Chapter 1
Prevalence, Consequences, Causes and Management of Obesity

Paramjit S. Tappia and Danielle Defries

Abstract Obesity is a growing global health problem and is well-recognized to be a major contributing factor for increased risk of several non-communicable diseases including cardiovascular disease, diabetes and cancer in both the developed and developing world. This development is multi-factorial, but an increasingly sedentary lifestyle coupled with unhealthy dietary practices are key risk factors. Effective interventions for weight management would therefore not only be seen to reduce the epidemic of obesity, but also to lessen the risk for obesity-related morbidities. This article will briefly describe some factors that can cause obesity. Since men and women are different in their fat mass and distribution profile, and that ethnic groups are disproportionately affected by obesity, it is conceivable that disparities also exist in the occurrence of obesity and the consequential development of non-communicable diseases. Although the major adverse health outcomes due to obesity are mentioned, the influence and the role of sex, specifically women's health, and ethnicity in the increased risk as well as development of obesity-induced health complications will also be discussed.

Keywords Obesity · Non-communicable diseases · Women's health · Ethnicity · Weight management

P. S. Tappia (✉)
Asper Clinical Research Institute, St. Boniface Hospital, CR3129-369 Tache Avenue, Winnipeg, Manitoba R2H 2A6, Canada
e-mail: ptappia@sbrc.ca

D. Defries
Department of Kinesiology and Applied Health, University of Winnipeg, Winnipeg, Manitoba R3B 2E9, Canada

P. S. Tappia et al. (eds.), *Pathophysiology of Obesity-Induced Health Complications*, Advances in Biochemistry in Health and Disease 19,
https://doi.org/10.1007/978-3-030-35358-2_1

Introduction

A healthy body weight is dependent on age and development phase of an individual that is both achievable and sustainable. A healthy body weight would also be associated with normal blood pressure, normal glycemia and circulating lipid levels. The genetic makeup, family history of body type as well as good eating habits and physical activity are additional factors that can influence healthy body weight. The body mass index (BMI) is a well-established method for assessing healthy body weight, however; this ratio does not measure body fat and it is simply a measure of weight to height. On the other hand, body composition is an optimal tool for determining health risk. In this regard, several techniques have been developed, including underweight weighing, the BODPOD, which is an Air Displacement Plethysmograph (ADP) that uses whole-body densitometry to determine body composition (fat vs. lean). Similar in principle to underwater weighing, the BODPOD measures body mass (weight) using a very precise scale, and volume by sitting inside the BODPOD; the bioelectrical impedance analysis (BIA), which is a commonly used method for estimating body composition, in particular body fat and muscle mass. In BIA, a weak electric current flow is sent through the body and the voltage is measured to calculate impedance of the body. Lean tissue, which is >70% water, is a good conductor of electrical current, whereas fatty tissue, which is hydrophobic and low in water, is not. Thus, an increase in body fat is associated with increased electrical resistance combined with a skinfold thickness measure for subcutaneous fat.

A healthy body fat level in men is considered to be between 12 and 18% (3% is essential for insulation and to protect vital organs). For males, a body fat level of >25% would be considered as obese. For women, a healthy body fat level falls between 20 and 25% (12% is considered essential for normal reproductive function), whereas a body fat level between 30 and 35% in women is categorized as obese. Men and women are different in their fat mass and distribution pattern (Fig. 1.1). It should be noted that body fat distribution is determined by genetics and that the level of subcutaneous fat is positively correlated to increased risk of obesity, which is more common in women than men, whereas visceral fat is positively correlated to risk of obesity in men than women. In addition, a waist circumference of >102 cm in men and >88 cm in women is linked to an increase risk of obesity. In this regard, a CT scan would be used to determine levels of visceral fat, but it can also be readily estimated by measuring the waist circumference.

According to the World Health Organization (WHO) [1], worldwide obesity has nearly tripled since 1975. In 2016, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 650 million were obese. Nearly 39% of adults aged 18 years and over were classified as overweight in 2016, and 13% were obese. It is noteworthy that most of the world's population live in countries where being

