecular pathways are indeed relevant to the disease pathophysiology in humans [174]. To date, weight loss remains the only established treatment for NAFDL. Early and aggressive

weight management interventions should be offered to these patients, as well as appropriate treatment for coexisting metabolic syndrome manifestations (e.g. for T2DM, dyslipidemia and hypertension) in order not only to improve the underlying liver pathology, but to further address the associated high CVD morbidity and mortality [168, 169]. Notably, the role of insulin-sensitizing agents in NAFLD treatment appears promising even in non-diabetic patients [175, 176]. Although not consistently, metformin is shown to reduce steatosis, liver inflammation and hepatocellular injury [177-179], and trials with pioglitazone and rosiglitazone have also produced favorable results [180-182]. However, further long-term studies are required to establish their efficacy in NAFLD and NASH, while especially for glitazones their safety profile should be additionally established for these patients due to the associated risk of weight gain, osteoporosis and heart failure [183-190].

Obesity and gallbladder disease

Gallbladder disease is a common gastrointestinal disorder in Western countries with cholelithiasis being the most frequent hepatobiliary pathology, primarily with gallstones composed of cholesterol. It is estimated that in the US alone more than 700,000 cholecystectomies are performed per year with annual costs of approximately 6.5 billion dollars [191]. Female gender, increasing age, and family history are typical risk factors for gallstones, while the main modifiable risk factors include obesity, metabolic syndrome and high caloric intake [191-193]. Overall, cholelithiasis is strongly associated with overweight and obesity and a classic medical textbook mnemonic for gallstone risk factors is known as the "4 Fs" ("fat, female, fertile, and forty") [23, 193-198]. The relative risk of gallstone formation appears to rise as body weight increases exhibiting a positive correlation with increasing BMI which is more pronounced when BMI exceeds 30 kg/m^2 [23, 194-196]. In the Nurses' Health Study, women with BMI over 30 kg/m^2 had twice the risk of gallstones compared to non-obese women, while a seven-fold excess risk was noted in women with a BMI over 45 kg/m^2 compared to those with BMI less than 24 kg/m^2 [195]. It is interesting that obesity and female gender remain risk factors for gallstone disease even in children and adolescents [199]. Higher prevalence of cholelithiasis with increasing BMI is also reported in men, however this association appears less potent and is regarded to depend more on abdominal fat accumulation than on body weight alone [194, 200, 201]. Indeed, large prospective studies among US adults of both genders indicate that measures of central obesity, such as waist circumference and waist-to-hip ratio, can predict the risk of gallstones and cholecystectomy independent of BMI [202, 203]. In addition to higher prevalence of cholesterol gallstones, a recent study on gallbladder pathology in morbidly obese individuals has further documented significantly increased prevalence of cholecystitis and cholesterolosis [204]. Notably, current evidence suggests that obesity is associated with inflammation and fatty infiltration of the gallbladder, described as cholecystosteatosis, which results in abnormal wall structure and decreased contractility [205]. This bears resemblance to steatohepatitis and it has been reported that NASH prevalence in patients with morbid obesity and gallbladder disease can reach 18%, with insulin resistance being more common in concurrent NASH and gallbladder disease [206]. Finally, it is worth

mentioning that obesity increases the risk of hospital admission and prolongs the length of hospital stay for gallbladder disease [207].

Several mechanisms have been proposed to explain the association between excess body weight and formation of cholesterol gallstones, focusing primarily on secretion of supersaturated bile and gallbladder stasis [208-212]. Obesity is characterized by a high daily cholesterol turnover which is proportional to the total body fat mass and can result in elevated biliary cholesterol secretion. This leads to supersaturation of the bile which becomes more lithogenic with high cholesterol concentrations relative to bile acids and phospholipids. Notably, in obese patients the bile also remains supersaturated for much longer periods of time and not only during the fasting state. Furthermore, obesity is associated with gallbladder hypo-motility and stasis which predispose to gallstones formation. Increased fasting and residual volumes, as well as decreased fractional emptying of the gallbladder have been reported in obese patients [213-216]. Interestingly, hyperinsulinemia may cause both increased cholesterol supersaturation and gallbladder dysmotility [217-220].

Rapid weight loss in obese patients is additionally associated with increased risk of gallstone formation [221-226]. This is particularly significant following weight loss through surgical interventions and it is suggested that every morbidly obese patient undergoing bariatric surgery should be considered at high risk for developing gallstone disease independently of other risk factors [224-226]. Indeed, a recent retrospective study regarding predictors of gallstone formation after bariatric surgery reported that weight loss exceeding 25% of the initial body weight was the only post-operative factor that helped in selecting patients for postoperative ultrasound surveillance and subsequent cholecystectomy once gallstones were identified [226]. Notably, weight cycling is also shown to increase the risk of cholecystectomy, independent of BMI [227]. Increased bile lithogenicity during weight loss is potentially attributed to an enhanced flux of cholesterol through the biliary system, while low intake of dietary fat may further impair gallbladder motility and cause stasis [221-223]. Thus, diets with moderate levels of fat may reduce cholelithiasis risk by triggering gallbladder contractions and maintaining an adequate gallbladder emptying [222]. Use of ursodeoxycholic acid can also prevent gallstone formation after bariatric surgery [228]. Finally, several studies have

advocated concomitant prophylactic cholecystectomy with bariatric procedures in order to prevent post-operative gallstone formation [229, 230].

Gallstones are the major risk factor for biliary tract cancers and particularly for gallbladder cancer; however gallbladder cancer is rare in Europe and North America reflecting the widespread and earlier adoption of cholecystectomy (high-risk areas remain mainly in South America and India where access to gall-bladder surgery is still inadequate) [231, 232]. Subsequently, studies on the relationship between obesity and gallbladder cancer are limited. Although restricted, available data are consistent in indicating that obesity is indeed associated with an increased risk of gallbladder cancer, attributed to higher risk of cholelithiasis and chronic inflammation [232]. A recent a meta-analysis that included eleven studies (three case-control and eight cohort studies with a total of 3288 cases) confirmed that excess body weight could be considered a risk factor for gallbladder cancer based on existing evidence [233]. The summary relative risk of gallbladder cancer for overweight and obese individuals was 1.15 (95% CI, 1.01-1.30) and 1.66 (95% CI, 1.47-1.88), respectively, compared to normal weight persons. Notably, the documented association with obesity was stronger for women (relative risk of 1.88; 95% CI, 1.66-2.13) than for men (1.35; 95% CI, 1.09-1.68).

Obesity and reproduction

Obesity can cause hypothalamic-pituitary-gonadal (HPG) axis dysfunction in both genders. Reproductive disorders are more frequent in obese women, presenting with a wide range of manifestations that extend from menstrual abnormalities to infertility, while obese men can exhibit decreased libido, sub-fertility and more rarely hypogonadism [234]. Despite recent progress in our understanding regarding the role of adipose tissue in multiple neuro-endocrine networks, the exact pathogenetic mechanisms linking excess fat accumulation to HPG dysfunction remain unclear. Current research is focused on interactions between adipokines and the HPG axis, highlighting leptin as a pleiotropic modulator of energy homeostasis and reproduction [235-237]. Furthermore, increased metabolism of sex steroids within adipose tissue depots can lead to abnormal plasma levels of androgens and estrogens, thus, potentially affecting the reproductive axis in obesity [238-240]. Sex hormone binding globulin (SHBG) also plays a crucial role in obesity-related dysfunction by regulating the bio-availability of sex steroids. Obese patients exhibit decreased circulating SHBG levels and thus higher bio-available sex-steroid levels and increased sex-steroid clearance. This appears related to direct suppression of SHBG synthesis in the liver by insulin which is more pronounced in central obesity due to related insulin resistance and hyperinsulinemia [239-241]. Finally, it must be noted that, a strong psychological component is also present, with clear reciprocal relationships between obesity and psychological comorbidities, especially anxiety and depression, which can significantly contribute to male and female sexual dysfunction manifested as decreased sexual desire, lack of sexual activity enjoyment, difficulties in sexual performance and avoidance of sexual encounters [242, 243].

Female reproductive system and obesity

In 1952, Rogers *et al.* first published a study documenting the relation of obesity to menstrual abnormalities [244]. Since then it has become evident that, in females a close link exists between body weight and reproductive health from menarche to menopause and beyond (Figure 11). From an evolutionary perspective, menarche marks the beginning of reproductive potential which requires sufficient energy stores to facilitate pregnancy and lactation. Thus, it is not surprising that the onset of

menstruation is considered related to the presence of a critical body fat mass [245, 246]. Recent epidemiological studies documented a clear correlation between obesity and earlier puberty onset in obese girls [247-250]. Indeed, in Western societies the age of pubertal maturation appears to be decreasing among girls in relation to increased prevalence rates of childhood and adolescent obesity [251, 252]. However, this is often linked to decreased reproductive performance later in life and current evidence suggests that weight gain can also lead to earlier ovarian failure and menopause [253, 254].

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Menstrual disturbances are the most common manifestation of HPG dysfunction in obese women, extending from dysmenorrhea and dysfunctional uterine bleeding to amenorrhea [255, 256]. The degree of clinical manifestations is reported to have a strong correlation with BMI and, furthermore, appears related to fat distribution since central obesity commonly leads to more severe symptoms [234, 255-257]. Abnormal menstrual patterns in obese women are primarily attributed to altered androgen, estrogen and progesterone levels (Figure 11), and, indeed, weight loss can restore regular menstrual cycles by decreasing androgen aromatization to estrogens in adipose tissue depots. Obese women with polycystic ovary syndrome (PCOS) constitute a distinct category characterized by (1) polycystic ovaries; (2) oligo- or anovulation; and (3) clinical and/or biochemical signs of hyperandrogenism (2 out of 3 according to the Rotterdam consensus diagnostic criteria for PCOS - PCOS will be reviewed in detail in the relevant chapter in Endotext-Female Reproductive Endocrinology) [258]. Notably, obese PCOS women exhibit higher risk of menstrual abnormalities compared to BMI matched women without PCOS attributed to worse endocrine and metabolic profiles, involving various degrees of hyperinsulinemia and insulin resistance in combination with hyperandrogenism [259].

Female obesity is additionally associated with decreased fertility due to chronic anovulation [234, 255, 256]. Indeed, several studies have reported higher risk of anovulatory infertility with increasing BMI [260-264]. Central fat distribution is considered to play a crucial role in this

association through hyperinsulinemic hyperandrogenemia that disrupts ovulation, as also documented in PCOS [255, 256, 265]. Interestingly, prehistoric statuettes which are presumed to be fertility idols, including the famous "Venus of Willendorf", depict rather obese women, yet characterized by pronounced buttocks and thighs [266, 267]. Furthermore, obesity can also decrease the success rate of assisted conception methods such as *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) [268-271]. Although additional data are still required, obese women appear to require higher doses of ovarian stimulation drugs and have increased risk of cycle cancellation and fewer oocytes collected, as well as lower pregnancy and live birth rates compared to normal-weight women [255, 256, 271-275]. Thus, weight loss, even modest, is advised for obese women seeking fertility treatment in order to increase the chances of a favorable outcome [276]. Overall, pregnant obese women can be classified as having a high risk pregnancy associated to increased rates of miscarriage, in addition to a spectrum of both maternal (e.g. gestational diabetes, hypertension and pre-eclampsia, urinary tract infections, thromboembolism, increased incidence of operative delivery, anesthetic risks and postpartum hemorrhage) and fetal (e.g. macrosomia, neural-tube defects and stillbirth) risks [277, 278].

Finally, it must be noted that, obesity is a risk factor for endometrial, postmenopausal breast and ovarian cancer, although the data for the later are relatively limited [279, 280]. A higher risk for these hormone-sensitive gynecologic malignancies in obese women is attributed to elevated endogenous estrogen levels that persist even after menopause (adipose tissue consists the major source of postmenopausal estrogen production from androgens), while hyperinsulinemia appears to also independently contribute to carcinogenesis, as will be reviewed in the following section of this chapter about obesity and cancer [281, 282].

Male reproductive system and obesity

Men appear to exhibit clinical manifestations of obesity-related HPG axis dysfunction less frequently compared to obese women. However, research has been focused mainly on the impact of obesity on female reproductive health, thus, underestimating adverse effects on male reproduction. In recent years, following the increasing availability of assisted conception methods, a growing body of

evidence indicates that obesity can also impair male reproductive functions leading to decreased libido, sub-fertility and even infertility (Figure 12) [234, 239, 253].

FOR PEER REVIEW PLEASE SEE FIGURE 12

Data regarding secular trends of pubertal maturation in boys and possible relationships to obesity are less clear and partly conflicting [247, 249, 251, 252]. Indeed, various studies have reported that increasing BMI and adiposity can be associated with either earlier or later pubertal onset in boys, while lack of correlation has also been reported [247, 283-286]. Furthermore, assessing male puberty can be more subjective and unreliable due to lack of a landmark pubertal event such as menarche in girls. Thus, current evidence regarding the impact of childhood obesity on male sexual maturation is inconclusive and further data are required to clarify such potential associations.

Impaired male fertility is also associated with increasing BMI, especially in men with morbid obesity when BMI exceeds 40 kg/m^2 [234, 287-289]. Semen quality can be significantly affected and it is reported that both overweight and obese men exhibit markedly higher incidence of oligozoospermia and asthenospermia compared to normal-weight men [290-293]. This is primarily attributed to decreased circulating testosterone levels due to higher aromatization of androgens to estrogens in adipose tissue depots, while SHBG levels can also be reduced (Figure 12) [239-241, 253, 294]. In addition to hormonal changes, obese men are predisposed to elevated scrotal temperature, since the scrotum remains in close contact with surrounding tissues, which can potentially increase the risk of altered semen parameters and infertility [295]. Finally, morbid and longstanding obesity is often associated with comorbidities such as diabetes and macrovascular disease that increase the risk of sexual dysfunction in men and can lead to sub-fertility.

Evidence on the precise association between obesity and prostate cancer is inconsistent [296, 297]. Current data from large prospective studies indicate that obesity increases the risk of aggressive (high-grade) disease, while on the contrary is inversely associated with indolent (low-grade) tumors [298-300]. However, epidemiologic data on prostate cancer incidence should be interpreted with caution since obese men tend to exhibit larger sized prostates and lower prostate-specific antigen

(PSA) levels, parameters affecting the sensitivity and specificity of both PSA screening and prostate needle biopsy in this population [297, 301]. More consistently obesity has been associated with a higher risk of prostate cancer-specific mortality [296, 297, 302]. The underlying pathophysiologic mechanisms for these associations are considered multifactorial, including effects of decreased androgen levels, increased circulating adipokines, hyperinsulinemia and the low-grade chronic inflammation state in obesity [297, 303].

Obesity, stress and psychiatric co-morbidities

A growing body of evidence indicates that depression and other common psychological disorders constitute independent risk factors for developing obesity and metabolic syndrome manifestations [304, 305]. Prospective data from the Whitehall II cohort documented that common mental disorders increase the risk of obesity in a dose-dependant manner (more episodes of the disorder correlated with higher future obesity risk) [306]. Notably, the odds of obesity in the presence of mental disorders tend to increase with age [307]. Indeed, in a large community-based cohort of elderly persons, followed for 5 years, baseline depression was associated with increased abdominal fat accumulation, independent of overall obesity, suggesting pathogenetic links between depression and central obesity [308]. Furthermore, recent studies additionally report that prolonged and/or intense stress can lead to subsequent weight gain. In the Hoorn Study, enhanced visceral adiposity and higher probability of previously undiagnosed T2DM were associated to the number of major stressful life events during a 5-year preceding period [309]. Chronic work-related stress has also been identified as an independent predictive factor for general and central obesity during midlife [310, 311]. Interestingly, weight gain in female UK students during their first year at university was related to higher levels of perceived stress [312].

On the other hand, epidemiologic data further support positive correlations between obesity and both depression and anxiety disorders risk [313, 314]. These associations appear primarily concentrated among individuals with severe obesity and among obese females [315-319]. To date, the level of existing evidence is considered weak or moderate, since gender differences and multiple obesity-depression covariations are probable, while only a few high-quality prospective studies have been published [320-323]. However, the “jolly fat” hypothesis, associating obesity with decreased depression risk, should be, at least partially, revisited [324-327]. Notably, a U-shaped quadratic relationship between BMI and depression can be proposed [328]. In accord with available epidemiologic data, there is now an increasing number of prospective, controlled studies reporting remission of depressive symptoms and improved psychological functioning following weight loss through bariatric procedures [329-334]. Thus, reversibility is indeed noted regarding adverse effects of obesity on mental health. Conversely, it must be also stressed that, depressive and anxiety disorders

are shown to have strong predictive value for weight loss in obese patients even when surgical interventions are applied [335].

Overall, obesity can be considered to hold a bi-directional association with psychological well-being, especially with chronic stress and mood disorders [304]. This reciprocal relationship is complex and conclusions for causal effects cannot be drawn based on existing evidence. However, several mechanisms have been proposed to explain links between obesity and mental health in both directions, mainly focusing on over-activation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS), as well as on the role of health risk behaviors (Figure 13) [336-339].

FOR PEER REVIEW PLEASE SEE FIGURE 13

Obesity, particularly central, induces an unremitting low-grade inflammatory state, characterized by constantly high plasma levels of pro-inflammatory adipokines [71]. This adverse adipokine profile (decreased adiponectin and increased TNF-α, IL-6, and leptin levels) can act as a persistent stress stimulus, leading to chronic hypercortisolemia and SNS activation which predispose to depression and anxiety [43]. Conversely, chronic stress and depression, associated with mild hypercortisolemia and increased sympathoadrenal activity, favor visceral fat accumulation and progressive obesity (e.g. favoring enhanced appetite, insulin resistance and increased adipogenesis) [340-343]. It is interesting to note that, sleep disorders, such as chronic insomnia, inadequate sleep or poor sleep quality, are also shown to exhibit associations with dysregulated energy balance, obesity and T2DM, mediated through SNS activation and changes in adipokines (e.g. leptin, TNF-α and IL-6) and gut hormones (e.g. ghrelin) [344, 345]. Thus, a deleterious vicious cycle appears to be formed, where weight gain causes prolonged stress system activation (manifested with depression, anxiety and even sleep disorders) and *vice versa*, mediated through hormonal and adipokine effects on multiple endocrine axes and the central nervous system [336, 341, 342]. Furthermore, obesity is associated with sedentary lifestyle and socioeconomic disadvantage which increase the risk of depression [346]. In turn, over-nutrition, comfort eating, alcohol abuse and low physical activity are common features of depressive and anxiety

disorders promoting the development of obesity. Notably, even though obesity constitutes a chronic disease, obese individuals often additionally experience obesity-related stigma and discrimination that further contribute to clinical manifestations of depression and low self-esteem [347, 348]. The aforementioned associations highlight the importance of assessing and treating psychiatric co-morbidity as part of weight management interventions [317, 335]. In the context of such a multidisciplinary approach, clinicians should also take into consideration that, several widely prescribed antidepressants and antipsychotic agents can induce weight gain (e.g. tricyclic antidepressants, paroxetine, mirtazapine, monoamine oxidase inhibitors, lithium, clozapine, olanzapine, risperidone) [349].

Obesity and cancer risk

Over the last two decades, compelling data have accumulated indicating that obesity is associated with higher incidence, morbidity and mortality of several common cancers. Sufficient evidence is now available to support such associations between increasing BMI and endometrium cancer, post-menopausal breast cancer, colorectal cancer, kidney (renal cell) cancer, oesophageal and gastric cardia adenocarcinoma (Figure 14) [350-358]. Indeed, obese patients are shown to have approximately 1.5 to 3.5 higher risk of developing these cancers compared to normal-weight individuals [356]. Further studies have reported that excess body weight may also increase the risk of liver, pancreas and gallbladder cancers, as well as haematopoietic and lymphoid tissue malignancies [350-356]. In accord to what is noted for the majority of obesity-related co-morbidities, central obesity is identified as an independent, at least partially, predictor of increased cancer risk. Waist circumference correlates primarily with endometrium, breast, colon, pancreas and liver cancers, thus, suggesting pathogenetic links between visceral adiposity and carcinogenesis at these sites [359-361]. Pancreatic and hepatocellular cancer incidence is more distinctly related with T2DM, highlighting the adverse role of underlying insulin resistance and hyperinsulinemia [352, 362, 363]. Interestingly, some studies have also suggested that long-standing T2DM may diminish the increased risk of certain cancers, potentially due to progressive beta-cell failure and deteriorating insulin secretion over time [364, 365]. It is important to stress that, whether long-acting insulin analogs (particularly insulin glargine) exert an additional effect on cancer risk remains unproven based on available data and deserves further study, however treatment with high insulin doses can accelerate the growth of existing tumors [366-377]. On the other hand, metformin therapy appears to decrease colon and pancreas cancer risk in T2DM patients compared to treatment with insulin or insulin secretagogues [376, 377].

FOR PEER REVIEW PLEASE SEE FIGURE 14

Prospective studies have established that weight gain in adult life is a risk factor for colorectal cancer, while post-menopausal fat accumulation in women is associated with breast cancer [354, 378,

379]. Notably, obesity may protect pre-menopausal women against breast cancer, probably attributed to tendency for increased cycle length and decreased ovulation [353]. Both gender and ethnic differences appear to exist regarding the impact of obesity and weight gain on certain tumors, thus, significantly stronger association is documented between BMI and colon cancer in males, while correlations between BMI and breast cancer risk are more potent in the Asia-Pacific region compared to Europe, North America, and Australia [380]. Overall, cancer risk in adults increases when BMI exceeds 22 kg/m^2, hence the current cancer prevention recommendation regarding body adiposity from the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) is to stay as lean as possible within the normal BMI range (recommended public health goal for a median BMI between 21 and 23 kg/m^2 in adults depending on normal ranges for different ethnic populations) [353, 381, 382]. Childhood obesity is also implicated, since excess adiposity in adolescence tends to persist into adulthood and is shown to have long-term effects doubling the risk of death from colon cancer [383, 384]. Recent estimates in the European Union suggest that approximately 5% of all incident cancers can be attributed to excess body weight (3% and 6% in men and women, respectively) [385]. In US adults (50 years of age or older) the proportion of all deaths from cancer that is attributable to overweight and obesity may reach 14% in men and 20% in women [358]. Globally, obesity and physical inactivity are now recognized among the most important modifiable risk factors, together with tobacco control, for primary cancer prevention. Indeed, maintaining normal BMI in adulthood exerts a cancer-preventive effect on colorectal, endometrium, post-menopausal breast, renal cell and oesophageal cancers [350-353]. Furthermore, in clinical practice emphasis must be placed on growing evidence supporting the impact of weight loss in reducing obesity-related cancer risk [386, 387].

In general, overweight and obesity also constitute adverse prognostic factors among cancer survivors (individuals who are living with a diagnosis of cancer or have recovered from the disease), associated with worse survival rates and increased recurrence risk for several cancers [353]. Indeed, most studies associate increased BMI with breast cancer recurrence and compromised survival [388]. For colorectal cancer, increases in both adiposity and waist circumference have been shown to correlate to higher disease specific mortality [389]. Overall mortality and disease recurrence among

women with colon carcinoma (stage II-III) appears to increase with obesity [390]. Current data further relate excess body weight to increased prostate cancer-specific mortality and risk of aggressive prostate cancer [296-300, 302].

Notably, studies have suggested an association between obesity and delayed cancer detection in clinical practice attributed either to weight-related barriers and patient delay (the period from first onset of symptoms to first medical consultation) or to greater difficulty in performing clinical examinations (e.g. examination of larger breasts in obese women or abdominal examination in central obesity) and diagnostic procedures (e.g. less accurate biopsy detection of prostate cancer in obese men due to larger sized prostates) [296, 391-394]. Furthermore, it is important to underline that the disease burden may be higher in obese cancer patients due to increased risk for both cardiometabolic co-morbidity (e.g. T2DM and ischemic heart disease) and post-chemotherapy or postoperative complications.

Several mechanisms have been proposed to explain the described epidemiologic associations between obesity and cancer in addition to environmental factors and genetic predisposition. Insulin resistance and compensatory chronic hyperinsulinemia hold a cardinal role in proposed models for obesity-related carcinogenesis which may vary depending on cancer site (Figure 15) [351, 362, 395-397]. Increased insulin levels have been shown to induce mitogenic effects and contribute to tumorigenesis through activation of both the insulin receptor and the insulin-like growth factor 1 (IGF-1) receptor. Notably, hyperinsulinemia can suppress the synthesis of insulin-like growth factor binding protein 1 (IGFBP-1) in the liver and locally in other tissues, while is also associated with reduced plasma IGFBP-2. In turn, this decrease in IGFBP-1 and IGFBP-2 levels leads to increased bio-availability of IGF-1 which promotes cellular proliferation and inhibits apoptosis through its receptor in several tissues [398, 399]. Increased levels of estrogens and androgens are also considered to mediate carcinogenic effects, particularly for endometrium and post-menopausal breast cancers. Circulating SHBG levels are markedly decreased in patients with central obesity and hyperinsulinemia due to suppression of SHBG synthesis in the liver by insulin. Thus, higher free sex-steroid levels are present in the circulation increasing the risk for hormone-sensitive gynecologic malignancies [239-241]. Enhanced metabolism of sex steroids within adipose tissue depots can further contribute to

increased plasma levels of androgens and estrogens in obesity (Figure 15) [238-240]. Finally, current evidence suggests that adipokine changes (e.g. hypoadiponectinemia and hyperleptinemia) and the chronic low-grade inflammatory state in obesity may directly promote carcinogenesis [400].

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Various weight-related co-morbidities

The aforementioned co-morbidities are closely related to adipose tissue secretion of multiple adipokines, hormones and factors that induce deleterious autocrine, paracrine and endocrine effects. A second principal mechanism leading to obesity-related disease reflects increased physical burdens imposed by excess fat mass to various body sites [401]. Indeed, enhanced local biomechanic stress due to accumulated fat and increased body weight (e.g. on joints, on the respiratory tract, on blood vessels or within the abdominal compartment) causes and/or exacerbates several co-morbidities which are common in obese patients, such as knee osteoarthritis, back pain, restrictive lung disease, obstructive sleep apnea, gastroesophageal reflux disease, hernias, and chronic venous insufficiency. Notably, even these complications are further aggravated by the adverse metabolic profile and chronic inflammatory state in obesity, multiplying the overall burden of the disease and creating a vicious cycle that can be broken only by weight loss.

Weight-related co-morbidities of the musculoskeletal system and skin

Osteoarthritis (OA) is the most frequent joint disorder worldwide and one of the leading causes of chronic pain and disability in the adult population of Western societies, particularly among the elderly [402]. Obesity is a major risk factor for knee OA, with available data indicating that weight gain can precede the disease onset by several years and that this increased risk begins as early as the third decade of life [403-407]. A recent prospective study in Finland (population-based with follow-up of 22 years) documented a strong association between BMI and risk of knee OA, with relative odds ratio of 7.0 (95% CI 3.5, 14.10; adjusted for age, gender and other covariates) for obese persons compared to individuals with BMI less than 25 kg/m^2 [408]. Overall, each additional BMI unit above 27 kg/m^2 can lead to a 15% increase of the risk of knee OA, with the association being stronger in women compared to men and for bilateral than for unilateral disease [409, 410]. Obesity appears to also increase the risk of hip and hand osteoarthritis, although these associations are less consistent [411-416]. Furthermore, excess body weight is an important predictor of progressive knee and hip osteoarthritis with obese patients exhibiting higher risk for deteriorating disease and development of disability [401, 407, 417]. Notably, it has been shown that weight loss of approximately 5.1 kg over a

10-year period can reduce the odds of developing symptomatic knee OA by more than 50% [418]. Functional disability in obese patients diagnosed with knee osteoarthritis may also be improved with weight reduction over 5% or at the rate of more than 0.25% per week within a 20 week-period [419]. The association of obesity with OA of weight-bearing joints is primarily attributed to repetitive over-loading during daily activities which progressively causes destruction of cartilage and damage to ligaments and other support structures, while muscle weakness, abnormal gait and alignment disorders may be further contributing factors [410, 420, 421]. It is interesting to note that increasing BMI is associated with higher injury rates, including those related to falls, sprains/strains, joint dislocations and lower extremity fractures [422]. In turn, joint injuries (e.g. meniscal ligament tears in the knee, fractures and dislocations) increase the risk of later development of OA in the injured joint [401, 423]. OA in non-weight-bearing joints (e.g. in the hand) and increased frequency of OA in obese women indicate that a metabolic component may also link obesity to OA, in addition to biomechanic causes. Indeed, current evidence suggests that adverse hormonal and metabolic profiles in obesity (e.g. changes in leptin, adiponectin, TNF-α and IL-6, as well as hyperglycemia, lipid abnormalities and chronic inflammation) can play a crucial role in the pathogenesis of OA [424-426]. Increasing attention is focused on leptin effects and local dysregulation of adipokine production in osteoarthritic joints [424-427], while recent data obtained from the cohort of the Chingford Study showed that individuals were more likely to be diagnosed as having radiographic knee OA if they had a higher BMI and increased circulating levels of IL-6, highlighting the potential implication of this pro-inflammatory cytokine in the disease process [428].

Obesity is also associated with several dermatologic conditions [429-431]. Striae distensae (striae or stretch marks) is a common dermatosis in obese patients representing linear atrophic plaques which are created due to tension and skin stretching from expanding fat deposits. Obesity-related striae are distributed primarily in the abdomen, breasts, buttocks and thighs and pose more of a cosmetic problem. Clinically, these striae appear to be lighter, narrower, and less atrophic than striae in Cushing's syndrome which are characterized by more intense color and inordinate breadth and depth. Acanthosis nigricans can be noted in obese patients with insulin resistance and hyperinsulinemia manifested with hyperpigmented, velvety, irregular plaques often in the folds of the

back of the neck, axilla and groin, as well as on knuckles, extensor surfaces and face. Skin tags are also commonly associated with hyperinsulinemia and acanthosis nigricans. Obese women may exhibit hirsutism and acne vulgaris as a result of both hyperandrogenism and hyperinsulinemia. Weight gain is also associated with cellulite due to changes in the epidermis and dermis mostly in women and in areas such as the thighs, buttocks and abdomen. Due to excessive sweating and increased friction between skin surfaces, a number of skin infections are more frequent in obesity including oppositional intertrigo (inflammation-rash in body folds), candidiasis, candida folliculitis, folliculitis and less often cellulitis, erysipelas or fasciitis. Finally, obesity is a risk factor for lower limb lymphedema, chronic venous insufficiency and stasis pigmentation, while wound healing may be slower in obese patients.

Weight-related co-morbidities of the respiratory system

Increased body weight and fat accumulation in the abdomen and chest wall can have a significant impact on respiratory physiology leading to deterioration of pulmonary function, attributed primarily to increased mechanical pressure on the thoracic cage and trunk [432-434]. Although the effects on conventional respiratory function tests are often modest until BMI exceeds 40 kg/m^2, obese patients may exhibit reductions in lung volumes and respiratory compliance, as well as in respiratory efficiency [434, 435]. Morbid obesity is associated with decreased total lung capacity (TLC), expiratory reserve volume (ERV) and functional residual capacity (FRC), as a result of mass loading, splinting and restricted decent of the diaphragm [432-435]. Reduced FRC impairs the capacity to tolerate periods of apnea and represents the most consistently documented effect of obesity on respiratory function [435-437]. FRC can be reduced even in overweight individuals and declines exponentially with increasing BMI to the extent that it may approach residual volume (RV) [435, 436]. On the other hand, RV is usually found within the normal range in obese patients, but it can also be increased suggesting concurrent obstructive airway disease and gas trapping [435-437]. Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) are also modestly affected in obesity and, thus, these spirometric variables frequently remain within normal limits in otherwise healthy obese adults and children [438, 439]. However, both FEV1 and FVC exhibit a tendency to decrease with weight gain and improvements have been reported following weight loss [439-442].

Longitudinal studies have demonstrated this inverse association between BMI and FEV1 [443, 444], while it is important to note that pulmonary function and FEV1 is regarded as an independent predictor of all-cause mortality and a risk factor for CVD, stroke and lung cancer [445, 446]. Furthermore, increasing BMI is related to an exponential decline in respiratory compliance which is attributed primarily to reduced lung compliance due to increased pulmonary blood volume and also to reductions in chest wall compliance due to local fat accumulation [447, 448]. Decreased respiratory compliance is associated with FRC reductions and impaired gas exchange [437, 449]. Conversely, total respiratory resistance is increased in severe obesity mainly due to increases in lung resistance [447, 448]. These changes in respiratory compliance and resistance are more marked in the supine position and can affect the breathing pattern which becomes shallow and rapid. Overall, the work of breathing is enhanced and can lead to restricted maximum ventilatory capacity and respiratory muscle inefficiency with heightened demand for ventilation and relative hypoventilation during activity [434]. The impact of obesity on respiratory function is generally greater in men compared to women, probably attributed to gender-related differences in fat distribution, highlighting the crucial role of central obesity [450-452]. Indeed, indices of visceral adiposity are considered better predictors of respiratory function than body weight or BMI and an inverse association exists between waist circumference and both FEV1 and FVC, with data showing that, on average, an increase in waist circumference of 1 cm is associated with reductions of 13 ml and 11 ml in FVC and FEV1, respectively, after adjustment for gender, age, height, weight and pack-years of smoking [452, 453]. Adverse effects on the lungs caused by circulating adipokines and chronic inflammation in central obesity are considered to mediate these heighten associations with respiratory dysfunction.

Obesity is further associated with a spectrum of distinct respiratory conditions including obstructive sleep apnea, obesity hypoventilation syndrome, asthma, and chronic obstructive pulmonary disease [432, 454-457].

Obstructive sleep apnea (OSA) is a common respiratory disorder characterized by recurrent episodes of temporary airflow cessation (apnea) or reduction (hypopnea) during sleep which are caused by total or partial upper airway collapse and result in decreased oxygen saturation (repeated episodes of hypoxemia and hypercapnia) [454]. Airflow is restored with arousal, thus disrupting the

normal sleep pattern and adversely affecting sleep quality. Subsequently, OSA can lead to various clinical manifestations including snoring, choking episodes during sleep, nocturia, restless and un-refreshing sleep, daytime hypersomnolence and impaired concentration, hypertension, decreased libido, irritability and personality changes, while it is also distinctly associated with increased incidence of motor vehicle accidents. Screening for OSA can be performed through validated questionnaires (e.g. the Epworth Sleepiness Scale and the Berlin Questionnaire) and OSA diagnosis relies on polysomnography which remains the "gold standard" diagnostic method [454, 458, 459]. By consensus, an apnea is defined as airflow cessation for at least 10 seconds and is classified as obstructive or central based on presence or absence of respiratory effort, respectively [460]. A hypopnea is defined based on the presence of either (1) reduced airflow by ≥30% from baseline for at least 10 seconds with ≥4% desaturation from baseline or (2) reduced airflow by ≥50% for at least 10 seconds with ≥3% desaturation or an arousal [460]. OSA severity is usually defined by the apnea-hypopnea index (AHI), which represents the number of apneas plus hypopneas per hour of documented sleep (mild OSA: AHI of 5 to 15; moderate OSA: AHI of more than 15 to 30; and severe OSA: AHI of more than 30) [461]. However, it must be noted that AHI does not necessarily reflect the severity of clinical symptoms and use of other indices has been suggested (e.g. based on hypoxemia) [462, 463]. A long-term consequence of OSA is alterations in the central control of breathing, with episodes of central apnea due to progressive desensitization of respiratory centers to hypercapnia. These episodes are initially limited during sleep, but eventually can lead to the obesity hypoventilation syndrome (Pickwickian syndrome) which is characterized by obesity, sleep disordered breathing, alveolar hypoventilation, chronic hypercapnia and hypoxia, hypersomnolence, right ventricular failure and polycythemia [464].

OSA prevalence is increasing in Western societies and appears to be higher in men and among the elderly [465]. US data from the Wisconsin Sleep Cohort Study reported that the estimated population prevalence of OSA (AHI of 5 or more) in middle-aged men and women (30-60 years old) was 24% and 9%, respectively, with 4% of men and 2% of women also presenting daytime hypersomnolence [466]. Obesity, especially central, is recognized as a major risk factor for OSA [454, 465, 467]. Several studies have reported a consistent association between increased BMI and OSA risk

with an extremely high OSA incidence among morbidly obese subjects (55-100% in patients evaluated for bariatric surgery) [468-470]. Notably, a prospective population-based study documented that even moderate weight gain can increase OSA risk with a 10% weight gain predicting a six-fold (95% CI, 2.2-17.0) increase in the odds of developing moderate to severe sleep-disordered breathing, while a 10% weight loss predicted a 26% (95% CI, 18%-34%) decrease in the AHI [471]. Neck circumference, reflecting central obesity and fat deposition around the upper airways, is regarded as a better predictor of OSA risk compared to body weight and BMI [472]. Available data further suggest that waist circumference can exhibit a stronger association with OSA risk compared to BMI and even neck circumference, highlighting the role of upper body fat distribution in OSA pathophysiology [473].

Multiple mechanisms appear to mediate the association between obesity and OSA [454, 467]. Contributing factors for development of sleep-disordered breathing include older age, male gender, anatomically narrow upper airways, increased tendency for upper airway collapse, and variations in neuromuscular control of upper airway muscles and in ventilatory control mechanisms [454]. Cervical fat deposition in obesity with fat deposits in the lateral wall of the pharynx may decrease the caliber of the upper airways and increase their collapsibility, mainly due to increased thickness of the lateral pharyngeal muscle wall [474-476]. Furthermore, impairment of upper airway dilator muscles is suggested in obese patients with data reporting increased genioglossus fatigability [477]. Abdominal fat accumulation also leads to decreased longitudinal upper airway tension and increased upper airway collapsibility due to the aforementioned changes in respiratory function and lung volumes [432-435]. Insulin resistance, circulating adipokines (e.g. leptin), pro-inflammatory cytokines (e.g. IL-6 and TNF-α), reactive oxygen species (ROS) production and oxidative stress are also considered to further aggravate OSA, particularly in central obesity (Figure 16) [478-481]. Finally, research attention is focused on the role of increased SNS activity which appears implicated in the inter-relationships between weight gain, OSA and hypertension in obese patients [482-484].

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Weight loss can significantly reduce the AHI and improve clinical manifestations of OSA. Promising results are reported from studies on the impact of bariatric surgery and according to meta-analysis data up to 85% of OSA patients may exhibit remission and complete resolution of sleep-disordered breathing [485]. However, it is important to highlight that although weight reduction improves OSA, morbidly obese patients undergoing bariatric surgery should not necessarily expect to be cured of OSA following weight loss. Indeed, a recent meta-analysis regarding effects of surgical weight loss on measures of OSA demonstrated that the mean AHI after weight loss with bariatric procedures was consistent with moderately severe OSA (a pooled baseline AHI of 54.7 events per hour was reduced to a final value of 15.8 events per hour) [486]. Interestingly, recurrence of OSA can be noted following initial improvements with weight loss even without concomitant weight regain [487]. This can be attributed to variation in fat loss from different body sites with persisting fat deposition in the neck and to other mechanisms contributing to increased upper airway collapsibility, independent of body weight [467]. In clinical practice, physicians should also be reminded that the link between OSA and obesity is bi-directional with untreated OSA predisposing to weight gain and obesity. Short sleep duration predicts future obesity and newly diagnosed OSA patients often experience a history of recent excessive weight gain in the period preceding the diagnosis [488, 489]. Finally, a significant proportion of OSA patients remains undiagnosed and this poses an additional risk to bariatric surgery candidates since OSA is associated with higher risk of adverse outcomes occurring within 30 days after surgery (e.g. death, deep-vein thrombosis or venous thromboembolism, reintervention with percutaneous, endoscopic or operative techniques and failure to be discharged from the hospital within 30 days after surgery) [468, 490, 491].

Conclusions

In this chapter we have discussed some of the key disorders that are associated with obesity and are potentially caused, at least in part, by adipose tissue accumulation. These include disturbances of glucose metabolism, manifestations of the metabolic syndrome, non-alcoholic fatty liver disease, gallbladder disease, osteoarthritis, obstructive sleep apnea, and various cancers, as well as unfavorable outcomes regarding reproduction, stress levels, and psychiatric disorders.

However, it should be noted that obesity does not necessarily imply disease. Indeed, obese individuals often largely differ regarding manifestations of obesity-related morbidity [38] and it appears that patterns of lipid partitioning are a major determinant of the metabolic profile. Distribution of body fat appears to play an important role in this context. As such particularly visceral accumulation of excess body fat, clinically manifested with an increased waist circumference, is shown to be associated with most of the obesity-related disorders including insulin resistance [492], and T2DM [493], as well as with all-cause mortality [494], whereas increased subcutaneous fat depots can even have protective metabolic effects [495-497]. Although not all previous studies showed an independent effect of the subcutaneous abdominal fat on insulin sensitivity [498] and controversial findings have also been reported [499], a growing body of evidence suggests that an expanded fat mass particularly of subcutaneous adipose tissue may function as a sink for glucose uptake resulting in compensatory improvement of insulin sensitivity [496]. In agreement with this hypothesis, it was recently shown that enabling a massive expansion of the subcutaneous adipose tissue mass in the ob/ob mouse model potently counteracts the strong trends toward development of insulin resistance associated with excess caloric intake [500]. In conclusion the metabolically “healthy obese” individual with a predominantly female type of fat distribution appears to exist, but other parameters such as osteoarthritis, disability and effects on psychological well-being need to be further considered when discussing benefits of weight management interventions.

References

1. James WP. The epidemiology of obesity: the size of the problem. J Intern Med. 2008; 263(4):336-52.

2. Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. Int J Pediatr Obes. 2006; 1(1):11-25.

3. World Health Organization: Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. WHO: Geneva, 2004.

4. James WP. WHO recognition of the global obesity epidemic. Int J Obes (Lond). 2008; 32 Suppl 7:S120-6.

5. World Health Organization. Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors. WHO: Geneva, 2004.

6. Kopelman P. Health risks associated with overweight and obesity. Obes Rev. 2007; 8 Suppl 1:13-7.

7. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med. 1999; 7; 341(15):1097-105.

8. Klein S, Allison DB, Heymsfield SB, Kelley DE, Leibel RL, Nonas C, Kahn R; Association for Weight Management and Obesity Prevention; NAASO; Obesity Society; American Society for Nutrition; American Diabetes Association. Waist circumference and cardiometabolic risk: a consensus statement from shaping America's health: Association for Weight Management and Obesity Prevention; NAASO, the Obesity Society; the American Society for Nutrition; and the American Diabetes Association. Diabetes Care. 2007; 30(6):1647-52.

9. Snijder MB, Zimmet PZ, Visser M, Dekker JM, Seidell JC, Shaw JE. Independent and opposite associations of waist and hip circumferences with diabetes, hypertension and dyslipidemia: the AusDiab Study. Int J Obes Relat Metab Disord. 2004; 28(3):402-9.

10. James WP. Assessing obesity: are ethnic differences in body mass index and waist classification criteria justified? Obes Rev. 2005; 6(3), 179-81.

11. James WP, Rigby N, Leach R. Obesity and the metabolic syndrome: the stress on society. Ann N Y Acad Sci. 2006; 1083, 1-10.

12. Barnett AH, Dixon AN, Bellary S, Hanif MW, O'hare JP, Raymond NT, Kumar S. Type 2 diabetes and cardiovascular risk in the UK south Asian community. Diabetologia. 2006; 49(10):2234-46.

13. WHO expert consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004; 363, 157-63.

14. Huxley R, Barzi F, Stolk R, Caterson I, Gill T, Lam TH, Omari A, Woodward M; Obesity in Asia Collaboration (OAC). Ethnic comparisons of obesity in the Asia-Pacific region: protocol for a collaborative overview of cross-sectional studies. Obes Rev. 2005; 6(3):193-8.

15. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr; International Diabetes Federation Task Force on Epidemiology and Prevention; Hational Heart, Lung, and Blood Institute; American Heart Association; World Heart

Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009; 120(16):1640-5.

16. Tsigos C, Hainer V, Basdevant A, Finer N, Fried M, Mathus-Vliegen E, Micic D, Maislos M, Roman G, Schutz Y, Toplak H, Zahorska-Markiewicz B; Obesity Management Task Force of the European Association for the Study of Obesity. Management of obesity in adults: European clinical practice guidelines. Obes Facts. 2008; 1(2):106-16.

17. Reynolds SL, Saito Y, Crimmins EM. The impact of obesity on active life expectancy in older American men and women. Gerontologist. 2005; 45(4):438-44.

18. Alley DE, Chang VW. The changing relationship of obesity and disability, 1988-2004. JAMA. 2007, 7; 298(17): 2020-7.

19. Walter S, Kunst A, Mackenbach J, Hofman A, Tiemeier H. Mortality and disability: the effect of overweight and obesity. Int J Obes (Lond). 2009; 33(12):1410-8.

20. Allender S, Rayner M. The burden of overweight and obesity-related ill health in the UK. Obes Rev. 2007; 8(5):467-73.

21. House of Commons Health Committee. Obesity. London: The Stationery Office. 2004.

22. Bajekal, M., Primatesta, P. & Prior, G. (eds) Health Survey for England. London: Department of Health, HMSO 2003.

23. Field AE, Coakley EH, Must A, Spadano JL, Laird N, Dietz WH, Rimm E, Colditz GA. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. Arch Intern Med. 2001 9;161(13):1581-6.

24. Smyth S, Heron A. Diabetes and obesity: the twin epidemics. Nat Med 2006 12(1), 75-80.

25. Astrup A, Finer N. Redefining type 2 diabetes: “diabesity” or “obesity dependent diabetes mellitus”? Obes Rev 2000 1(2), 57-9.

26. Wannamethee SG, Shaper AG. Weight change and duration of overweight and obesity in the incidence of type 2 diabetes. Diabetes Care 1999 22, 1266-72.

27. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med. 1995 Apr 1;122(7):481-6.

28. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care. 1994; 17(9):961-9.

29. Schienkiewitz A, Schulze MB, Hoffmann K, Kroke A, Boeing H. Body mass index history and risk of type 2 diabetes: results from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. Am J Clin Nutr. 2006; 84(2):427-33.

30. Regitz-Zagrosek V, Lehmkuhl E, Weickert MO. Gender differences in the metabolic syndrome and their role for cardiovascular disease. Clin Res Cardiol. 2006; 95(3):136-47.

31. Kautzky-Willer A, Handisurya A. Metabolic diseases and associated complications: sex and gender matter! Eur J Clin Invest. 2009; 39(8):631-48.
32. Ehm MG, Karnoub MC, Sakul H, Gottschalk K, Holt DC, Weber JL, Vaske D, Briley D, Briley L, Kopf J, McMillen P, Nguyen Q, Reisman M, Lai EH, Joslyn G, Shepherd NS, Bell C, Wagner MJ, Burns DK; American Diabetes Association GENNID Study Group. Genetics of NIDDM. Genomewide search for type 2 diabetes susceptibility genes in four American populations. Am J Hum Genet. 2000; 66(6):1871-81.
33. Alberti G, Zimmet P, Shaw J, Bloomgarden Z, Kaufman F, Silink M; Consensus Workshop Group. Type 2 diabetes in the young: the evolving epidemic: the international diabetes federation consensus workshop. Diabetes Care. 2004; 27(7):1798-811.
34. SEARCH for Diabetes in Youth Study Group, Liese AD, D'Agostino RB Jr, Hamman RF, Kilgo PD, Lawrence JM, Liu LL, Loots B, Linder B, Marcovina S, Rodriguez B, Standiford D, Williams DE. The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. Pediatrics. 2006; 118(4):1510-8.
35. Pi-Sunyer FX. The epidemiology of central fat distribution in relation to disease. Nutr Rev 2004; 62(7 Pt 2), S120-6.
36. Després JP. Intra-abdominal obesity: an untreated risk factor for Type 2 diabetes and cardiovascular disease. J Endocrinol Invest. 2006; 29(3 Suppl):77-82.
37. Schneider HJ, Glaesmer H, Klotsche J, Böhler S, Lehnert H, Zeiher AM, März W, Pittrow D, Stalla GK, Wittchen HU; DETECT Study Group. Accuracy of anthropometric indicators of obesity to predict cardiovascular risk. J Clin Endocrinol Metab. 2007; 92(2):589-94.
38. Weiss R. Fat distribution and storage: how much, where, and how? Eur J Endocrinol 2007 157 Suppl 1, S39-45.
39. Björntorp P. "Portal" adipose tissue as a generator of risk factors for cardiovascular disease and diabetes. Arteriosclerosis 1990 10(4), 493-6.
40. Montague CT, O'Rahilly S. The perils of portliness: causes and consequences of visceral adiposity. Diabetes 2000 49(6), 883-8.
41. Yang X, Smith U. Adipose tissue distribution and risk of metabolic disease: does thiazolidinedione-induced adipose tissue redistribution provide a clue to the answer? Diabetologia 2007 50(6), 1127-39.
42. Björntorp P, Rosmond R. Neuroendocrine abnormalities in visceral obesity. Int J Obes Relat Metab Disord 2000 24 Suppl 2, S80-5.
43. Kyrou I, Chrousos GP, Tsigos C. Stress, visceral obesity, and metabolic complications. Ann N Y Acad Sci 2006 1083, 77-110.
44. Seckl JR, Morton NM, Chapman KE. Glucocorticoids and 11beta-hydroxysteroid dehydrogenase in adipose tissue. Recent Prog Horm Res. 2004 59:359-93.

45. Najjar SM, Yang Y, Fernström MA, Lee SJ, Deangelis AM, Rjaily GA, Al-Share QY, Dai T, Miller TA, Ratnam S, Ruch RJ, Smith S, Lin SH, Beauchemin N, Oyarce AM. Insulin acutely decreases hepatic fatty acid synthase activity. Cell Metab. 2005; 2(1):43-53.

46. Schenk S, Davidson CJ, Zderic TW, Byerley LO, Coyle EF. Different glycemic indexes of breakfast cereals are not due to glucose entry into blood but to glucose removal by tissue. Am J Clin Nutr. 2003; 78(4):742-8.

47. Weickert MO, Mohlig M, Koebnick C, Holst JJ, Namsolleck P, Ristow M, Osterhoff M, Rochlitz H, Rudovich N, Spranger J, Pfeiffer AF. Impact of cereal fibre on glucose-regulating factors. Diabetologia. 2005; 48(11):2343-53.

48. Due A, Toubro S, Skov AR, Astrup A. Effect of normal-fat diets, either medium or high in protein, on body weight in overweight subjects: a randomised 1-year trial. Int J Obes Relat Metab Disord. 2004; 28(10):1283-90.

49. Clifton PM, Bastiaans K, Keogh JB. High protein diets decrease total and abdominal fat and improve CVD risk profile in overweight and obese men and women with elevated triacylglycerol. Nutr Metab Cardiovasc Dis. 2009; 19(8):548-54.

50. Davis JN, Alexander KE, Ventura EE, Toledo-Corral CM, Goran MI. Inverse relation between dietary fiber intake and visceral adiposity in overweight Latino youth. Am J Clin Nutr. 2009; 90(5):1160-6.

51. McKeown NM, Yoshida M, Shea MK, Jacques PF, Lichtenstein AH, Rogers G, Booth SL, Saltzman E. Whole-grain intake and cereal fiber are associated with lower abdominal adiposity in older adults. J Nutr. 2009; 139(10):1950-5.

52. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. Med Clin North Am 2004; 88(4), 787-835.

53. Bays H, Mandarino L, DeFronzo RA. Role of the adipocyte, free fatty acids, and ectopic fat in pathogenesis of type 2 diabetes mellitus: peroxisomal proliferator-activated receptor agonists provide a rational therapeutic approach. J Clin Endocrinol Metab 2004; 89 (2), 463-78.

54. Boden G. Effects of free fatty acids (FFA) on glucose metabolism: significance for insulin resistance and type 2 diabetes. Exp Clin Endocrinol Diabetes 2003; 111(3), 121-4.

55. Weickert MO, Pfeiffer AF. Signalling mechanisms linking hepatic glucose and lipid metabolism. Diabetologia. 2006; 49(8):1732-41.

56. Roden M, Bernroider E. Hepatic glucose metabolism in humans--its role in health and disease. Best Pract Res Clin Endocrinol Metab. 2003; 17(3):365-83.

57. DeFronzo RA, Ferrannini E, Simonson DC. Fasting hyperglycemia in non-insulin-dependent diabetes mellitus: contributions of excessive hepatic glucose production and impaired tissue glucose uptake. Metabolism 1989; 38(4), 387-95.

58. Shulman GI, Rothman DL, Jue T, Stein P, DeFronzo RA, Shulman RG. Quantitation of muscle glycogen synthesis in normal subjects and subjects with non-insulin-dependent diabetes by 13C nuclear magnetic resonance spectroscopy. N Engl J Med. 1990 25;322(4):223-8.
59. McGarry JD. Banting lecture 2001: dysregulation of fatty acid metabolism in the etiology of type 2 diabetes. Diabetes 2002; 51(1), 7-18.
60. Kashyap S, Belfort R, Gastaldelli A, Pratipanawatr T, Berria R, Pratipanawatr W, Bajaj M, Mandarino L, DeFronzo R, Cusi K. A sustained increase in plasma free fatty acids impairs insulin secretion in nondiabetic subjects genetically predisposed to develop type 2 diabetes. Diabetes. 2003; 52(10):2461-74.
61. Cusi K, Kashyap S, Gastaldelli A, Bajaj M, Cersosimo E. Effects on insulin secretion and insulin action of a 48-h reduction of plasma free fatty acids with acipimox in nondiabetic subjects genetically predisposed to type 2 diabetes. Am J Physiol Endocrinol Metab. 2007; 292(6):E1775-81.
62. Ferrannini E, Gastaldelli A, Miyazaki Y, Matsuda M, Pettiti M, Natali A, Mari A, DeFronzo RA. Predominant role of reduced beta-cell sensitivity to glucose over insulin resistance in impaired glucose tolerance. Diabetologia. 2003; 46(9):1211-9.
63. Ferrannini E, Gastaldelli A, Miyazaki Y, Matsuda M, Mari A, DeFronzo RA. beta-Cell function in subjects spanning the range from normal glucose tolerance to overt diabetes: a new analysis. J Clin Endocrinol Metab. 2005; 90(1):493-500.
64. Klein S, Sheard NF, Pi-Sunyer X, Daly A, Wylie-Rosett J, Kulkarni K, Clark NG; American Diabetes Association; North American Association for the Study of Obesity; American Society for Clinical Nutrition. Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies: a statement of the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition. Diabetes Care. 2004; 27(8):2067-73.
65. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001 3;344(18):1343-50.
66. Laaksonen DE, Lindström J, Lakka TA, Eriksson JG, Niskanen L, Wikström K, Aunola S, Keinänen-Kiukaanniemi S, Laakso M, Valle TT, Ilanne-Parikka P, Louheranta A, Hämäläinen H, Rastas M, Salminen V, Cepaitis Z, Hakumäki M, Kaikkonen H, Härkönen P, Sundvall J, Tuomilehto J, Uusitupa M; Finnish diabetes prevention study. Physical activity in the prevention of type 2 diabetes: the Finnish diabetes prevention study. Diabetes. 2005; 54(1):158-65.
67. Lindström J, Ilanne-Parikka P, Peltonen M, Aunola S, Eriksson JG, Hemiö K, Hämäläinen H, Härkönen P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Mannelin M, Paturi M, Sundvall J, Valle TT, Uusitupa M, Tuomilehto J; Finnish Diabetes Prevention Study Group. Sustained reduction

in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet. 2006 11;368(9548):1673-9.
68. Fujimoto WY, Jablonski KA, Bray GA, Kriska A, Barrett-Connor E, Haffner S, Hanson R, Hill JO, Hubbard V, Stamm E, Pi-Sunyer FX; Diabetes Prevention Program Research Group. Body size and shape changes and the risk of diabetes in the diabetes prevention program. Diabetes. 2007; 56(6):1680-5.
69. Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, Hamman RF, Christophi CA, Hoffman HJ, Brenneman AT, Brown-Friday JO, Goldberg R, Venditti E, Nathan DM. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet. 2009 14;374(9702):1677-86.
70. Penn L, White M, Oldroyd J, Walker M, Alberti KG, Mathers JC. Prevention of type 2 diabetes in adults with impaired glucose tolerance: the European Diabetes Prevention RCT in Newcastle upon Tyne, UK. BMC Public Health. 2009 16;9:342.
71. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006 14;444(7121):860-7.
72. Maury E, Brichard SM. Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. Mol Cell Endocrinol. 2010 15;314(1):1-16.
73. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest. 2006; 116(7):1793-801.
74. Libby P. Inflammation in atherosclerosis. Nature. 2002 19-26;420(6917):868-74.
75. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003; 112(12):1796-808.
76. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, Chen H. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest. 2003; 112(12):1821-30.
77. Wellen KE, Hotamisligil GS. Obesity-induced inflammatory changes in adipose tissue. J Clin Invest. 2003; 112(12):1785-8.
78. Carey AL, Febbraio MA. Interleukin-6 and insulin sensitivity: friend or foe? Diabetologia. 2004; 47(7):1135-42.
79. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol. 2006; 6(10):772-83.
80. Yudkin JS. Inflammation, obesity, and the metabolic syndrome. Horm Metab Res. 2007; 39(10):707-9.
81. Nieuwdorp M, Stroes ES, Meijers JC, Büller H. Hypercoagulability in the metabolic syndrome. Curr Opin Pharmacol. 2005; 5(2):155-9.
82. Kannel WB, Wolf PA, Castelli WP, D'Agostino RB. Fibrinogen and risk of cardiovascular disease. The Framingham Study. JAMA. 1987 4;258(9):1183-6.

83. Ernst E, Resch KL. Fibrinogen as a cardiovascular risk factor: a meta-analysis and review of the literature. Ann Intern Med. 1993 15;118(12):956-63.
84. Alessi MC, Juhan-Vague I. PAI-1 and the metabolic syndrome: links, causes, and consequences. Arterioscler Thromb Vasc Biol. 2006; 26(10):2200-7.
85. Woodward M, Lowe GD, Rumley A, Tunstall-Pedoe H, Philippou H, Lane DA, Morrison CE. Epidemiology of coagulation factors, inhibitors and activation markers: The Third Glasgow MONICA Survey. II. Relationships to cardiovascular risk factors and prevalent cardiovascular disease. Br J Haematol. 1997; 97(4):785-97.
86. Duncan BB, Schmidt MI, Chambless LE, Folsom AR, Carpenter M, Heiss G. Fibrinogen, other putative markers of inflammation, and weight gain in middle-aged adults--the ARIC study. Atherosclerosis Risk in Communities. Obes Res.; 8(4):279-86.
87. Juhan-Vague I, Pyke SD, Alessi MC, Jespersen J, Haverkate F, Thompson SG. Fibrinolytic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. ECAT Study Group. European Concerted Action on Thrombosis and Disabilities. Circulation. 1996 1;94(9):2057-63.
88. Matsuzawa Y. The metabolic syndrome and adipocytokines. FEBS Lett. 2006 22;580(12):2917-21.
89. Shimomura I, Funahashi T, Takahashi M, Maeda K, Kotani K, Nakamura T, Yamashita S, Miura M, Fukuda Y, Takemura K, Tokunaga K, Matsuzawa Y. Enhanced expression of PAI-1 in visceral fat: possible contributor to vascular disease in obesity. Nat Med. 1996; 2(7):800-3.
90. Mertens I, Ballaux D, Funahashi T, Matsuzawa Y, Van der Planken M, Verrijken A, Ruige JB, Van Gaal LF. Inverse relationship between plasminogen activator inhibitor-I activity and adiponectin in overweight and obese women. Interrelationship with visceral adipose tissue, insulin resistance, HDL-chol and inflammation. Thromb Haemost. 2005; 94(6):1190-5.
91. Lehrke M, Lazar MA. Inflamed about obesity. Nat Med. 2004; 10(2):126-7.
92. Creely SJ, McTernan PG, Kusminski CM, Fisher M, Da Silva NF, Khanolkar M, Evans M, Harte AL, Kumar S. Lipopolysaccharide activates an innate immune system response in human adipose tissue in obesity and type 2 diabetes. Am J Physiol Endocrinol Metab. 2007; 292(3):E740-7.
93. Cousin B, Munoz O, Andre M, Fontanilles AM, Dani C, Cousin JL, Laharrague P, Casteilla L, Pénicaud L. A role for preadipocytes as macrophage-like cells. FASEB J. 1999 Feb;13(2):305-12.
94. Cousin B, André M, Casteilla L, Pénicaud L. Altered macrophage-like functions of preadipocytes in inflammation and genetic obesity. J Cell Physiol. 2001; 186(3):380-6.
95. Clement K, Langin D. Regulation of inflammation-related genes in human adipose tissue. J Intern Med. 2007; 262(4):422-30.
96. Ferrante AW Jr. Obesity-induced inflammation: a metabolic dialogue in the language of inflammation. J Intern Med. 2007; 262(4):408-14.

97. Schäffler A, Schölmerich J, Salzberger B. Adipose tissue as an immunological organ: Toll-like receptors, C1q/TNFs and CTRPs. Trends Immunol. 2007; 28(9):393-9.
98. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988; 37(12):1595-607.
99. Kaplan NM. The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. Arch Intern Med. 1989; 149(7):1514-20.
100. World Health Organization. Definition, Diagnosis, and Classification of Diabetes Mellitus and its Complications: Report of a WHO Consultation. 1999 WHO. Geneva.
101. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal. Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2005; 48(9):1684-99.
102. Pi-Sunyer X. The metabolic syndrome: how to approach differing definitions. Med Clin North Am. 2007; 91(6):1025-40.
103. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998; 15(7):539-53.
104. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR) Diabet Med. 1999; 16(5):442-3.
105. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001 16;285(19):2486-97.
106. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome--a new worldwide definition. Lancet. 2005 24-30;366(9491):1059-62.
107. International Diabetes Federation (IDF) Consensus Worldwide Definition of the Metabolic Syndrome. 2006 http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf
108. Hara K, Matsushita Y, Horikoshi M, Yoshiike N, Yokoyama T, Tanaka H, Kadowaki T. A proposal for the cutoff point of waist circumference for the diagnosis of metabolic syndrome in the Japanese population. Diabetes Care. 2006; 29(5):1123-4.
109. Oka R, Kobayashi J, Yagi K, Tanii H, Miyamoto S, Asano A, Hagishita T, Mori M, Moriuchi T, Kobayashi M, Katsuda S, Kawashiri MA, Nohara A, Takeda Y, Mabuchi H, Yamagishi M. Reassessment of the cutoff values of waist circumference and visceral fat area for identifying Japanese subjects at risk for the metabolic syndrome. Diabetes Res Clin Pract. 2008 Mar;79(3):474-81.
110. Zhou BF; Cooperative Meta-Analysis Group of the Working Group on Obesity in China. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults--study on optimal cut-off points of body mass index and waist circumference in Chinese adults. Biomed Environ Sci. 2002; 15(1):83-96.

111. Grundy SM. Metabolic syndrome: a multiplex cardiovascular risk factor. J Clin Endocrinol Metab. 2007;92(2):399-404.
112. Reaven GM. The metabolic syndrome: requiescat in pace. Clin Chem. 2005; 51(6):931-8.
113. Sattar N. Why metabolic syndrome criteria have not made prime time: a view from the clinic. Int J Obes (Lond). 2008; 32 Suppl 2:S30-4.
114. Preiss D, Sattar N. Metabolic syndrome: collapsing under its own weight? Diabet Med. 2009; 26(5):457-9.
115. Ford ES, Li C, Sattar N. Metabolic syndrome and incident diabetes: current state of the evidence. Diabetes Care. 2008; 31(9):1898-904.
116. Sattar N, McConnachie A, Shaper AG, Blauw GJ, Buckley BM, de Craen AJ, Ford I, Forouhi NG, Freeman DJ, Jukema JW, Lennon L, Macfarlane PW, Murphy MB, Packard CJ, Stott DJ, Westendorp RG, Whincup PH, Shepherd J, Wannamethee SG. Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. Lancet. 2008 7;371(9628):1927-35.
117. Simmons RK, Alberti KG, Gale EA, Colagiuri S, Tuomilehto J, Qiao Q, Ramachandran A, Tajima N, Brajkovich Mirchov I, Ben-Nakhi A, Reaven G, Hama Sambo B, Mendis S, Roglic G. The metabolic syndrome: useful concept or clinical tool? Report of a WHO Expert Consultation. Diabetologia. 2009 Dec 11. [Epub ahead of print]
118. de Zeeuw D, Bakker SJ. Does the metabolic syndrome add to the diagnosis and treatment of cardiovascular disease? Nat Clin Pract Cardiovasc Med. 2008; 5 Suppl 1:S10-4.
119. Gale EA. The myth of the metabolic syndrome. Diabetologia. 2005; 48(9):1679-83.
120. Chávez-Tapia NN, Uribe M, Ponciano-Rodríguez G, Medina-Santillán R, Méndez-Sánchez N. New insights into the pathophysiology of nonalcoholic fatty liver disease. Ann Hepatol. 2009;8 Suppl 1:S9-17.
121. Marchesini G, Moscatiello S, Di Domizio S, Forlani G. Obesity-associated liver disease. J Clin Endocrinol Metab. 2008; 93(11 Suppl 1):S74-80.
122. Abdelmalek MF, Diehl AM. Nonalcoholic fatty liver disease as a complication of insulin resistance. Med Clin North Am 2007; 91(6), 1125-49.
123. Fabbrini E, Sullivan S, Klein S. Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. Hepatology. 2010; 51(2):679-89.
124. Zelman S. The liver in obesity. AMA Arch Intern Med. 1952; 90(2), 141-56.
125. Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc. 1980; 55(7):434-8.
126. Hoyumpa AM Jr, Greene HL, Dunn GD, Schenker S. Fatty liver: biochemical and clinical considerations. Am J Dig Dis. 1975; 20(12):1142-70.
127. Yeh MM, Brunt EM. Pathology of nonalcoholic fatty liver disease. Am J Clin Pathol. 2007 128(5), 837-47.

128. Brunt EM. Nonalcoholic steatohepatitis. Semin Liver Dis. 2004 24(1), 3-20.
129. Burt AD, Mutton A, Day CP. Diagnosis and interpretation of steatosis and steatohepatitis. Semin Diagn Pathol. 1998 15(4), 246-58.
130. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology. 1999; 116(6):1413-9.
131. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med. 2002 18;346(16), 1221-31.
132. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, Ferrell LD, Liu YC, Torbenson MS, Unalp-Arida A, Yeh M, McCullough AJ, Sanyal AJ; Nonalcoholic Steatohepatitis Clinical Research Network. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005; 41(6):1313-21.
133. Qureshi K, Abrams GA. Metabolic liver disease of obesity and role of adipose tissue in the pathogenesis of nonalcoholic fatty liver disease. World J Gastroenterol. 2007 14;13(26), 3540-53.
134. Clark JM. The epidemiology of nonalcoholic fatty liver disease in adults. J Clin Gastroenterol. 2006 40 (3 Suppl 1), S5-10.
135. Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. Hepatology. 2006 43 (2 Suppl 1), S99-S112.
136. Angulo P. GI epidemiology: nonalcoholic fatty liver disease. Aliment Pharmacol Ther. 2007 15;25(8), 883-9.
137. Bellentani S, Tiribelli C, Saccoccio G, Sodde M, Fratti N, De Martin C, Cristianini G. Prevalence of chronic liver disease in the general population of northern Italy: the Dionysos Study. Hepatology. 1994; 20(6):1442-9.
138. Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. Hepatology. 2005; 42(1):44-52.
139. Nomura H, Kashiwagi S, Hayashi J, Kajiyama W, Tani S, Goto M. Prevalence of fatty liver in a general population of Okinawa, Japan. Jpn J Med. 1988; 27(2):142-9.
140. Jimba S, Nakagami T, Takahashi M, Wakamatsu T, Hirota Y, Iwamoto Y, Wasada T. Prevalence of non-alcoholic fatty liver disease and its association with impaired glucose metabolism in Japanese adults. Diabet Med. 2005; 22(9):1141-5.
141. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology. 2004; 40(6):1387-95.
142. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterol. 2003; 98(5), 960-7.
143. Clark JM, Brancati FL, Diehl AM. Nonalcoholic fatty liver disease. Gastroenterology. 2002 122(6), 1649-57.

144. Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. Hepatology. 2003 37(5), 1202-19.
145. Beymer C, Kowdley KV, Larson A, Edmonson P, Dellinger EP, Flum DR. Prevalence and predictors of asymptomatic liver disease in patients undergoing gastric bypass surgery. Arch Surg. 2003; 138(11):1240-4.
146. Machado M, Marques-Vidal P, Cortez-Pinto H. Hepatic histology in obese patients undergoing bariatric surgery. J Hepatol. 2006 45(4), 600-6.
147. Nobili V, Alisi A, Raponi M. Pediatric non-alcoholic fatty liver disease: preventive and therapeutic value of lifestyle intervention. World J Gastroenterol. 2009 28;15(48):6017-22.
148. Day CP. Genes or environment to determine alcoholic liver disease and non-alcoholic fatty liver disease. Liver Int. 2006 26(9), 1021-8.
149. Sanyal AJ. Nonalcoholic fatty liver disease in the Indian subcontinent: a medical consequence of globalization? Indian J Gastroenterol 2001 20(6), 215-6.
150. Weston SR, Leyden W, Murphy R, Bass NM, Bell BP, Manos MM, Terrault NA. Racial and ethnic distribution of nonalcoholic fatty liver in persons with newly diagnosed chronic liver disease. Hepatology. 2005; 41(2):372-9.
151. Chitturi S, Farrell GC, Hashimoto E, Saibara T, Lau GK, Sollano JD; Asia-Pacific Working Party on NAFLD. Non-alcoholic fatty liver disease in the Asia-Pacific region: definitions and overview of proposed guidelines. J Gastroenterol Hepatol. 2007; 22(6):778-87.
152. Angulo P. Long-term mortality in nonalcoholic fatty liver disease: is liver histology of any prognostic significance? Hepatology. 2010; 51(2):373-5.
153. Day CP. Natural history of NAFLD: remarkably benign in the absence of cirrhosis. Gastroenterology. 2005 129(1), 375-8.
154. Falck-Ytter Y, Younossi ZM, Marchesini G, McCullough AJ. Clinical features and natural history of nonalcoholic steatosis syndromes. Semin Liver Dis. 2001; 21(1):17-26.
155. Ratziu V, Poynard T. Assessing the outcome of nonalcoholic steatohepatitis? It's time to get serious. Hepatology. 2006 44(4):802-5.
156. Siegel AB, Zhu AX. Metabolic syndrome and hepatocellular carcinoma: two growing epidemics with a potential link. Cancer. 2009 15;115(24):5651-61.
157. Ong JP, Younossi ZM. Epidemiology and natural history of NAFLD and NASH. Clin Liver Dis. 2007 11(1), 1-16.
158. Ekstedt M, Franzén LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, Kechagias S. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology 2006; 44(4):865-73.
159. Söderberg C, Stål P, Askling J, Glaumann H, Lindberg G, Marmur J, Hultcrantz R. Decreased survival of subjects with elevated liver function tests during a 28-year follow-up. Hepatology. 2010; 51(2):595-602.

160. Maheshwari A, Thuluvath PJ. Cryptogenic cirrhosis and NAFLD: are they related? Am J Gastroenterol. 2006 101(3), 664-8.
161. Day CP, James OF. Steatohepatitis: a tale of two "hits"? Gastroenterology. 1998 114(4), 842-5.
162. Day CP. Pathogenesis of steatohepatitis. Best Pract Res Clin Gastroenterol. 2002 16(5), 663-78.
163. Day CP. From fat to inflammation. Gastroenterology. 2006 130(1), 207-10.
164. Nielsen S, Guo Z, Johnson CM, Hensrud DD, Jensen MD. Splanchnic lipolysis in human obesity. J Clin Invest. 2004; 113(11):1582-8.
165. Gibbons G. Old fat, make way for new fat. Nat Med. 2005; 11(7):722-3.
166. Roden M. Mechanisms of Disease: hepatic steatosis in type 2 diabetes--pathogenesis and clinical relevance. Nat Clin Pract Endocrinol Metab. 2006; 2(6):335-48.
167. Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J Clin Invest. 2005; 115(5):1343-51.
168. Younossi ZM. Review article: current management of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2008; 28(1):2-12.
169. Vuppalanchi R, Chalasani N. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: Selected practical issues in their evaluation and management. Hepatology. 2009; 49(1):306-17.
170. Marra F, Bertolani C. Adipokines in liver diseases. Hepatology. 2009 Sep;50(3):957-69.
171. Ikejima K, Okumura K, Kon K, Takei Y, Sato N. Role of adipocytokines in hepatic fibrogenesis. J Gastroenterol Hepatol. 2007; 22 Suppl 1:S87-92.
172. Li Z, Diehl AM. Innate immunity in the liver. Curr Opin Gastroenterol. 2003 19(6), 565-71.
173. Tomita K, Tamiya G, Ando S, Ohsumi K, Chiyo T, Mizutani A, Kitamura N, Toda K, Kaneko T, Horie Y, Han JY, Kato S, Shimoda M, Oike Y, Tomizawa M, Makino S, Ohkura T, Saito H, Kumagai N, Nagata H, Ishii H, Hibi T. Tumour necrosis factor alpha signalling through activation of Kupffer cells plays an essential role in liver fibrosis of non-alcoholic steatohepatitis in mice. Gut. 2006; 55(3):415-24.
174. Valenti L, Rametta R, Dongiovanni P, Maggioni M, Fracanzani AL, Zappa M, Lattuada E, Roviaro G, Fargion S. Increased expression and activity of the transcription factor FOXO1 in nonalcoholic steatohepatitis. Diabetes. 2008; 57(5):1355-62.
175. Khashab M, Chalasani N. Use of insulin sensitizers in NASH. Endocrinol Metab Clin North Am 2007 36(4), 1067-87.
176. Angelico F, Burattin M, Alessandri C, Del Ben M, Lirussi F. Drugs improving insulin resistance for non-alcoholic fatty liver disease and/or non-alcoholic steatohepatitis. Cochrane Database Syst Rev. 2007 24;(1):CD005166.
177. Haukeland JW, Konopski Z, Eggesbø HB, von Volkmann HL, Raschpichler G, Bjøro K, Haaland T, Løberg EM, Birkeland K. Metformin in patients with non-alcoholic fatty liver disease: a randomized, controlled trial. Scand J Gastroenterol. 2009;44(7):853-60.

178. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Zoli M, Melchionda N. Metformin in non-alcoholic steatohepatitis. Lancet. 2001 15;358(9285):893-4.
179. Bugianesi E, Gentilcore E, Manini R, Natale S, Vanni E, Villanova N, David E, Rizzetto M, Marchesini G. A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. Am J Gastroenterol. 2005; 100(5):1082-90.
180. McCullough AJ. Thiazolidinediones for nonalcoholic steatohepatitis-promising but not ready for prime time. N Engl J Med 2006 30;355(22), 2361-3.
181. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, Balas B, Gastaldelli A, Tio F, Pulcini J, Berria R, Ma JZ, Dwivedi S, Havranek R, Fincke C, DeFronzo R, Bannayan GA, Schenker S, Cusi K. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med. 2006 30;355(22):2297-307.
182. Ratziu V, Charlotte F, Bernhardt C, Giral P, Halbron M, Lenaour G, Hartmann-Heurtier A, Bruckert E, Poynard T; LIDO Study Group. Long-term efficacy of rosiglitazone in nonalcoholic steatohepatitis: results of the fatty liver improvement by rosiglitazone therapy (FLIRT 2) extension trial. Hepatology. 2010; 51(2):445-53.
183. Henriksen JH, Ring-Larsen H. Rosiglitazone: Possible complications and treatment of non-alcoholic steatohepatitis (NASH). J Hepatol 2008 48(1):174-6.
184. McDonough AK, Rosenthal RS, Cao X, Saag KG. The effect of thiazolidinediones on BMD and osteoporosis. Nat Clin Pract Endocrinol Metab. 2008; 4(9):507-13.
185. Juurlink DN, Gomes T, Lipscombe LL, Austin PC, Hux JE, Mamdani MM. Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study. BMJ. 2009 Aug 18;339:b2942. doi: 10.1136/bmj.b2942.
186. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ; RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009 20;373(9681):2125-35.
187. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007 14;356(24):2457-71.
188. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. CMAJ. 2009 6;180(1):32-9..
189. Komajda M, McMurray JJ, Beck-Nielsen H, Gomis R, Hanefeld M, Pocock SJ, Curtis PS, Jones NP, Home PD. Heart failure events with rosiglitazone in type 2 diabetes: data from the RECORD clinical trial. Eur Heart J. 2010 Jan 29. [Epub ahead of print]
190. Kaul S, Bolger AF, Herrington D, Giugliano RP, Eckel RH. Thiazolidinedione Drugs and Cardiovascular Risks. A Science Advisory From the American Heart Association and American College of Cardiology Foundation. Circulation. 2010 Feb 23. [Epub ahead of print]

191. Shaffer EA. Gallstone disease: Epidemiology of gallbladder stone disease. Best Pract Res Clin Gastroenterol. 2006; 20(6):981-96.
192. Marschall HU, Einarsson C. Gallstone disease. J Intern Med. 2007; 261(6):529-42.
193. Shaffer EA.Epidemiology and risk factors for gallstone disease: has the paradigm changed in the 21st century? Curr Gastroenterol Rep. 2005; 7(2):132-40.
194. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. JAMA. 1999 27;282(16):1523-9.
195. 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(3):652-8.
196. 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 31;321(9):563-9.
197. Tucker LE, Tangedahl TN, Newmark SR. Prevalence of gallstones in obese Caucasian American women. Int J Obes. 1982; 6(3):247-51.
198. Attili AF, Capocaccia R, Carulli N, Festi D, et el. Factors associated with gallstone disease in the MICOL experience. Multicenter Italian Study on Epidemiology of Cholelithiasis. Hepatology. 1997; 26(4):809-18.
199. Kaechele V, Wabitsch M, Thiere D, Kessler AL, Haenle MM, Mayer H, Kratzer W. Prevalence of gallbladder stone disease in obese children and adolescents: influence of the degree of obesity, sex, and pubertal development. J Pediatr Gastroenterol Nutr. 2006; 42 (1):66-70.
200. Heaton KW, Braddon FEM, Emmett PM, Mountford RA, Hughes AP, Bolton CH, et al. Why domen get gallstones? Roles of abdominal fat and hyperinsulinaemia. Eur J Gastroenterol Hepatol 1991; 3:745-51.
201. Ruhl CE, Everhart JE. Relationship of serum leptin concentration and other measures of adiposity with gallbladder disease. Hepatology. 2001; 34(5):877-83.
202. 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(1):38-44.
203. Tsai CJ, Leitzmann MF, Willett WC, Giovannucci EL. Central adiposity, regional fat distribution, and the risk of cholecystectomy in women. Gut. 2006; 55(5):708-14.
204. Dittrick GW, Thompson JS, Campos D, Bremers D, Sudan D. Gallbladder pathology in morbid obesity. Obes Surg. 2005; 15 (2):238-42.
205. Tsai CJ. Steatocholecystitis and fatty gallbladder disease. Dig Dis Sci. 2009 Sep;54(9):1857-63.
206. Liew PL, Lee WJ, Wang W, Lee YC, Chen WY, Fang CL, Huang MT. Fatty liver disease: predictors of nonalcoholic steatohepatitis and gallbladder disease in morbid obesity. Obes Surg. 2008; 18(7):847-53.
207. Liu B, Balkwill A, Spencer E, Beral V; Million Women Study Collaborators. Relationship between body mass index and length of hospital stay for gallbladder disease. J Public Health (Oxf). 2008; 30(2):161-6.

208. Mabee TM, Meyer P, DenBesten L, Mason EE. The mechanism of increased gallstone formation in obese human subjects. Surgery. 1976; 79(4):460-8.
209. Madura JA, Loomis RC, Harris RA, Grosfeld J, Tompkins RK. Relationship of obesity to bile lithogenicity in man. Ann Surg. 1979; 189(1):106-11.
210. Angelin B, Einarsson K, Ewerth S, Leijd B. Biliary lipid composition in obesity. Scand J Gastroenterol. 1981; 16(8):1015-9.
211. Petroni ML. Review article: gall-bladder motor function in obesity. Aliment Pharmacol Ther. 2000; 14 Suppl 2:48-50.
212. Mathus-Vliegen EM, Van Ierland-Van Leeuwen ML, Terpstra A. Determinants of gallbladder kinetics in obesity. Dig Dis Sci. 2004; 49(1):9-16.
213. Vezina WC, Paradis RL, Grace DM, Zimmer RA, Lamont DD, Rycroft KM, King ME, Hutton LC, Chey WY. Increased volume and decreased emptying of the gallbladder in large (morbidly obese, tall normal, and muscular normal) people. Gastroenterology. 1990; 98(4):1000-7.
214. Palasciano G, Serio G, Portincasa P, Palmieri V, Fanelli M, Velardi A, Calo' Gabrieli B, Vinciguerra V. Gallbladder volume in adults, and relationship to age, sex, body mass index, and gallstones: a sonographic population study. Am J Gastroenterol. 1992; 87(4):493-7.
215. Hendel HW, Højgaard L, Andersen T, Pedersen BH, Paloheimo LI, Rehfeld JF, Gotfredsen A, Rasmussen MH. Fasting gall bladder volume and lithogenicity in relation to glucose tolerance, total and intra-abdominal fat masses in obese non-diabetic subjects. Int J Obes Relat Metab Disord. 1998; 22(4):294-302.
216. Caroli-Bosc FX, Pugliese P, Peten EP, Demarquay JF, Montet JC, Hastier P, Staccini P, Delmont JP. Gallbladder volume in adults and its relationship to age, sex, body mass index, body surface area and gallstones. An epidemiologic study in a nonselected population in France. Digestion. 1999; 60(4):344-8.
217. Nepokroeff CM, Lakshmanan MR, Ness GC, Dugan RE, Porter JW. Regulation of the diurnal rhythm of rat liver beta-hydroxy-beta-methylglutaryl coenzmye A reductase activity by insulin, glucagon, cyclic AMP and hydrocortisone. Arch Biochem Biophys. 1974; 160(2):387-96.
218. Chait A, Bierman EL, Albers JJ. Low-density lipoprotein receptor activity in cultured human skin fibroblasts. Mechanism of insulin-induced stimulation. J Clin Invest. 1979; 64(5):1309-19.
219. Gielkens HA, Lam WF, Coenraad M, Frölich M, van Oostayen JA, Lamers CB, Masclee AA. Effect of insulin on basal and cholecystokinin-stimulated gallbladder motility in humans. J Hepatol. 1998; 28(4):595-602.
220. Nakeeb A, Comuzzie AG, Al-Azzawi H, Sonnenberg GE, Kissebah AH, Pitt HA. Insulin resistance causes human gallbladder dysmotility. J Gastrointest Surg. 2006; 10(7):940-8; discussion 948-9.

221. Gebhard RL, Prigge WF, Ansel HJ, Schlasner L, Ketover SR, Sande D, Holtmeier K, Peterson FJ. The role of gallbladder emptying in gallstone formation during diet-induced rapid weight loss. Hepatology. 1996; 24(3):544-8.
222. Festi D, Colecchia A, Orsini M, Sangermano A, Sottili S, Simoni P, Mazzella G, Villanova N, Bazzoli F, Lapenna D, Petroni ML, Pavesi S, Neri M, Roda E. Gallbladder motility and gallstone formation in obese patients following very low calorie diets. Use it (fat) to lose it (well). Int J Obes Relat Metab Disord. 1998; 22(6):592-600.
223. Zapata R, Severín C, Manríquez M, Valdivieso V. Gallbladder motility and lithogenesis in obese patients during diet-induced weight loss. Dig Dis Sci. 2000; 45(2):421-8.
224. Kiewiet RM, Durian MF, van Leersum M, Hesp FL, van Vliet AC. Gallstone formation after weight loss following gastric banding in morbidly obese Dutch patients. Obes Surg 2006; 16(5):592-6.
225. Li VK, Pulido N, Martinez-Suartez P, Fajnwaks P, Jin HY, Szomstein S, Rosenthal RJ. Symptomatic gallstones after sleeve gastrectomy. Surg Endosc. 2009 Apr 4. [Epub ahead of print]
226. Li VK, Pulido N, Fajnwaks P, Szomstein S, Rosenthal R, Martinez-Duartez P. Predictors of gallstone formation after bariatric surgery: a multivariate analysis of risk factors comparing gastric bypass, gastric banding, and sleeve gastrectomy. Surg Endosc. 2009; 23(7):1640-4.
227. Syngal S, Coakley EH, Willett WC, Byers T, Williamson DF, Colditz GA. Long-term weight patterns and risk for cholecystectomy in women. Ann Intern Med 1999; 130:471–477.
228. 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; 18(12):1532-8.
229. Tucker ON, Fajnwaks P, Szomstein S, Rosenthal RJ. Is concomitant cholecystectomy necessary in obese patients undergoing laparoscopic gastric bypass surgery? Surg Endosc. 2008; 22(11):2450-4.
230. Fuller W, Rasmussen JJ, Ghosh J, Ali MR. Is routine cholecystectomy indicated for asymptomatic cholelithiasis in patients undergoing gastric bypass? Obes Surg. 2007 Jun;17(6):747-51.
231. Randi G, Malvezzi M, Levi F, Ferlay J, Negri E, Franceschi S, La Vecchia C. Epidemiology of biliary tract cancers: an update. Ann Oncol. 2009; 20(1):146-59.
232. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. Int J Cancer. 2006 1;118(7):1591-602.
233. Larsson SC, Wolk A. Obesity and the risk of gallbladder cancer: a meta-analysis. Br J Cancer. 2007 7;96(9):1457-61.
234. Practice Committee of American Society for Reproductive Medicine. Obesity and reproduction: an educational bulletin. Fertil Steril. 2008; 90(5 Suppl):S21-9.
235. Budak E, Fernández Sánchez M, Bellver J, Cerveró A, Simón C, Pellicer A. Interactions of the hormones leptin, ghrelin, adiponectin, resistin, and PYY3-36 with the reproductive system. Fertil Steril. 2006; 85(6):1563-81.

236. Blüher S, Mantzoros CS. Leptin in reproduction. Curr Opin Endocrinol Diabetes Obes. 2007 14(6):458-64.
237. Israel D, Chua S Jr. Leptin receptor modulation of adiposity and fertility. Trends Endocrinol Metab. 2010; 21 (1):10-6.
238. Fischer-Posovszky P, Wabitsch M, Hochberg Z. Endocrinology of adipose tissue - an update. Horm Metab Res. 2007 39(5): 314-21.
239. Haffner SM. Sex hormones, obesity, fat distribution, type 2 diabetes and insulin resistance: epidemiological and clinical correlation. Int J Obes Relat Metab Disord. 2000 24 Suppl 2: S56-8.
240. Tchernof A, Després JP. Sex steroid hormones, sex hormone-binding globulin, and obesity in men and women. Horm Metab Res. 2000; 32(11-12): 526-36.
241. Weaver JU, Holly JM, Kopelman PG, Noonan K, Giadom CG, White N, Virdee S, Wass JA. Decreased sex hormone binding globulin (SHBG) and insulin-like growth factor binding protein (IGFBP-1) in extreme obesity. Clin Endocrinol (Oxf). 1990; 33(3):415-22.
242. Kolotkin RL, Binks M, Crosby RD, Østbye T, Gress RE, Adams TD. Obesity and sexual quality of life. Obesity (Silver Spring). 2006; 14(3):472-9.
243. Shah MB. Obesity and sexuality in women. Obstet Gynecol Clin North Am. 2009; 36(2):347-60.
244. Rogers J, Mitchell GW Jr. The relation of obesity to menstrual disturbances. N Engl J Med. 1952 10;247 (2):53-5.
245. Frisch RE, McArthur JW. Menstrual cycles: fatness as a determinant of minimum weight for height necessary for their maintenance or onset. Science 1974;185:949–51.
246. Casanueva FF, Dieguez C. Neuroendocrine regulation and actions of leptin. Front Neuroendocrinol. 1999 20, 317-63.
247. Wang Y. Is obesity associated with early sexual maturation? A comparison of the association in American boys versus girls. Pediatrics. 2002 110(5):903-10.
248. Kaplowitz PB. Link between body fat and the timing of puberty. Pediatrics 2008 121 (Suppl 3), S208-17.
249. Ahmed ML, Ong KK, Dunger DB. Childhood obesity and the timing of puberty. Trends Endocrinol. Metab. 2009 20, 237-42.
250. Roa J, García-Galiano D, Castellano JM, Gaytan F, Pinilla L, Tena-Sempere M. Metabolic control of puberty onset: New players, new mechanisms. Mol Cell Endocrinol. 2009 Dec 21. [Epub ahead of print]
251. Biro FM, Khoury P, Morrison JA. Influence of obesity on timing of puberty. Int J Androl. 2006; 29(1):272-7; discussion 286-90.
252. Himes JH. Examining the evidence for recent secular changes in the timing of puberty in U.S. children in light of increases in the prevalence of obesity. Mol Cell Endocrinol 2006; 254–5:12–3.
253. Bray GA. Obesity and reproduction. Hum Reprod. 1997 12 Suppl 1:26-32.

254. Kok HS, van Asselt KM, van der Schouw YT, van der Tweel I, Peeters PH, Wilson PW, Pearson PL, Grobbee DE. Heart disease risk determines menopausal age rather than the reverse. J Am Coll Cardiol. 2006 16;47 (10):1976-83.
255. Lash MM, Armstrong A. Impact of obesity on women's health. Fertil Steril. 2009; 91(5):1712-6.
256. Metwally M, Li TC, Ledger WL. The impact of obesity on female reproductive function. Obes Rev. 2007; 8(6):515-23.
257. Lake JK, Power C, Cole TJ. Women's reproductive health: the role of body mass index in early and adult life. Int J Obes Relat Metab Disord. 1997 21(6):432-8.
258. The Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004; 19(1):41-7.
259. Diamanti-Kandarakis E. Role of obesity and adiposity in polycystic ovary syndrome. Int J Obes (Lond). 2007; 31 Suppl 2:S8-13.
260. Green BB, Weiss NS, Daling JR. Risk of ovulatory infertility in relation to body weight. Fertil Steril 1988; 50: 721-6.
261. Grodstein F, Goldman MB, Cramer DW. Body mass index and ovulatory infertility. Epidemiology 1994; 5: 247-50.
262. Rich-Edwards JW, Goldman MB, Willett WC, Hunter DJ, Stampfer MJ, Colditz GA, Manson JE. Adolescent body mass index and infertility caused by ovulatory disorder. Am J Obstet Gynecol. 1994; 171(1):171-7.
263. Jensen TK, Scheike T, Keiding N, Schaumburg I, Grandjean P. Fecundability in relation to body mass and menstrual cycle patterns. Epidemiology 1999; 10: 422-8.
264. Ramlau-Hansen CH, Thulstrup AM, Nohr EA, Bonde JP, Sorensen TIA, Olsen J. Subfecundity in overweight and obese couples. Hum Reprod 2007; 22:1634–7.
265. Pasquali R, Pelusi C, Genghini S, Cacciari M, Gambineri A. Obesity and reproductive disorders in women. Hum Reprod Update. 2003; 9(4):359-72.
266. Colman E. Obesity in the Paleolithic era? The Venus of Willendorf. Endocr Pract 1998; 4(1): 58-59.
267. Christopoulou-Aletra H, Papavramidou N, Pozzilli P. Obesity in the Neolithic era: a Greek female figurine. Obes Surg. 2006; 16(8):1112-4.
268. Loveland JB, McClamrock HD, Malinow AM, Sharara FI. Increased body mass index has a deleterious effect on in vitro fertilization outcome. J Assist Reprod Genet 2001; 18: 382-6.
269. Fedorcsak P, Storeng R, Dale PO, Tanbo T, Abyholm T. Obesity is a risk factor for early pregnancy loss after IVF or ICSI. Acta Obstet Gynecol Scand 2000; 79: 43-8.
270. Lintsen AM, Pasker-de Jong PC, de Boer EJ, Burger CW, Jansen CA, Braat DD, van Leeuwen FE. Effects of subfertility cause, smoking and body weight on the success rate of IVF. Hum Reprod 2005; 20: 1867-75.

271. Fedorcsak P, Dale PO, Storeng R, Ertzeid G, Bjercke S, Oldereid N, Omland AK, Abyholm T, Tanbo T. Impact of overweight and underweight on assisted reproduction treatment. Hum Reprod 2004; 19: 2523-8.
272. Dokras A, Baredziak L, Blaine J, Syrop C, VanVoorhis BJ, Sparks A. Obstetric outcomes after in vitro fertilization in obese and morbidly obese women. Obstet Gynecol 2006;108:61–9.
273. Imani B, Eijkemans MJ, Faessen GH, Bouchard P, Giudice LC, Fauser BC. Prediction of the individual follicle-stimulating hormone threshold for gonadotropin induction of ovulation in normogonadotropic anovulatory infertility: an approach to increase safety and efficiency. Fertil Steril 2002;77:83–90.
274. Wang JX, Davies M, Norman RJ. Body mass and probability of pregnancy during assisted reproduction treatment: retrospective study. BMJ 2000; 321: 1320-1.
275. Awartani KA, Nahas S, Al Hassan SH, Al Deery MA, Coskun S. Infertility treatment outcome in sub groups of obese population. Reprod Biol Endocrinol. 2009 27;7:52.
276. Norman RJ, Noakes M, Wu R, Davies MJ, Mora L, Wang JX. Improving reproductive performance in overweight/obese women with effective weight management. Hum Reprod Update 2004;10: 267-80.
277. Dixit A, Girling JC. Obesity and pregnancy. J Obstet Gynaecol. 2008; 28(1):14-23.
278. Joy S, Istwan N, Rhea D, Desch C, Stanziano G. The impact of maternal obesity on the incidence of adverse pregnancy outcomes in high-risk term pregnancies. Am J Perinatol. 2009; 26(5):345-9.
279. Modesitt SC, van Nagell JR Jr. The impact of obesity on the incidence and treatment of gynecologic cancers: a review. Obstet Gynecol Surv. 2005; 60(10):683-92.
280. Bray GA. The underlying basis for obesity: relationship to cancer. J Nutr. 2002 132(11 Suppl): 3451S-5.
281. Fader AN, Arriba LN, Frasure HE, von Gruenigen VE. Endometrial cancer and obesity: epidemiology, biomarkers, prevention and survivorship. Gynecol Oncol. 2009; 114(1):121-7.
282. Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, Manson JE, Li J, Ho GY, Xue X, Anderson GL, Kaplan RC, Harris TG, Howard BV, Wylie-Rosett J, Burk RD, Strickler HD. Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. J Natl Cancer Inst. 2009 7;101(1):48-60.
283. Laron, Z. Is obesity associated with early sexual maturation? Pediatrics 2004 113, 171-2.
284. He Q, Karlberg J. BMI in childhood and its association with height gain, timing of puberty, and final height. Pediatr Res. 2001 49(2): 244-51.
285. Karpati AM, Rubin CH, Kieszak SM, Marcus M, Troiano RP. Stature and pubertal stage assessment in American boys: the 1988-1994 Third National Health and Nutrition Examination Survey. J Adolesc Health. 2002 Mar;30(3):205-12.
286. Denzer C, Weibel A, Muche R, Karges B, Sorgo W, Wabitsch M. Pubertal development in obese children and adolescents. Int J Obes (Lond). 2007; 31(10):1509-19.

287. Pasquali R. Obesity and androgens: facts and perspectives. Fertil Steril 2006; 85:1319-40.
288. Hammoud AO, Gibson M, Peterson CM, Meikle AW, Carrell DT. Impact of male obesity on infertility: a critical review of the current literature. Fertil Steril. 2008 Oct;90(4):897-904.
289. Loret de Mola JR. Obesity and its relationship to infertility in men and women. Obstet Gynecol Clin North Am. 2009; 36(2):333-46.
290. Goulis DG, Tarlatzis BC. Metabolic syndrome and reproduction: I. testicular function. Gynecol Endocrinol. 2008; 24(1):33-9.
291. Sallmén M, Sandler DP, Hoppin JA, Blair A, Baird DD. Reduced fertility among overweight and obese men. Epidemiology. 2006; 17(5):520-3.
292. Ghiyath Shayeb G, Bhattacharya S. Male obesity and reproductive potential. The British Journal of Diabetes & Vascular Disease 2009; 9: 7-12.
293. Hammoud AO, Wilde N, Gibson M, Parks A, Carrell DT, Meikle AW. Male obesity and alteration in sperm parameters. Fertil Steril. 2008; 90(6):2222-5.
294. Jarow JP, Kirkland J, Koritnik DR, Cefalu WT. Effect of obesity and fertility status on sex steroid levels in men. Urology 1993; 42:171-4.
295. Jung A, Schill WB. Male infertility. Current life style could be responsible for infertility. MMW Fortschr Med 2000; 142:31-3.
296. Freedland SJ, Platz EA. Obesity and prostate cancer: making sense out of apparently conflicting data. Epidemiol Rev. 2007;29:88-97.
297. Hsing AW, Sakoda LC, Chua S Jr. Obesity, metabolic syndrome, and prostate cancer. Am J Clin Nutr. 2007 Sep;86(3):s843-57.
298. Wright ME, Chang SC, Schatzkin A, Albanes D, Kipnis V, Mouw T, Hurwitz P, Hollenbeck A, Leitzmann MF. Prospective study of adiposity and weight change in relation to prostate cancer incidence and mortality. Cancer. 2007 15;109(4):675-84.
299. Gong Z, Neuhouser ML, Goodman PJ, Albanes D, Chi C, Hsing AW, Lippman SM, Platz EA, Pollak MN, Thompson IM, Kristal AR. Obesity, diabetes, and risk of prostate cancer: results from the prostate cancer prevention trial. Cancer Epidemiol Biomarkers Prev. 2006; 15(10):1977-83.
300. Rodriguez C, Freedland SJ, Deka A, Jacobs EJ, McCullough ML, Patel AV, Thun MJ, Calle EE. Body mass index, weight change, and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. Cancer Epidemiol Biomarkers Prev. 2007; 16(1):63-9.
301. Culp S, Porter M. The effect of obesity and lower serum prostate-specific antigen levels on prostate-cancer screening results in American men. BJU Int. 2009; 104(10):1457-61.
302. Efstathiou JA, Bae K, Shipley WU, Hanks GE, Pilepich MV, Sandler HM, Smith MR. Obesity and mortality in men with locally advanced prostate cancer: analysis of RTOG 85-31. Cancer. 2007 15;110(12):2691-9.
303. Mistry T, Digby JE, Desai KM, Randeva HS. Obesity and prostate cancer: a role for adipokines. Eur Urol. 2007; 52(1):46-53.

304. Atlantis E, Goldney RD, Wittert GA. Obesity and depression or anxiety. BMJ. 2009 6;339:b3868. doi:10.1136/bmj.b3868.
305. Blaine B. Does depression cause obesity? A meta-analysis of longitudinal studies of depression and weight control. J Health Psychol. 2008; 13(8):1190-7.
306. Kivimäki M, Lawlor DA, Singh-Manoux A, Batty GD, Ferrie JE, Shipley MJ, Nabi H, Sabia S, Marmot MG, Jokela M. Common mental disorder and obesity: insight from four repeat measures over 19 years: prospective Whitehall II cohort study. BMJ. 2009 6;339:b3765. doi: 10.1136/bmj.b3765.
307. Kivimäki M, Batty GD, Singh-Manoux A, Nabi H, Sabia S, Tabak AG, Akbaraly TN, Vahtera J, Marmot MG, Jokela M. Association between common mental disorder and obesity over the adult life course. Br J Psychiatry. 2009; 195(2):149-55.
308. Vogelzangs N, Kritchevsky SB, Beekman AT, Newman AB, Satterfield S, Simonsick EM, Yaffe K, Harris TB, Penninx BW. Depressive symptoms and change in abdominal obesity in older persons. Arch Gen Psychiatry. 2008; 65(12):1386-93.
309. Mooy JM, de Vries H, Grootenhuis PA, Bouter LM, Heine RJ. Major stressful life events in relation to prevalence of undetected type 2 diabetes: the Hoorn Study. Diabetes Care 2000 23(2):197-201.
310. Chandola T, Brunner E, Marmot M. Chronic stress at work and the metabolic syndrome: prospective study. BMJ 2006 4;332(7540):521-5.
311. Brunner EJ, Chandola T, Marmot MG. Prospective effect of job strain on general and central obesity in the Whitehall II Study. Am J Epidemiol 2007 1;165(7):828-37.
312. Serlachius A, Hamer M, Wardle J. Stress and weight change in university students in the United Kingdom. Physiol Behav 2007, 23;92(4):548-53.
313. Gariepy G, Nitka D, Schmitz N. The association between obesity and anxiety disorders in the population: a systematic review and meta-analysis. Int J Obes (Lond). 2009 Dec 8. [Epub ahead of print]
314. Atlantis E, Baker M. Obesity effects on depression: systematic review of epidemiological studies. Int J Obes (Lond). 2008; 32(6):881-91.
315. Onyike CU, Crum RM, Lee HB, Lyketsos CG, Eaton WW. Is obesity associated with major depression? Results from the Third National Health and Nutrition Examination Survey. Am J Epidemiol. 2003 15;158(12):1139-47.
316. Simon GE, Von Korff M, Saunders K, Miglioretti DL, Crane PK, van Belle G, Kessler RC. Association between obesity and psychiatric disorders in the US adult population. Arch Gen Psychiatry. 2006; 63(7):824-30.
317. Petry NM, Barry D, Pietrzak RH, Wagner JA. Overweight and obesity are associated with psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychosom Med. 2008; 70 (3):288-97.

318. Scott KM, Bruffaerts R, Simon GE, Alonso J, Angermeyer M, de Girolamo G, Demyttenaere K, Gasquet I, Haro JM, Karam E, Kessler RC, Levinson D, Medina Mora ME, Oakley Browne MA, Ormel J, Villa JP, Uda H, Von Korff M. Obesity and mental disorders in the general population: results from the world mental health surveys. Int J Obes (Lond). 2008; 32(1):192-200.

319. Zhao G, Ford ES, Dhingra S, Li C, Strine TW, Mokdad AH. Depression and anxiety among US adults: associations with body mass index. Int J Obes (Lond). 2009; 33(2):257-66.

320. Roberts RE, Kaplan GA, Shema SJ, Strawbridge WJ. Are the obese at greater risk for depression? Am J Epidemiol 2000; 152: 163-170.

321. Roberts RE, Strawbridge WJ, Deleger S, Kaplan GA. Are the fat more jolly? Ann Behav Med 2002; 24: 169-180.

322. Roberts RE, Deleger S, Strawbridge WJ, Kaplan GA. Prospective association between obesity and depression: evidence from the Alameda County Study. Int J Obes Relat Metab Disord 2003; 27: 514-21.

323. Herva A, Laitinen J, Miettunen J, Veijola J, Karvonen JT, Läksy K, Joukamaa M. Obesity and depression: results from the longitudinal Northern Finland 1966 Birth Cohort Study. Int J Obes (Lond). 2006; 30(3):520-7.

324. Crisp AH, McGuinness B. Jolly fat: relation between obesity and psychoneurosis in general population. Br Med J 1976; 1:7-9.

325. Crisp AH, Queenan M, Sittampaln Y, Harris G. 'Jolly fat' revisited. J Psychosom Res. 1980; 24(5):233-41.

326. Palinkas LA, Wingard DL, Barrett-Connor E. Depressive symptoms in overweight and obese older adults: a test of the "jolly fat" hypothesis. J Psychosom Res. 1996; 40(1):59-66.

327. Jansen A, Havermans R, Nederkoorn C, Roefs A. Jolly fat or sad fat? Subtyping non-eating disordered overweight and obesity along an affect dimension. Appetite. 2008; 51(3):635-40.

328. de Wit LM, van Straten A, van Herten M, Penninx BW, Cuijpers P. Depression and body mass index, a u-shaped association. BMC Public Health. 2009 13; 9:14.

329. Dixon JB, Dixon ME, O'Brien PE. Depression in association with severe obesity: changes with weight loss. Arch Intern Med 2003; 163: 2058-65.

330. Karlsson J, Taft C, Sjostrom L, Torgerson JS, Sullivan M. Psychosocial functioning in the obese before and after weight reduction: construct validity and responsiveness of the obesity related Problems scale. Int J Obes Relat Metab Disord 2003; 27: 617-30.

331. Vage V, Solhaug JH, Viste A, Bergsholm P, Wahl AK. Anxiety, depression and health-related quality of life after jejunoileal bypass: a 25-year follow-up study of 20 female patients. Obes Surg 2003; 13: 706-13.

332. Larsen JK, Geenen R, van Ramshorst B, Brand N, de Wit P, Stroebe W, van Doornen LJ. Psychosocial functioning before and after laparoscopic adjustable gastric banding: a cross-sectional study. Obes Surg. 2003; 13(4):629-36.

333. Schowalter M, Benecke A, Lager C, Heimbucher J, Bueter M, Thalheimer A, Fein M, Richard M, Faller H. Changes in depression following gastric banding: a 5- to 7-year prospective study. Obes Surg. 2008; 18 (3):314-20.
334. Zeller MH, Modi AC, Noll JG, Long JD, Inge TH. Psychosocial functioning improves following adolescent bariatric surgery. Obesity (Silver Spring). 2009; 17(5):985-90.
335. Legenbauer T, De Zwaan M, Benecke A, Muhlhans B, Petrak F, Herpertz S. Depression and Anxiety: Their Predictive Function for Weight Loss in Obese Individuals. Obes Facts 2009; 2(4):227-234.
336. Kyrou I, Tsigos C. Stress hormones: physiological stress and regulation of metabolism. Curr Opin Pharmacol. 2009; 9(6):787-93.
337. Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol 2009, 5(7):374-81.
338. Dallman MF, Pecoraro NC, La Fleur SE, Warne JP, Ginsberg AB, Akana SF, Laugero KC, Houshyar H, Strack AM, Bhatnagar S, Bell ME. Glucocorticoids, chronic stress, and obesity. Prog Brain Res. 2006; 153:75-105.
339. Torres SJ, Nowson CA. Relationship between stress, eating behavior, and obesity. Nutrition. 2007; 23(11-12):887-94.
340. Rosmond R, Dallman MF, Björntorp P. Stress-related cortisol secretion in men: relationships with abdominal obesity and endocrine, metabolic and hemodynamic abnormalities. J Clin Endocrinol Metab 1998, 83(6):1853-9.
341. Björntorp P. Do stress reactions cause abdominal obesity and comorbidities? Obes Rev 2001, 2(2):73-86.
342. Anagnostis P, Athyros VG, Tziomalos K, Karagiannis A, Mikhailidis DP. Clinical review: The pathogenetic role of cortisol in the metabolic syndrome: a hypothesis. J Clin Endocrinol Metab. 2009; 94(8):2692-701.
343. Adam TC, Epel ES. Stress, eating and the reward system. Physiol Behav 2007, 24; 91(4):449-58.
344. Gangwisch JE. Epidemiological evidence for the links between sleep, circadian rhythms and metabolism. Obes Rev. 2009; 10 Suppl 2:37-45.
345. Motivala SJ, Tomiyama AJ, Ziegler M, Khandrika S, Irwin MR. Nocturnal levels of ghrelin and leptin and sleep in chronic insomnia. Psychoneuroendocrinology. 2009; 34(4):540-5.
346. Strine TW, Mokdad AH, Balluz LS, Gonzalez O, Crider R, Berry JT, Kroenke K. Depression and anxiety in the United States: findings from the 2006 Behavioral Risk Factor Surveillance System. Psychiatr Serv. 2008; 59 (12):1383-90.
347. Atlantis E, Ball K. Association between weight perception and psychological distress. Int J Obes (Lond). 2008; 32(4):715-21.
348. Friedman KE, Ashmore JA, Applegate KL. Recent experiences of weight-based stigmatization in a weight loss surgery population: psychological and behavioral correlates. Obesity (Silver Spring). 2008; 16 Suppl 2:S69-74.

349. Malone M. Medications associated with weight gain. Ann Pharmacother. 2005; 39(12):2046-55.
350. World Health Organization. Diet, Nutrition and the Prevention of Chronic Diseases. 2003 Technical Report 916 WHO: Geneva.
351. Bianchini F, Kaaks R, Vainio H. Weight control and physical activity in cancer prevention. Obes Rev. 2002; 3(1):5-8.
352. Hjartåker A, Langseth H, Weiderpass E. Obesity and diabetes epidemics: cancer repercussions. Adv Exp Med Biol. 2008; 630:72-93.
353. World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, and Physical Activity, and the Prevention of Cancer: A Global Perspective. Washington, DC: AICR 2007.
354. Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D; Million Women Study Collaboration. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. BMJ 2007 1;335(7630):1134.
355. Calle EE. Obesity and cancer. BMJ 2007 1;335(7630): 1107-8.
356. Pischon T, Nöthlings U, Boeing H. Obesity and cancer. Proc Nutr Soc. 2008; 67(2):128-45.
357. Calle EE, Teras LR, Thun MJ. Obesity and mortality. N Engl J Med. 2005 17;353(20):2197-9.
358. 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 24;348(17):1625-38.
359. Berrington de González A, Spencer EA, Bueno-de-Mesquita HB, Roddam A, Stolzenberg-Solomon R, Halkjaer J, Tjønneland A, Overvad K, Clavel-Chapelon F, Boutron-Ruault MC, Boeing H, Pischon T, Linseisen J, Rohrmann S, Trichopoulou A, Benetou V, Papadimitriou A, Pala V, Palli D, Panico S, Tumino R, Vineis P, Boshuizen HC, Ocke MC, Peeters PH, Lund E, Gonzalez CA, Larrañaga N, Martinez-Garcia C, Mendez M, Navarro C, Quirós JR, Tormo MJ, Hallmans G, Ye W, Bingham SA, Khaw KT, Allen N, Key TJ, Jenab M, Norat T, Ferrari P, Riboli E. Anthropometry, physical activity, and the risk of pancreatic cancer in the European prospective investigation into cancer and nutrition. Cancer Epidemiol Biomarkers Prev. 2006; 15(5):879-85.
360. Friedenreich C, Cust A, Lahmann PH, Steindorf K, Boutron-Ruault MC, Clavel-Chapelon F, Mesrine S, Linseisen J, Rohrmann S, Boeing H, Pischon T, Tjønneland A, Halkjaer J, Overvad K, Mendez M, Redondo ML, Garcia CM, Larrañaga N, Tormo MJ, Gurrea AB, Bingham S, Khaw KT, Allen N, Key T, Trichopoulou A, Vasilopoulou E, Trichopoulos D, Pala V, Palli D, Tumino R, Mattiello A, Vineis P, Bueno-de-Mesquita HB, Peeters PH, Berglund G, Manjer J, Lundin E, Lukanova A, Slimani N, Jenab M, Kaaks R, Riboli E. Anthropometric factors and risk of endometrial cancer: the European prospective investigation into cancer and nutrition. Cancer Causes Control. 2007; 18(4):399-413.
361. Wang Y, Jacobs EJ, Patel AV, Rodríguez C, McCullough ML, Thun MJ, Calle EE. A prospective study of waist circumference and body mass index in relation to colorectal cancer incidence. Cancer Causes Control. 2008; 19(7):783-92.

362. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer. 2009; 16 (4):1103-23.
363. Czyzyk A, Szczepanik Z. Diabetes mellitus and cancer. Eur J Intern Med. 2000; 11(5):245-252.
364. Shoff SM, Newcomb PA. Diabetes, body size, and risk of endometrial cancer. Am J Epidemiol. 1998 Aug 1;148(3):234-40.
365. Hu FB, Manson JE, Liu S, Hunter D, Colditz GA, Michels KB, Speizer FE, Giovannucci E. Prospective study of adult onset diabetes mellitus (type 2) and risk of colorectal cancer in women. J Natl Cancer Inst. 1999 17;91(6):542-7.
366. Butler PC. Insulin glargine controversy: a tribute to the editorial team at Diabetologia. Diabetes. 2009 ;58 (11):2427-8.
367. Smith U, Gale EA. Does diabetes therapy influence the risk of cancer? Diabetologia. 2009; 52(9):1699-708.
368. de Miguel-Yanes JM, Meigs JB. When "flawed" translates into "flood": the unproven association between cancer incidence and glargine insulin therapy. Oncologist. 2009; 14(12):1175-7.
369. Ehninger G, Schmidt AH. Putting insulin glargine and malignancies into perspective. The Oncologist 2009;14:1169-74.
370. Vigneri R. Diabetes: diabetes therapy and cancer risk. Nat Rev Endocrinol. 2009; 5(12):651-2.
371. Hemkens LG, Grouven U, Bender R, Günster C, Gutschmidt S, Selke GW, Sawicki PT. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. Diabetologia. 2009; 52(9):1732-44.
372. Jonasson JM, Ljung R, Talbäck M, Haglund B, Gudbjörnsdòttir S, Steineck G. Insulin glargine use and short-term incidence of malignancies-a population-based follow-up study in Sweden. Diabetologia. 2009; 52(9):1745-54.
373. Colhoun HM; SDRN Epidemiology Group. Use of insulin glargine and cancer incidence in Scotland: A study from the Scottish Diabetes Research Network Epidemiology Group. Diabetologia 2009; 52: 1755-1765.
374. Home PD, Lagarenne P. Combined randomised controlled trial experience of malignancies in studies using insulin glargine. Diabetologia. 2009; 52(12):2499-506.
375. Dejgaard A, Lynggaard H, Råstam J, Krogsgaard Thomsen M. No evidence of increased risk of malignancies in patients with diabetes treated with insulin detemir: a meta-analysis. Diabetologia. 2009; 52(12):2507-12.
376. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia. 2009; 52(9):1766-77.
377. Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. Gastroenterology. 2009; 137(2):482-8.
378. Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. JAMA. 2006 12;296(2):193-201.

379. Thygesen LC, Grønbaek M, Johansen C, Fuchs CS, Willett WC, Giovannucci E. Prospective weight change and colon cancer risk in male US health professionals. Int J Cancer. 2008 1;123(5):1160-5.
380. 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 16;371(9612):569-78.
381. Miles L. The new WCRF/AICR report: Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective 2008 Nutrition Bulletin 33; 1: 26-32.
382. Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Proc Nutr Soc. 2008; 67(3):253-6.
383. Bjørge T, Engeland A, Tverdal A, Smith GD. Body mass index in adolescence in relation to cause-specific mortality: a follow-up of 230,000 Norwegian adolescents. Am J Epidemiol 2008 1;168(1):30-7.
384. Engeland A, Bjørge T, Tverdal A, Søgaard AJ. Obesity in adolescence and adulthood and the risk of adult mortality. Epidemiology. 2004; 15(1):79-85.
385. Bergström A, Pisani P, Tenet V, Wolk A, Adami HO. Overweight as an avoidable cause of cancer in Europe. Int J Cancer. 2001 1;91(3):421-30.
386. Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, Lystig T, Sullivan M, Bouchard C, Carlsson B, Bengtsson C, Dahlgren S, Gummesson A, Jacobson P, Karlsson J, Lindroos AK, Lönroth H, Näslund I, Olbers T, Stenlöf K, Torgerson J, Agren G, Carlsson LM; Swedish Obese Subjects Study. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med. 2007 23;357(8):741-52.
387. Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, Lamonte MJ, Stroup AM, Hunt SC. Long-term mortality after gastric bypass surgery. N Engl J Med. 2007 23;357(8):753-61.
388. Carmichael AR, Bates T. Obesity and breast cancer: a review of the literature. Breast. 2004; 13(2):85-92.
389. Haydon AM, Macinnis RJ, English DR, Giles GG. Effect of physical activity and body size on survival after diagnosis with colorectal cancer. Gut. 2006; 55(1):62-7.
390. Meyerhardt JA, Catalano PJ, Haller DG, Mayer RJ, Benson AB 3rd, Macdonald JS, Fuchs CS. Influence of body mass index on outcomes and treatment-related toxicity in patients with colon carcinoma. Cancer. 2003 1;98(3):484-95.
391. Reeves MJ, Newcomb PA, Remington PL, Marcus PM, MacKenzie WR. Body mass and breast cancer. Relationship between method of detection and stage of disease. Cancer. 1996 15;77(2):301-7.
392. Amy NK, Aalborg A, Lyons P, Keranen L. Barriers to routine gynecological cancer screening for White and African-American obese women. Int J Obes (Lond). 2006; 30(1):147-55.

393. Arndt V, Stürmer T, Stegmaier C, Ziegler H, Dhom G, Brenner H. Patient delay and stage of diagnosis among breast cancer patients in Germany - a population based study. Br J Cancer. 2002 8;86(7):1034-40.
394. Cui Y, Whiteman MK, Flaws JA, Langenberg P, Tkaczuk KH, Bush TL. Body mass and stage of breast cancer at diagnosis. Int J Cancer. 2002 10;98(2):279-83.
395. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer. 2004; 4(8):579-91
396. Strickler HD, Wylie-Rosett J, Rohan T, Hoover DR, Smoller S, Burk RD, Yu H. The relation of type 2 diabetes and cancer. Diabetes Technol Ther. 2001 3(2):263-74.
397. Müssig K, Häring HU. Insulin Signal Transduction in Normal Cells and its Role in Carcinogenesis. Exp Clin Endocrinol Diabetes. 2010 Feb 5. [Epub ahead of print]
398. Khandwala HM, McCutcheon IE, Flyvbjerg A, Friend KE. The effects of insulin-like growth factors on tumorigenesis and neoplastic growth. Endocr Rev. 2000; 21(3):215-44.
399. Le Roith D. Regulation of proliferation and apoptosis by the insulin-like growth factor I receptor. Growth Horm IGF Res. 2000; 10 Suppl A:S12-3.
400. van Kruijsdijk RC, van der Wall E, Visseren FL. Obesity and cancer: the role of dysfunctional adipose tissue. Cancer Epidemiol Biomarkers Prev. 2009; 18(10):2569-78.
401. Bray GA. Medical consequences of obesity. J Clin Endocrinol Metab. 2004; 89(6):2583-9.
402. Arden N, Nevitt MC. Osteoarthritis: epidemiology. Best Pract Res Clin Rheumatol 2006 20(1):3-25.
403. Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis. The Framingham Study. Ann Intern Med. 1988 1;109(1):18-24.
404. Hart DJ, Doyle DV, Spector TD. Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women: the Chingford Study. Arthritis Rheum. 1999; 42(1):17-24.
405. Gelber AC, Hochberg MC, Mead LA, Wang NY, Wigley FM, Klag MJ. Body mass index in young men and the risk of subsequent knee and hip osteoarthritis. Am J Med. 1999; 107(6):542-8.
406. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage. 2010; 18(1):24-33.
407. March LM, Bagga H. Epidemiology of osteoarthritis in Australia. Med J Aust. 2004 1;180(5 Suppl):S6-10.
408. Toivanen AT, Heliövaara M, Impivaara O, Arokoski JP, Knekt P, Lauren H, Kröger H. Obesity, physically demanding work and traumatic knee injury are major risk factors for knee osteoarthritis--a population-based study with a follow-up of 22 years. Rheumatology (Oxford). 2010; 49(2):308-14.
409. Anderson JJ, Felson DT. Factors associated with osteoarthritis of the knee in the first national Health and Nutrition Examination Survey (HANES I). Evidence for an association with overweight, race, and physical demands of work. Am J Epidemiol. 1988; 128 (1):179-89.

410. Berenbaum F, Sellam J. Obesity and osteoarthritis: what are the links? Joint Bone Spine. 2008; 75(6):667-8.
411. Lievense AM, Bierma-Zeinstra SM, Verhagen AP, van Baar ME, Verhaar JA, Koes BW. Influence of obesity on the development of osteoarthritis of the hip: a systematic review. Rheumatology (Oxford). 2002; 41(10):1155-62.
412. Karlson EW, Mandl LA, Aweh GN, Sangha O, Liang MH, Grodstein F. Total hip replacement due to osteoarthritis: the importance of age, obesity, and other modifiable risk factors. Am J Med. 2003 1;114(2):93-8.
413. Gelber AC. Obesity and hip osteoarthritis: the weight of the evidence is increasing. Am J Med. 2003 1;114(2):158-9.
414. Grotle M, Hagen KB, Natvig B, Dahl FA, Kvien TK. Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up. BMC Musculoskelet Disord. 2008 2;9:132.
415. Oliveria SA, Felson DT, Cirillo PA, Reed JI, Walker AM. Body weight, body mass index, and incident symptomatic osteoarthritis of the hand, hip, and knee. Epidemiology. 1999; 10(2):161-6.
416. Carman WJ, Sowers M, Hawthorne VM, Weissfeld LA. Obesity as a risk factor for osteoarthritis of the hand and wrist: a prospective study. Am J Epidemiol. 1994 15;139(2):119-29.
417. Wilson MG, Michet CJ Jr, Ilstrup DM, Melton LJ 3rd. Idiopathic symptomatic osteoarthritis of the hip and knee: a population-based incidence study. Mayo Clin Proc. 1990; 65(9):1214-21.
418. Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study. Ann Intern Med. 1992 1;116(7):535-9.
419. Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. Ann Rheum Dis. 2007; 66(4):433-9.
420. Messier SP. Obesity and osteoarthritis: disease genesis and nonpharmacologic weight management. Med Clin North Am. 2009; 93(1):145-59.
421. Teichtahl AJ, Wang Y, Wluka AE, Cicuttini FM. Obesity and knee osteoarthritis: new insights provided by body composition studies. Obesity (Silver Spring). 2008; 16(2):232-40.
422. Finkelstein EA, Chen H, Prabhu M, Trogdon JG, Corso PS. The relationship between obesity and injuries among U.S. adults. Am J Health Promot. 2007; 21(5):460-8.
423. Cooper C, Snow S, McAlindon TE, Kellingray S, Stuart B, Coggon D, Dieppe PA. Risk factors for the incidence and progression of radiographic knee osteoarthritis. Arthritis Rheum. 2000; 43(5):995-1000.
424. Pottie P, Presle N, Terlain B, Netter P, Mainard D, Berenbaum F. Obesity and osteoarthritis: more complex than predicted! Ann Rheum Dis. 2006; 65(11):1403-5.
425. Sandell LJ. Obesity and osteoarthritis: is leptin the link? Arthritis Rheum. 2009; 60(10):2858-60.

426. Gegout PP, Francin PJ, Mainard D, Presle N. Adipokines in osteoarthritis: friends or foes of cartilage homeostasis? Joint Bone Spine. 2008; 75(6):669-71.
427. Gabay O, Hall DJ, Berenbaum F, Henrotin Y, Sanchez C. Osteoarthritis and obesity: experimental models. Joint Bone Spine. 2008; 75(6):675-9.
428. Livshits G, Zhai G, Hart DJ, Kato BS, Wang H, Williams FM, Spector TD. Interleukin-6 is a significant predictor of radiographic knee osteoarthritis: The Chingford Study. Arthritis Rheum. 2009; 60(7):2037-45.
429. Yosipovitch G, DeVore A, Dawn A. Obesity and the skin: skin physiology and skin manifestations of obesity. J Am Acad Dermatol. 2007; 56(6):901-16.
430. García Hidalgo L. Dermatological complications of obesity. Am J Clin Dermatol. 2002; 3(7):497-506.
431. Scheinfeld NS. Obesity and dermatology. Clin Dermatol. 2004; 22(4):303-9.
432. McClean KM, Kee F, Young IS, Elborn JS. Obesity and the lung: 1. Epidemiology. Thorax. 2008; 63(7):649-54.
433. O'Donnell CP, Holguin F, Dixon AE. Pulmonary physiology and pathophysiology in obesity. J Appl Physiol. 2010; 108(1):197-8.
434. Parameswaran K, Todd DC, Soth M. Altered respiratory physiology in obesity. Can Respir J. 2006 13(4):203-10.
435. Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. J Appl Physiol. 2010; 108(1):206-11.
436. Jones RL, Nzekwu MM. The effects of body mass index on lung volumes. Chest. 2006; 130(3):827-33.
437. Adams JP, Murphy PG. Obesity in anaesthesia and intensive care. Br J Anaesth. 2000; 85(1):91-108.
438. Schachter LM, Peat JK, Salome CM. Asthma and atopy in overweight children. Thorax. 2003; 58(12):1031-5.
439. Sin DD, Jones RL, Man SF. Obesity is a risk factor for dyspnea but not for airflow obstruction. Arch Intern Med. 2002 8;162(13):1477-81.
440. Morgan WK, Reger RB. Rise and fall of the FEV(1). Chest. 2000; 118(6):1639-44.
441. Hakala K, Mustajoki P, Aittomäki J, Sovijärvi AR. Effect of weight loss and body position on pulmonary function and gas exchange abnormalities in morbid obesity. Int J Obes Relat Metab Disord. 1995; 19(5):343-6.
442. Womack CJ, Harris DL, Katzel LI, Hagberg JM, Bleecker ER, Goldberg AP. Weight loss, not aerobic exercise, improves pulmonary function in older obese men. J Gerontol A Biol Sci Med Sci. 2000; 55(8):M453-7.
443. Wang ML, McCabe L, Petsonk EL, Hankinson JL, Banks DE. Weight gain and longitudinal changes in lung function in steel workers. Chest. 1997; 111(6):1526-32.

444. Bottai M, Pistelli F, Di Pede F, Carrozzi L, Baldacci S, Matteelli G, Scognamiglio A, Viegi G. Longitudinal changes of body mass index, spirometry and diffusion in a general population. Eur Respir J. 2002; 20(3):665-73.

445. Cook NR, Hebert PR, Satterfield S, Taylor JO, Buring JE, Hennekens CH. Height, lung function, and mortality from cardiovascular disease among the elderly. Am J Epidemiol. 1994 1;139(11):1066-76.

446. Schünemann HJ, Dorn J, Grant BJ, Winkelstein W Jr, Trevisan M. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. Chest. 2000; 118(3):656-64.

447. Pelosi P, Croci M, Ravagnan I, Vicardi P, Gattinoni L. Total respiratory system, lung, and chest wall mechanics in sedated-paralyzed postoperative morbidly obese patients. Chest. 1996; 109(1):144-51.

448. Pelosi P, Croci M, Ravagnan I, Tredici S, Pedoto A, Lissoni A, Gattinoni L. The effects of body mass on lung volumes, respiratory mechanics, and gas exchange during general anesthesia. Anesth Analg. 1998; 87(3):654-60.

449. Waltemath CL, Bergman NA. Respiratory compliance in obese patients. Anesthesiology. 1974; 41(1):84-5.

450. Harik-Khan RI, Wise RA, Fleg JL. The effect of gender on the relationship between body fat distribution and lung function. J Clin Epidemiol. 2001; 54(4):399-406.

451. Carey IM, Cook DG, Strachan DP. The effects of adiposity and weight change on forced expiratory volume decline in a longitudinal study of adults. Int J Obes Relat Metab Disord. 1999; 23(9):979-85.

452. Ochs-Balcom HM, Grant BJ, Muti P, Sempos CT, Freudenheim JL, Trevisan M, Cassano PA, Iacoviello L, Schünemann HJ. Pulmonary function and abdominal adiposity in the general population. Chest. 2006; 129(4):853-62.

453. Chen Y, Rennie D, Cormier YF, Dosman J. Waist circumference is associated with pulmonary function in normal-weight, overweight, and obese subjects. Am J Clin Nutr. 2007; 85(1):35-9.

454. Crummy F, Piper AJ, Naughton MT. Obesity and the lung: 2. Obesity and sleep-disordered breathing. Thorax. 2008; 63(8):738-46.

455. Malhotra A, Hillman D. Obesity and the lung: 3. Obesity, respiration and intensive care. Thorax. 2008; 63(10):925-31.

456. Sin DD, Sutherland ER. Obesity and the lung: 4. Obesity and asthma. Thorax. 2008; 63(11):1018-23.

457. Franssen FM, O'Donnell DE, Goossens GH, Blaak EE, Schols AM. Obesity and the lung: 5. Obesity and COPD. Thorax. 2008; 63(12):1110-7.

458. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991; 14(6):540-5.

459. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med. 1999 5;131(7):485-91.
460. The AASM Manual for the scoring of sleep and associated events, rules, terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine; 2007
461. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep. 1999 1;22(5):667-89.
462. Gottlieb DJ, Whitney CW, Bonekat WH, Iber C, James GD, Lebowitz M, Nieto FJ, Rosenberg CE. Relation of sleepiness to respiratory disturbance index: the Sleep Heart Health Study. Am J Respir Crit Care Med. 1999; 159(2):502-7.
463. Veasey SC. Obstructive sleep apnea: re-evaluating our index of severity. Sleep Med. 2006; 7(1):5-6.
464. Littleton SW, Mokhlesi B. The pickwickian syndrome-obesity hypoventilation syndrome. Clin Chest Med. 2009; 30(3):467-78.
465. Al Lawati NM, Patel SR, Ayas NT. Epidemiology, risk factors, and consequences of obstructive sleep apnea and short sleep duration. Prog Cardiovasc Dis. 2009; 51(4):285-93.
466. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993 29;328(17):1230-5.
467. Attal P, Chanson P. Endocrine aspects of obstructive sleep apnea. J Clin Endocrinol Metab. 2010; 95(2):483-95.
468. Vgontzas AN, Tan TL, Bixler EO, Martin LF, Shubert D, Kales A. Sleep apnea and sleep disruption in obese patients. Arch Intern Med. 1994 8;154(15):1705-11.
469. Frey WC, Pilcher J. Obstructive sleep-related breathing disorders in patients evaluated for bariatric surgery. Obes Surg. 2003; 13(5):676-83.
470. O'Keeffe T, Patterson EJ. Evidence supporting routine polysomnography before bariatric surgery. Obes Surg. 2004; 14(1):23-6.
471. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. JAMA. 2000 20;284(23):3015-21.
472. Flemons WW. Clinical practice. Obstructive sleep apnea. N Engl J Med. 2002 15;347(7):498-504.
473. Grunstein R, Wilcox I, Yang TS, Gould Y, Hedner J. Snoring and sleep apnoea in men: association with central obesity and hypertension. Int J Obes Relat Metab Disord. 1993; 17(9):533-40.
474. Horner RL, Mohiaddin RH, Lowell DG, Shea SA, Burman ED, Longmore DB, Guz A. Sites and sizes of fat deposits around the pharynx in obese patients with obstructive sleep apnoea and weight matched controls. Eur Respir J. 1989; 2(7):613-22.
475. Shelton KE, Woodson H, Gay S, Suratt PM. Pharyngeal fat in obstructive sleep apnea. Am Rev Respir Dis. 1993; 148(2):462-6.

476. Schwab RJ, Gupta KB, Gefter WB, Metzger LJ, Hoffman EA, Pack AI. Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. Am J Respir Crit Care Med. 1995; 152(5 Pt 1):1673-89.
477. Carrera M, Barbé F, Sauleda J, Tomás M, Gómez C, Santos C, Agustí AG. Effects of obesity upon genioglossus structure and function in obstructive sleep apnoea. Eur Respir J. 2004; 23(3):425-9.
478. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med. 2002 1;165(5):670-6.
479. Vgontzas AN. Does obesity play a major role in the pathogenesis of sleep apnoea and its associated manifestations via inflammation, visceral adiposity, and insulin resistance? Arch Physiol Biochem. 2008; 114(4):211-23.
480. Phillips BG, Kato M, Narkiewicz K, Choe I, Somers VK. Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea. Am J Physiol Heart Circ Physiol. 2000; 279(1):H234-7.
481. Arnardottir ES, Mackiewicz M, Gislason T, Teff KL, Pack AI. Molecular signatures of obstructive sleep apnea in adults: a review and perspective. Sleep. 2009; 32(4):447-70.
482. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. JAMA. 2003 8;290(14):1906-14.
483. Charkoudian N, Rabbitts JA. Sympathetic neural mechanisms in human cardiovascular health and disease. Mayo Clin Proc. 2009; 84(9):822-30.
484. Wolf J, Lewicka J, Narkiewicz K. Obstructive sleep apnea: an update on mechanisms and cardiovascular consequences. Nutr Metab Cardiovasc Dis. 2007; 17(3):233-40.
485. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, Schoelles K. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004 13;292(14):1724-37.
486. Greenburg DL, Lettieri CJ, Eliasson AH. Effects of surgical weight loss on measures of obstructive sleep apnea: a meta-analysis. Am J Med. 2009; 122(6):535-42.
487. Pillar G, Peled R, Lavie P. Recurrence of sleep apnea without concomitant weight increase 7.5 years after weight reduction surgery. Chest. 1994; 106(6):1702-4.
488. Patel SR, Hu FB. Short sleep duration and weight gain: a systematic review. Obesity (Silver Spring). 2008; 16(3):643-53.
489. Phillips BG, Hisel TM, Kato M, Pesek CA, Dyken ME, Narkiewicz K, Somers VK. Recent weight gain in patients with newly diagnosed obstructive sleep apnea. J Hypertens. 1999; 17(9):1297-300.
490. Chung SA, Yuan H, Chung F. A systemic review of obstructive sleep apnea and its implications for anesthesiologists. Anesth Analg. 2008; 107(5):1543-63.
491. Longitudinal Assessment of Bariatric Surgery (LABS) Consortium, Flum DR, Belle SH, King WC, Wahed AS, Berk P, Chapman W, Pories W, Courcoulas A, McCloskey C, Mitchell J, Patterson

E, Pomp A, Staten MA, Yanovski SZ, Thirlby R, Wolfe B. Perioperative safety in the longitudinal assessment of bariatric surgery. N Engl J Med. 2009 30;361(5):445-54.
492. Lebovitz HE, Banerji MA. Point: visceral adiposity is causally related to insulin resistance. Diabetes Care. 2005; 28(9):2322-5.
493. Seidell JC, Han TS, Feskens EJ, Lean ME. Narrow hips and broad waist circumferences independently contribute to increased risk of non-insulin-dependent diabetes mellitus. J Intern Med. 1997; 242(5):401-6.
494. Bigaard J, Frederiksen K, Tjønneland A, Thomsen BL, Overvad K, Heitmann BL, Sørensen TI. Waist and hip circumferences and all-cause mortality: usefulness of the waist-to-hip ratio? Int J Obes Relat Metab Disord. 2004; 28(6):741-7.
495. Goodpaster BH, Thaete FL, Simoneau JA, Kelley DE. Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. Diabetes. 1997; 46(10):1579-85.
496. Virtanen KA, Iozzo P, Hällsten K, Huupponen R, Parkkola R, Janatuinen T, Lönnqvist F, Viljanen T, Rönnemaa T, Lönnroth P, Knuuti J, Ferrannini E, Nuutila P. Increased fat mass compensates for insulin resistance in abdominal obesity and type 2 diabetes: a positron-emitting tomography study. Diabetes. 2005; 54(9):2720-6.
497. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, Vasan RS, Murabito JM, Meigs JB, Cupples LA, D'Agostino RB Sr, O'Donnell CJ. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation. 2007 3;116(1):39-48.
498. Goodpaster BH, Kelley DE, Wing RR, Meier A, Thaete FL. Effects of weight loss on regional fat distribution and insulin sensitivity in obesity. Diabetes. 1999; 48(4):839-47.
499. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM. Relationships of generalized and regional adiposity to insulin sensitivity in men. J Clin Invest. 1995; 96(1):88-98.
500. Kim JY, van de Wall E, Laplante M, Azzara A, Trujillo ME, Hofmann SM, Schraw T, Durand JL, Li H, Li G, Jelicks LA, Mehler MF, Hui DY, Deshaies Y, Shulman GI, Schwartz GJ, Scherer PE. Obesity-associated improvements in metabolic profile through expansion of adipose tissue. J Clin Invest. 2007; 117(9):2621-37.

Figure 1. Co-morbidities associated with overweight and obesity.

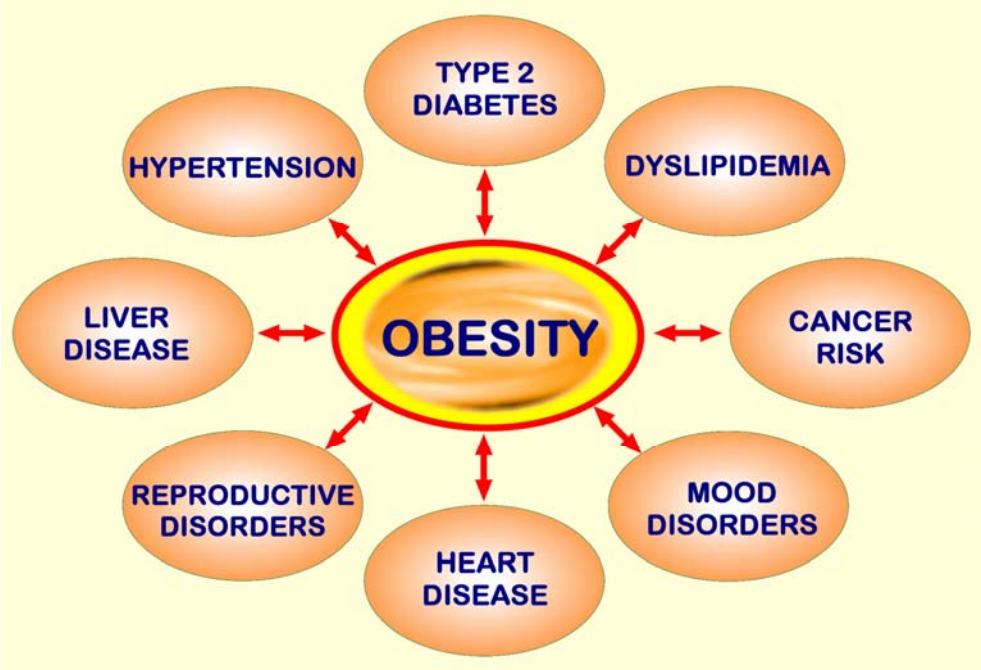


Figure 2. Relationship between body mass index (BMI) and mortality (data adopted from Calle et al. NEJM 1999 [7]).

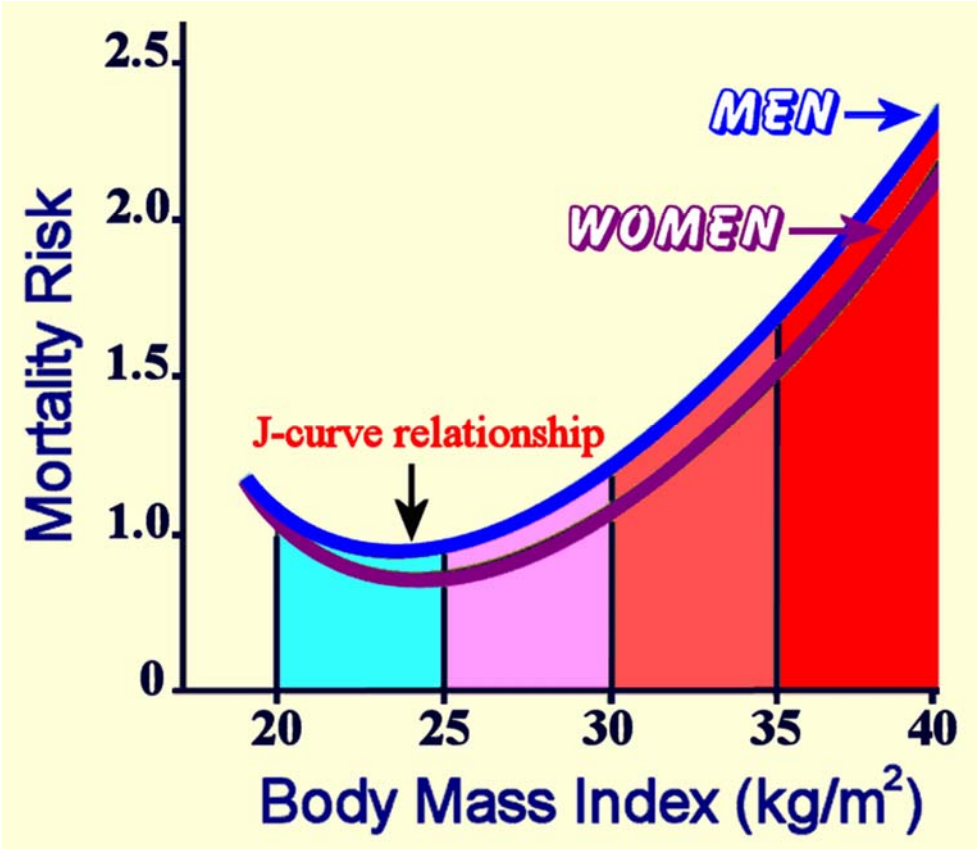


Figure 3. Risk of developing type 2 diabetes and body mass index (BMI) in male and female adults (based on data from Colditz GA et al. Ann Intern Med. 1995 [27] and Chan JM et al. Diabetes Care 1994 [28]).

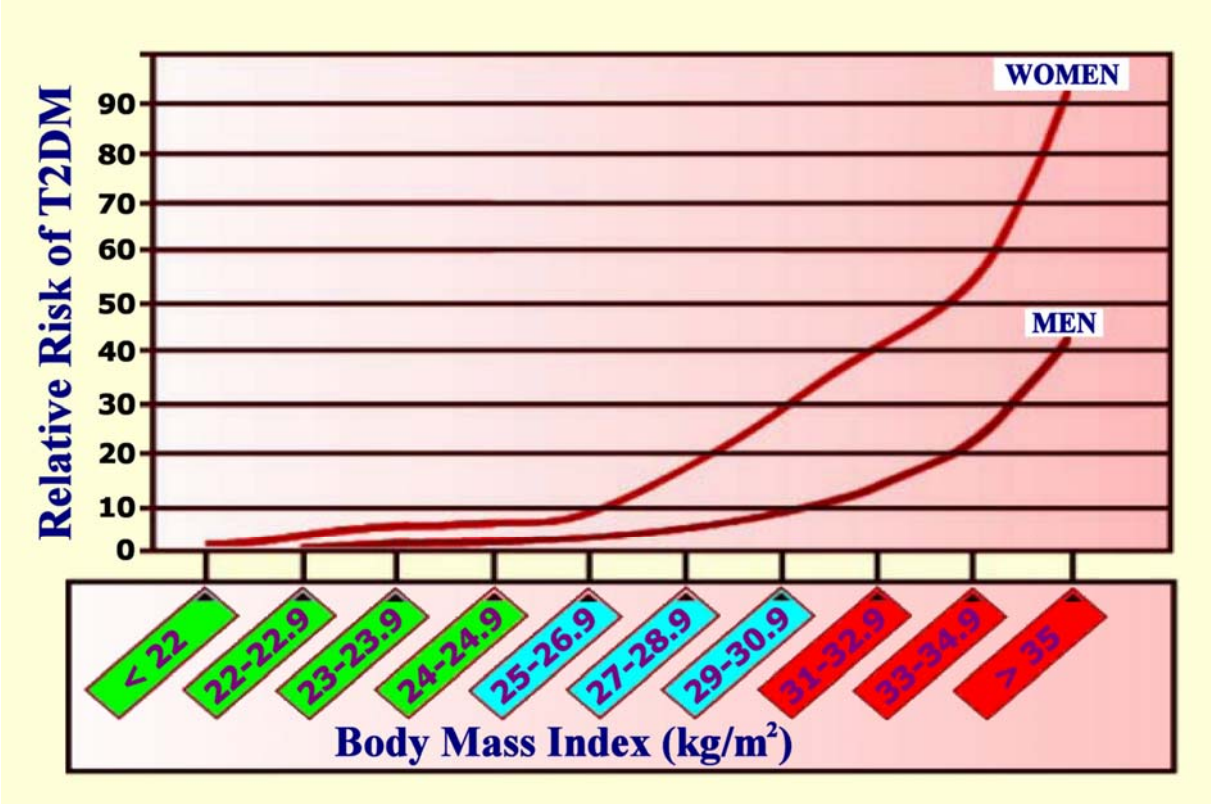


Figure 4. Adipose tissue and low-grade inflammatory state in obesity. Excess fat accumulation induces increasing secretion of pro-inflammatory adipokines and chemokines particularly by visceral adipose tissue depots into the circulation. In response to chemotactic stimuli, circulating mononuclear cells are recruited and transmigrate into the expanding adipose tissue, creating a growing population of resident macrophages. In turn, these adipose tissue macrophages are the major source of local cytokine secretion (e.g. TNF-α, IL1 and IL-6). It is evident that a vicious cycle is formed locally with adipocyte-derived free fatty acids (FFA) and adipokines stimulating macrophages to secrete cytokines and *vice versa*. The result is chronic sub-clinical inflammation within adipose tissue depots which persists for as long as the excess fat mass is maintained and leads to generalized inflammation and a procoagulant state due to unremitting release of pro-inflammatory adipokines. This finally can result in deleterious systemic cardiometabolic effects and clinical manifestations of the metabolic syndrome. TNF-α: tumor necrosis factor-α, MCP-1: monocyte chemotactic protein-1, IL-8: interleukin 8, IL-1: interleukin-1, IL-6: interleukin-6.

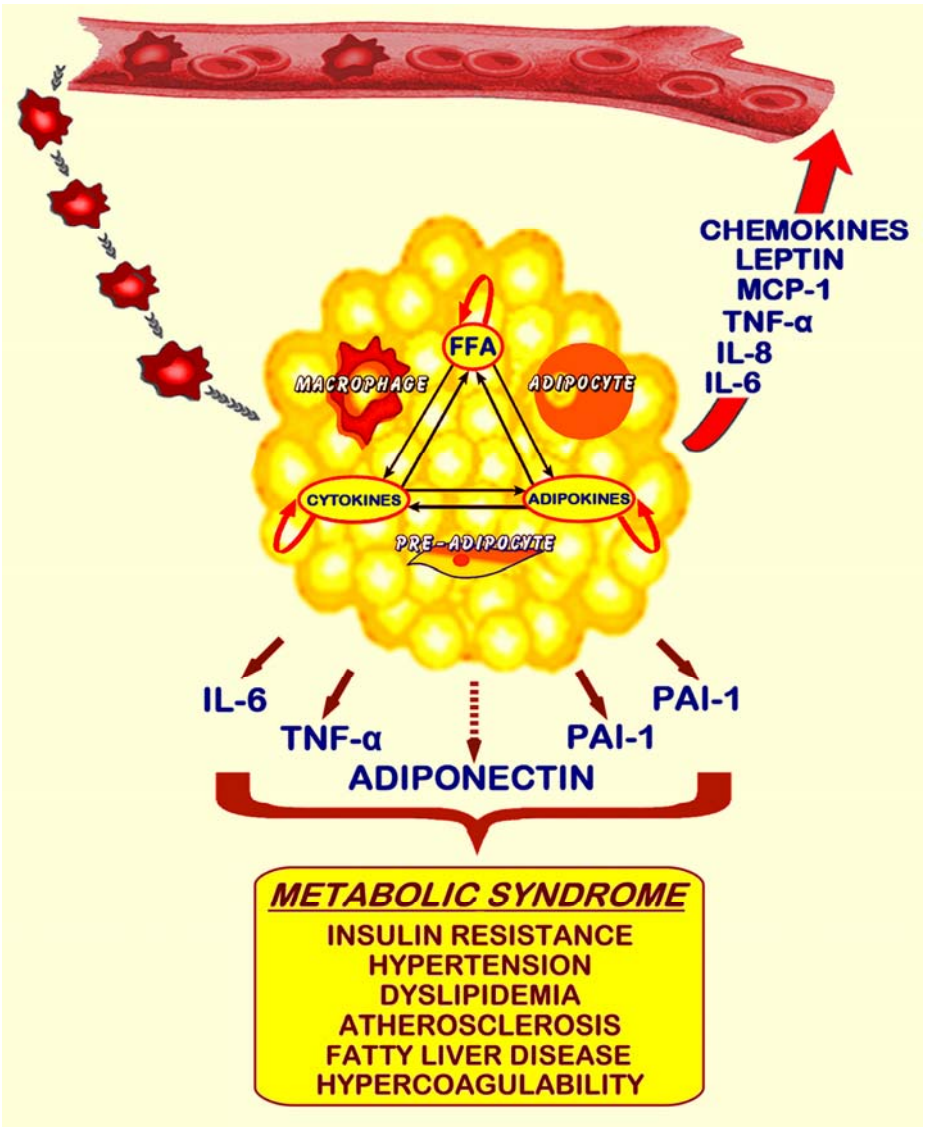


Figure 5. Different definitions of the metabolic syndrome.

DIFFERENT DEFINITIONS OF THE METABOLIC SYNDROME		
EGIR (1999)	**WHO (1999)**	**NCEP-ATP III (2001)**
Insulin resistance - hyperinsulinemia based on fasting insulin values (upper quartile of a non-diabetic population)	Diabetes, IFG, IGT or insulin resistance (by euglycemic hyperinsulinemic clamp - glucose uptake less than lowest quartile)	
Plus at least two of the following:	**Plus at least two of the following:**	**At least three of the following:**
1. Central obesity WC ≥94 cm (37 in) (M) WC ≥80 cm (31 in) (F)	1. Obesity with BMI >30 kg/m^2 or WHR >0.9 (M) WHR >0.85 (F)	1. Central obesity WC >102 cm (40 in) (M) WC >88 cm (35 in) (F)
2. TG >2.0 mmol/l (177 mg/dl) or HDL <1.0 (39 mg/dl) mmol/l	2. TG ≥1.7 mmol/l (150 mg/dl) or HDL-C <0.9 mmol/l (35 mg/dl) (M) HDL-C <1.0 mmol/l (39 mg/dl) (F)	2. TG ≥1.7 mmol/l (150 mg/dl) 3. HDL-C <1.04 mmol/l (40 mg/dl) (M) HDL-C <1.33 mmol/l (50 mg/dl) (F)
3. BP ≥140/90 mmHg or on antihypertensive medication	3. BP ≥140/90 mm Hg	4. BP ≥135/85 mmHg or on antihypertensive medication
4. FPG ≥6.1 mmol/l (110 mg/dl)	4. Albumin excretion rate ≥ 20 µg/min or albumin/creatinine ratio ≥ 30 mg/g	5. FPG ≥6.1 mmol/l (110 mg/dl)*
*changed to FPG ≥ 5.6 mmol/l (100 mg/dl) in 2004 EGIR: European Group for the Study of Insulin Resistance; WHO: World Health Organization; NCEP-ATP III: National Cholesterol Education Program-Adult Treatment Panel III; BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; FPG: fasting plasma glucose; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; M: men; F: women		

METABOLIC SYNDROME - IDF DEFINITION (2005)			
I. CENTRAL OBESITY			
ETHNIC GROUP	**MEN**	**WOMEN**	**Until more specific data are available:** **Sub-Saharan Africans - Eastern Mediterranean - Middle East (Arab) populations**: use European data **Ethnic South and Central Americans:** use South Asian recommendations
Europids	≥ 94 cm	≥ 80 cm	
South Asians	≥ 90 cm	≥ 80 cm	
Chinese	≥ 90 cm	≥ 80 cm	
Japanese	≥ 85 cm	≥ 90 cm	
II. PLUS ANY TWO OF THE FOUR FOLLOWING FACTORS:			
A. ↑ TG levels: ≥ 150 mg/dl (1.7 mmol/l) or specific treatment for this lipid abnormality			
B. ↓ HDL-c levels: males ≤ 40 mg/dl (1.03 mmol/l), females ≤ 50 mg/dl (1.29 mmol/l) or specific treatment for this lipid abnormality			
C. ↑ Blood pressure: systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg or Treatment of previously diagnosed hypertension			
D. ↑ FPG: ≥ 100 mg/dl (5.6 mmol/l) or previously diagnosed Type 2 Diabetes			
TG: triglycerides; HDL-c: high-density lipoprotein cholesterol; BP: blood pressure; FPG: fasting plasma glucose; IDF: International Diabetes Federation			

Figure 6. Criteria for clinical diagnosis of the metabolic syndrome proposed by a joint interim statement from the International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) and current recommended waist circumference thresholds for abdominal obesity by organization (adopted from Alberti et al. Circulation 2009 [15]).

CRITERIA FOR CLINICAL DIAGNOSIS OF THE METABOLIC SYNDROME

RISK FACTOR-MEASURE	CATEGORICAL CUT-OFF POINTS
1. Increased waist circumference *	Population- and country-specific definitions
2. Increased TG (drug treatment for increased triglycerides is an alternate indicator †)	≥150 mg/dL (1.7 mmol/L)
3. Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator †)	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in females
4. Increased blood pressure (antihypertensive drug treatment in a patient with a hypertension history is an alternate indicator)	Systolic BP ≥130 mm Hg and/or Diastolic BP ≥85 mm Hg
5. Increased fasting plasma glucose ‡ (drug treatment of increased glucose is an alternate indicator)	≥100 mg/dL

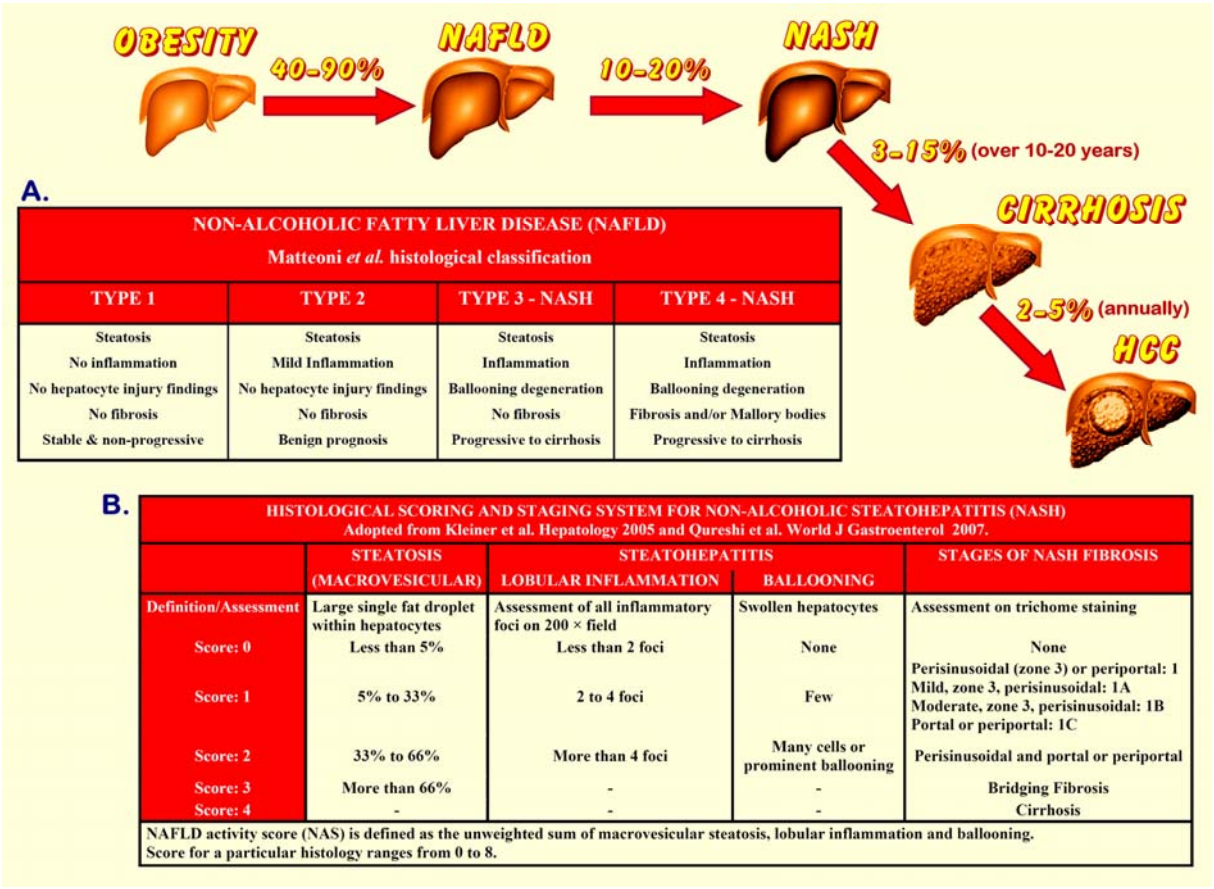
Presence of any 3 of 5 risk factors constitutes a diagnosis of metabolic syndrome
*: It is recommended that the IDF cut points be used for non-Europeans and either the IDF or AHA/NHLBI cut points used for people of European origin until more data are available.
†: The most commonly used drugs for increased triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking one of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose of ω-3 fatty acids presumes high triglycerides.
‡: Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria
HDL-C: high-density lipoprotein cholesterol; BP: blood pressure

RECOMMENDED WAIST CIRCUMFERENCE THRESHOLDS FOR ABDOMINAL OBESITY

POPULATION	WC IN MEN	WC IN WOMEN	ORGANIZATION
Europid	≥94 cm	≥80 cm	IDF
Caucasian	≥94 cm (increased risk) ≥102 cm (higher risk)	≥80 cm (increased risk) ≥88 cm (higher risk)	WHO
United States	≥102 cm	≥88 cm	AHA/NHLBI (ATP-III)
Canada	≥102 cm	≥88 cm	Health Canada
European	≥102 cm	≥88 cm	European CV Societies
Asian (including Japanese)	≥90 cm	≥80 cm	IDF
Asian	≥90 cm	≥80 cm	WHO
Japanese	≥85 cm	≥90 cm	Japanese Obesity Society
China	≥85 cm	≥80 cm	Cooperative Task Force
Middle East, Mediterranean	≥94 cm	≥80 cm	IDF
Sub-Saharan African	≥94 cm	≥80 cm	IDF
Ethnic Central & South American	≥90 cm	≥80 cm	IDF

WC: waist circumference; CV: cardiovascular; IDF: International Diabetes Federation; WHO: World Health Organization; AHA: American Heart Association; NHLBI: National Heart, Lung, and Blood Institute

Figure 7. Natural history of non-alcoholic fatty liver disease (NAFLD). **A.** Histological classification as proposed by Matteoni *et al.* [130]. Non-alcoholic steatohepatitis (NASH) represents the most severe form of NAFLD (NAFLD types 3 and 4) and can progress to cirrhosis and hepatocellular carcinoma (HCC). **B.** NAFLD activity score (NAS) proposed for histological scoring and staging of NAFLD in order to consistently assess the disease and compare outcomes of therapeutic interventions (adopted from Kleiner et al. Hepatology 2005 and Qureshi et al. World J Gastroenterol 2007 [132, 133]).



A.

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) Matteoni *et al.* histological classification			
TYPE 1	**TYPE 2**	**TYPE 3 - NASH**	**TYPE 4 - NASH**
Steatosis	Steatosis	Steatosis	Steatosis
No inflammation	Mild Inflammation	Inflammation	Inflammation
No hepatocyte injury findings	No hepatocyte injury findings	Ballooning degeneration	Ballooning degeneration
No fibrosis	No fibrosis	No fibrosis	Fibrosis and/or Mallory bodies
Stable & non-progressive	Benign prognosis	Progressive to cirrhosis	Progressive to cirrhosis

B.

HISTOLOGICAL SCORING AND STAGING SYSTEM FOR NON-ALCOHOLIC STEATOHEPATITIS (NASH) Adopted from Kleiner et al. Hepatology 2005 and Qureshi et al. World J Gastroenterol 2007.				
	STEATOSIS	**STEATOHEPATITIS**		**STAGES OF NASH FIBROSIS**
	(MACROVESICULAR)	**LOBULAR INFLAMMATION**	**BALLOONING**	
Definition/Assessment	Large single fat droplet within hepatocytes	Assessment of all inflammatory foci on 200 × field	Swollen hepatocytes	Assessment on trichome staining
Score: 0	Less than 5%	Less than 2 foci	None	None
Score: 1	5% to 33%	2 to 4 foci	Few	Perisinusoidal (zone 3) or periportal: 1 Mild, zone 3, perisinusoidal: 1A Moderate, zone 3, perisinusoidal: 1B Portal or periportal: 1C
Score: 2	33% to 66%	More than 4 foci	Many cells or prominent ballooning	Perisinusoidal and portal or periportal
Score: 3	More than 66%	-	-	Bridging Fibrosis
Score: 4	-	-	-	Cirrhosis
NAFLD activity score (NAS) is defined as the unweighted sum of macrovesicular steatosis, lobular inflammation and ballooning. Score for a particular histology ranges from 0 to 8.				

Figure 8. Signaling pathways leading to hepatic triglyceride accumulation in insulin-resistant states. In sensitive states, insulin binds to its receptor and activates IRS1 and IRS2 which, via PKB/Akt, block gluconeogenesis (FOXO1) and fatty acid oxidation (FOXA2). In insulin resistance the FOXA2 pathway may remain responsive to insulin when inhibition of FOXO1 is already impaired, resulting in decreased fatty acid oxidation. In turn, elevated glucose activates both SREBP-1c and ChREBP, and causes enhanced pancreatic insulin secretion (compensatory hyperinsulinemia). SREBP-1c blocks IRS2 signaling in the liver, further promoting hepatic glucose production, and probably counteracting the suppressive effect of SREBP-1c on gluconeogenic genes. Insulin, ChREBP and SREBP-1c also induce FASN and ACAC, leading to increased production of fatty acids. Thus, in insulin-resistant states hepatic triglycerides accumulate as a result of both reduced fatty acid oxidation and increased fatty acid production. Red arrows indicate the direction of changes in insulin-resistant states. ACAC: Acetyl-CoA carboxylase; ChREBP: carbohydrate response element-binding protein; FASN: fatty acid synthase; FOX: forkhead transcription factor; PKB: protein kinase B/Akt; SREBP: sterol response element-binding protein (adopted from Weickert et al. Diabetologia 2006 [55]).

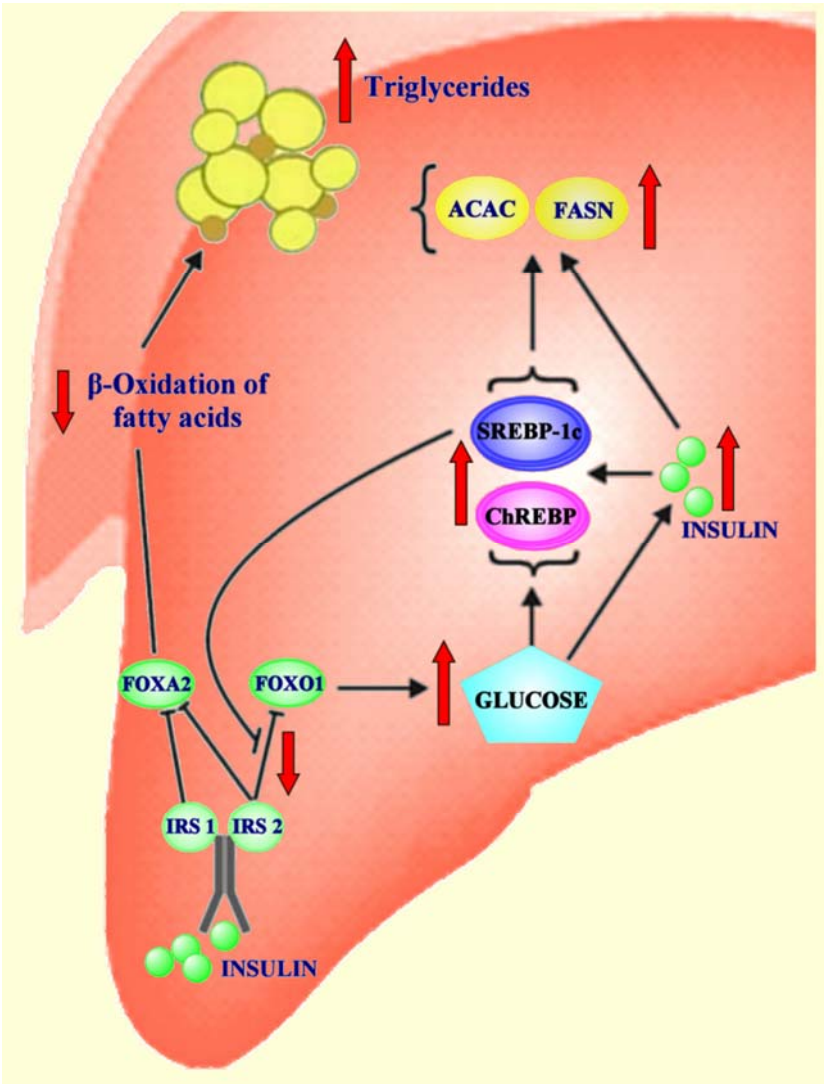


Figure 9. Pathogenesis of non-alcoholic fatty liver disease (NAFLD) based on the "two hit" model proposed by Day *et al*. [161-163]. The first "hit" induces steatosis primarily caused by increased circulating hepatic free fatty acids (FFA) released from insulin resistant adipocytes. Furthermore, due to hepatic insulin resistance, hyperinsulinemia and hyperglycemia also induce increased *de novo* lipogenesis (DNL), suppressed VLDL efflux and impaired fatty acid oxidation. Dietary fat may also increase hepatic triglycerides (TG) through delivery of chylomicrons from the intestines. The second "hit" is promoted by hyperleptinemia, hypoadiponectinemia and increased circulating levels of tumor necrosis-α (TNF-α) and interleukin-6 (IL-6), causing progression to steatohepatitis (NASH). Steatosis and the adverse adipokine profile in obesity further induce hepatic insulin resistance, hepatic lipid peroxidation, oxidative stress responses and endoplasmic reticulum (ER) stress responses, as well as activation of Kupffer and hepatic stellate cells. Thus, a chronic pro-inflammatory state develops inside the steatotic liver, progressively leading to hepatic cell injury, inflammation, apoptosis and fibrosis.

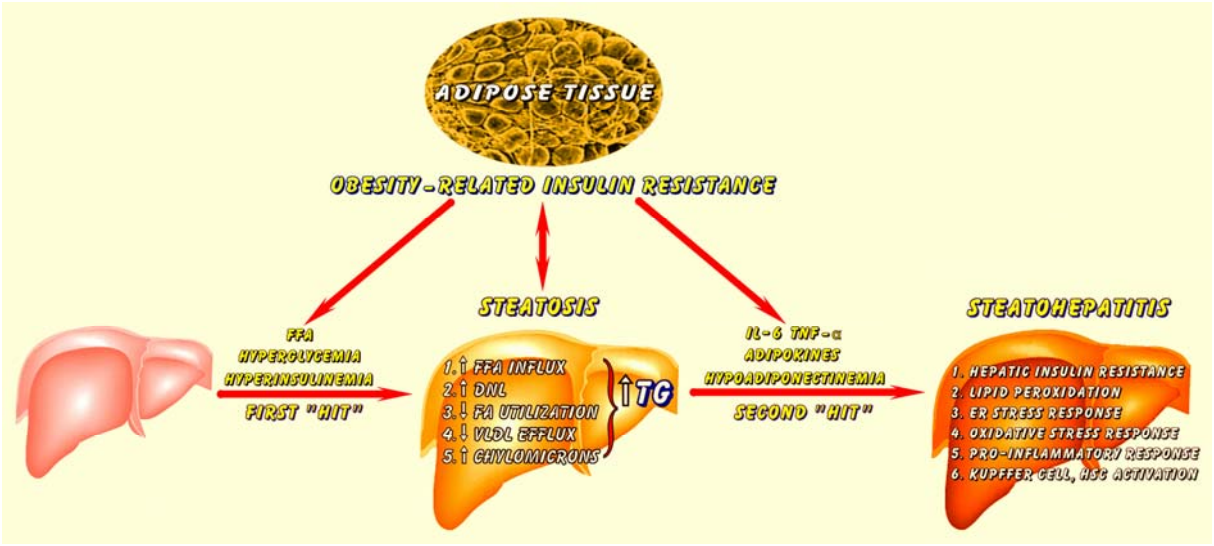


Figure 10. Free fatty acid (FFA) circulation through the liver (adapted from Roden et al. Nat Clin Pract Endocrinol Metab 2006 [166] with data from Nielsen et al. J Clin Invest 2004 [164]). Adipose tissue delivers approximately 80 percent of circulating free fatty acids (FFA) in the fasted state, with this proportion being reduced to 60 percent postprandially. In normal-weight persons dietary fat is responsible for the bulk of the portal supply to hepatic FFA, with the remaining proportion being derived mainly from subcutaneous fat. The contribution of FFA supplied from visceral adipose tissue increases in obese persons, whereas a lower percentage of FFA is supplied both from subcutaneous fat depots and dietary fat. This could be important given that the source of FFA might be relevant for metabolic effects of hepatic lipid accumulation (reviewed in Weickert et al. Diabetologia 2006 [55]). FACoA: long-chain fatty acids bound to coenzyme A.

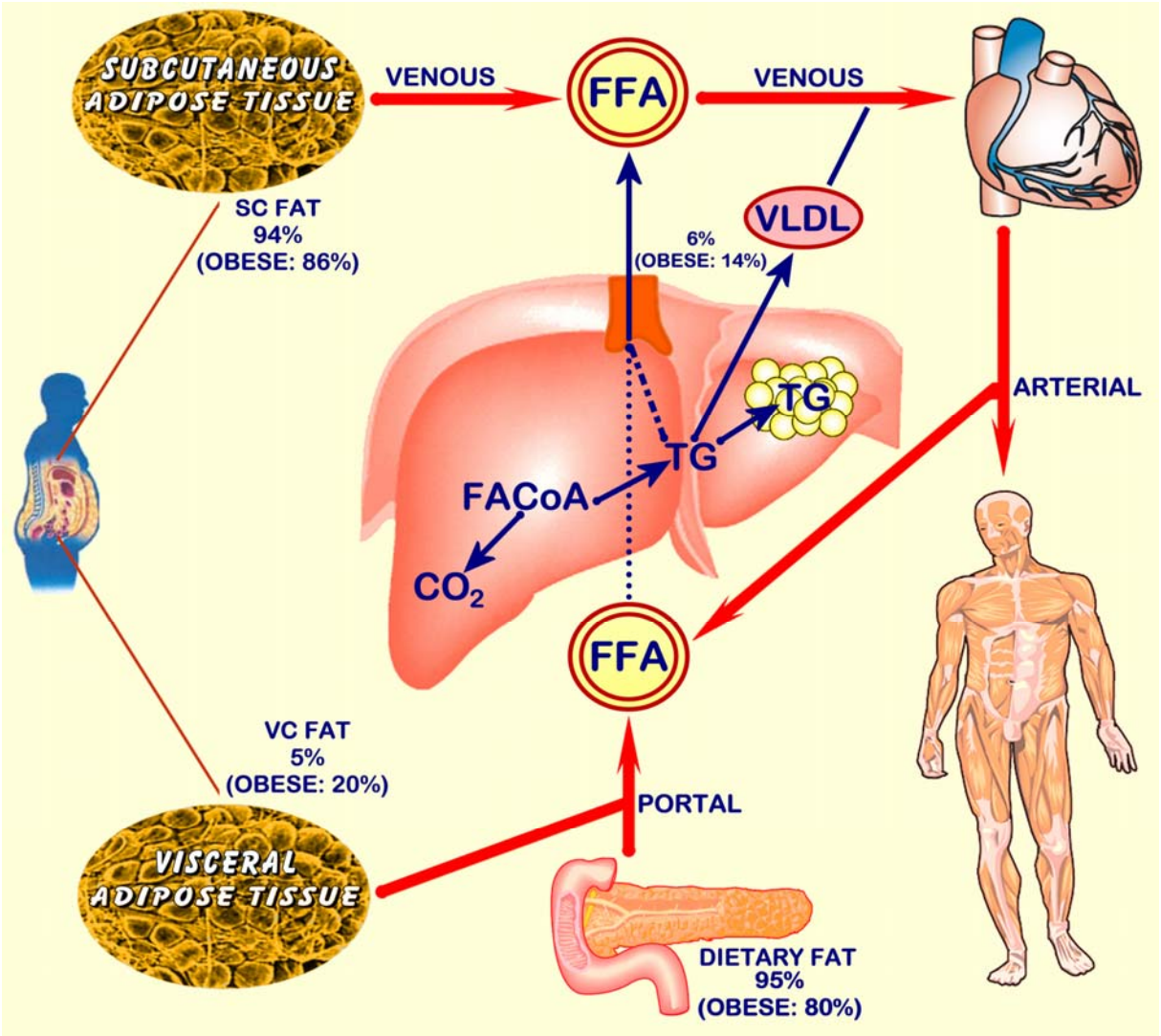


Figure 11. Hormonal changes and clinical manifestations of hypothalamic-pituitary-gonadal (HPG) axis dysfunction in obese females.

HYPOTHALAMIC-PITUITARY-GONADAL AXIS IN OBESE FEMALES	
Hormonal changes	**Clinical manifestations**
↑/↔ Estrogen & ↓/↔ Progesterone	Early menarche - Early menopause
↑ Testosterone	Menstrual disorders
↓ SHBG	Chronic oligo- anovulation
↔ basal FSH	Increased risk of miscarriage & pregnancy complications
↔ basal LH	Impaired fertility - Poor response to fertility treatment
↔ FSH after stimulation	Decreased contraceptive efficacy
↔ LH after stimulation	Increased risk of endometrial, ovarian & postmenopausal breast cancer
↔: normal levels; ↓: decreased levels; ↑: increased levels	

Figure 12. Hormonal changes and clinical manifestations of hypothalamic-pituitary-gonadal (HPG) axis dysfunction in obese males.

HYPOTHALAMIC-PITUITARY-GONADAL AXIS IN OBESE MALES	
Hormonal changes	**Clinical manifestations**
↓ Testosterone ↑ Estrogen ↓ SHBG ↓ / ↔ basal FSH ↓ / ↔ basal LH ↔ FSH after stimulation ↔ LH after stimulation	Reduced libido Impaired fertility Erectile dysfunction Potentially increased risk of high-grade prostate cancer and prostate cancer mortality
↔: normal levels; ↓: decreased levels; ↑: increased levels	

Figure 13. Reciprocal relations between obesity and stress. Chronic stress, manifested with depressive or anxiety symptoms, can induce prolonged activation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) which together with health risk behaviors, can progressively lead to visceral obesity and *vice versa* (adopted from Kyrou et al. Curr Opin Pharmacol. 2009 [33]).

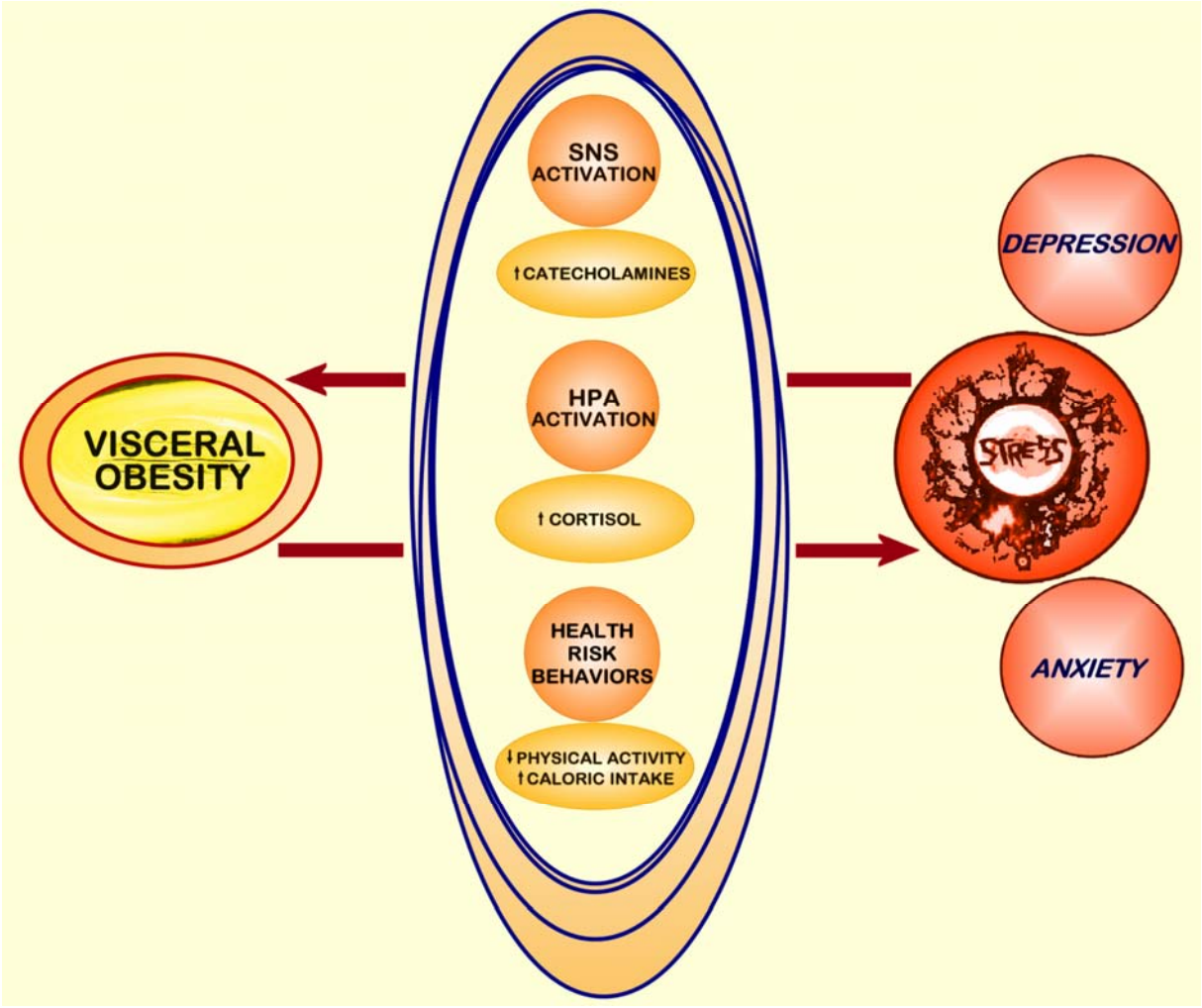


Figure 14. Level of evidence regarding obesity and risk of various cancers.

OBESITY AND INCREASED CANCER RISK		
SUFFICIENT EVIDENCE	**SUPPORTIVE DATA**	**INSUFFICIENT DATA**
Endometrial cancer	Pancreatic cancer	Lung cancer
Post-menopausal breast cancer	Liver cancer	Thyroid cancer
Kidney (renal cell) cancer	Gallbladder cancer	Bladder cancer
Colorectal cancer	Lymphoid malignancies	Cervix cancer
Oesophageal adenocarcinoma	Haematopoietic malignancies	Ovarian cancer
Gastric cardia adenocarcinoma		Prostate cancer
		Testicular cancer
		Malignant melanoma
		Noncardia gastric cancer

Figure 15. Proposed mechanisms linking obesity and increased cancer risk. Obesity, particularly central, causes insulin resistance and compensatory chronic hyperinsulinemia. Increased insulin levels directly induce mitogenic effects and contribute to tumorigenesis. Hyperinsulinemia can also suppress insulin-like growth factor binding protein 1 (IGFBP-1) and IGFBP-2 levels which, in turn, lead to increased insulin-like growth factor 1 (IGF-1) bio-availability. IGF-1 promotes cellular proliferation and inhibits apoptosis through its receptor in several tissues. Increased levels of estrogens and androgens additionally mediate carcinogenic effects, particularly for endometrium and post-menopausal breast cancers. Circulating SHBG levels are decreased in central obesity and hyperinsulinemia due to suppression of SHBG synthesis in the liver by insulin. Thus, higher free sex-steroid levels are present in the circulation increasing the risk for hormone-sensitive gynecologic malignancies. Enhanced metabolism of sex steroids within adipose tissue depots can further contribute to increased plasma levels of androgens and estrogens in obesity. Finally, obesity may directly promote carcinogenesis due to adipokine changes (e.g. hypoadiponectinemia and hyperleptinemia) and development of a chronic low-grade inflammatory state (adopted from Bianchini et al. Obes Rev. 2002 [351]).

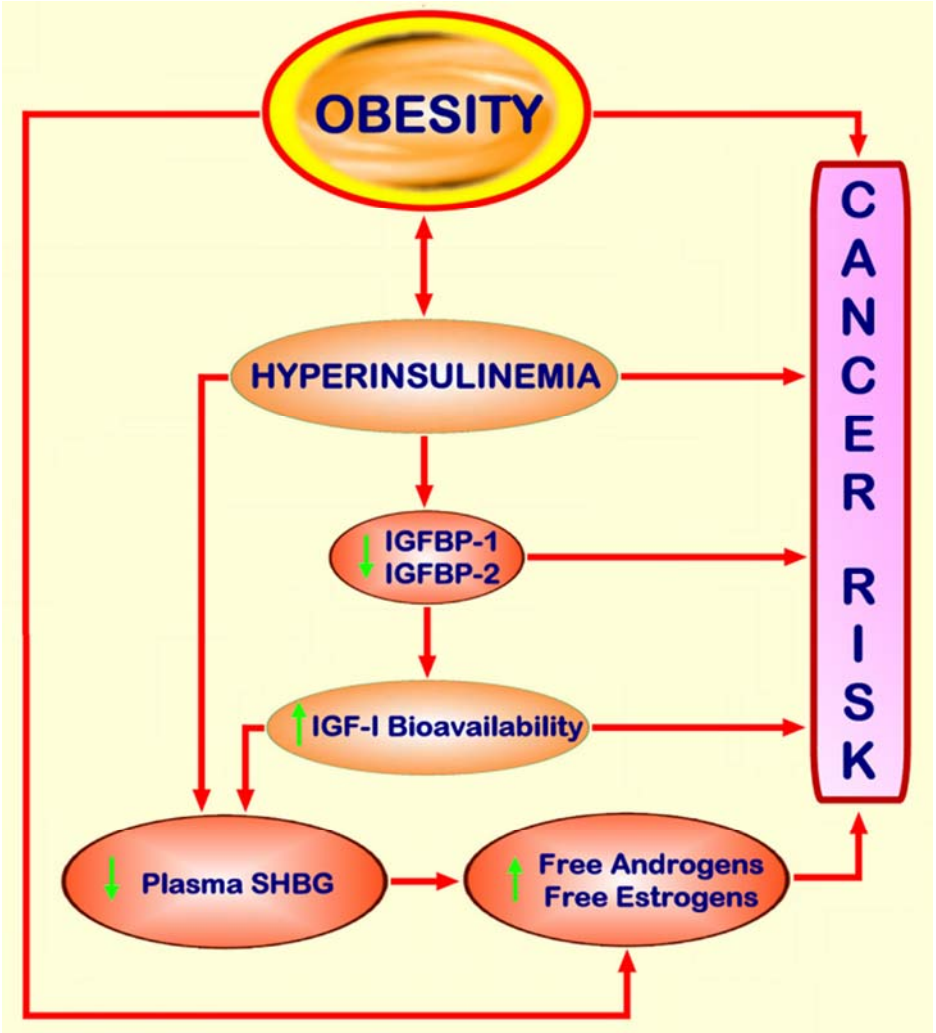


Figure 16. Potential mechanisms linking weight gain, insulin resistance, cardiovascular disease and hypertension in obese patients with obstructive sleep apnea (OSA). Chronic intermittent hypoxia in OSA may increase reactive oxygen species (ROS) production and oxidative stress. In addition, inflammatory pathways and activation of the sympathetic nervous system (SNS) are stimulated due to both chronic intermittent hypoxia and disruption of normal sleep patterns (sleep fragmentation and recurrent arousals). In turn, this induces progressive adverse effects on insulin sensitivity and cardiovascular risk mediated via circulating adipokines (e.g. leptin) and pro-inflammatory factors (e.g. IL-6 and TNF-α). Conversely, insulin resistance promotes further central fat accumulation and cardiovascular disease which aggravate OSA, thereby closing a viscous cycle (adapted from Arnarsdottir et al. Sleep 2009 [481]).