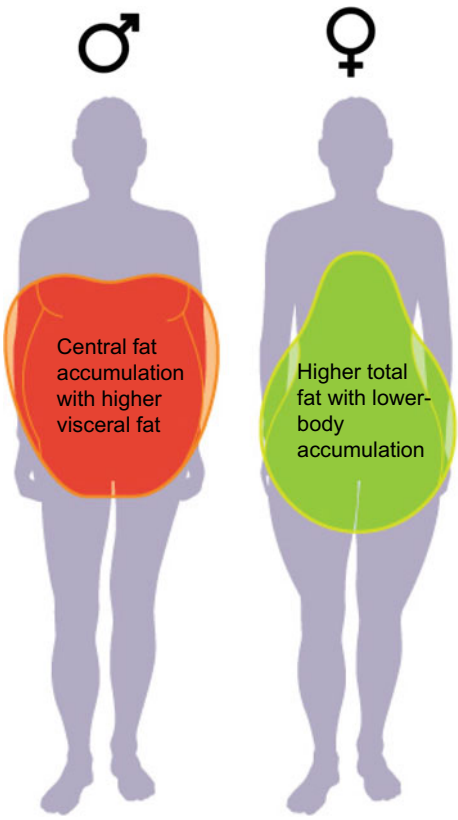

Fig. 1.1 Fat mass and distribution pattern in men and women. Women, compared to men, have higher percent body fat and deposit it in a different pattern, with relatively more adipose tissue in the hips and thighs in women and central obesity typical of men

overweight and obese has a higher mortality rate than malnutrition. It was reported that 41 million children under the age of 5 were overweight or obese in 2016. Furthermore, over 340 million children and adolescents aged 5-19 were overweight or obese in 2016. Most importantly, obesity is preventable. Being overweight and obese is a global epidemic that has been associated with a number of chronic diseases including hypertension, heart disease, diabetes and cancer [1–5]. Figure 1.2 shows the extent of the problem across the globe. It can be seen that obesity is a global concern affecting both developing and developed nations. Indeed, obesity is the most prevalent non-communicable disease in the 21st century. This chapter will briefly describe some factors that can cause obesity and the disparities that exist in its occurrence and consequent development of non-communicable diseases. In addition, the impact of obesity in women and the role of ethnicity in the increased risk as well as development of obesity-induced health complications will also be discussed.

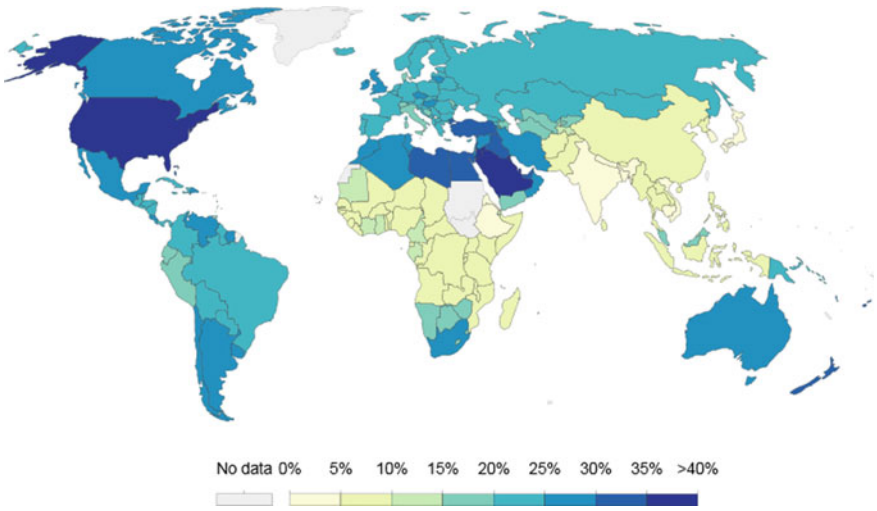

Fig. 1.2 Global distribution of obesity in 2016. Percentage of adults aged 18+ years of age who are defined as obese based on their BMI. A BMI ≥ 30 is defined as obese. body mass. *Source* WHO, Global Health Observatory

Energy Balance and Development of Overweight or Obesity

Energy expenditure is fuelled by the conversion of caloric energy from macronutrients to metabolic energy in the form of ATP. Energy balance occurs when caloric intake matches energy expenditure. When energy is consumed in excess of energy requirements, the extra is stored for later use. However, there is a limited capacity to store excess dietary carbohydrate as glycogen, and there is no storage form for excess protein. When glycogen stores are full, remaining carbohydrate must either be oxidized or metabolized to triglycerides and stored in adipose tissue. Similarly, excess protein remaining after synthesis of body proteins and non-protein nitrogenous compounds must either be oxidized, converted to glucose, or converted to triglycerides. In both situations, excess carbohydrate and protein is converted to triglyceride if immediate energy needs are satisfied. Adipose tissue has an unlimited capacity for triglyceride storage, and can increase to accommodate excess energy by increased sized of adipocytes or synthesis of new adipocytes from adipose progenitor cells [6]. Thus, increases in body weight during times of excess energy intake occur predominantly through expansion of white adipose tissue [7].

Sustained positive energy balance, where energy intake is consistently higher than expenditure, increases the risk of becoming overweight or obese. Several factors can contribute to this imbalance including family history, physical inactivity, and adverse social and behavioral patterns. However, it should be mentioned that such imbalance is necessary in pregnancy, infancy and childhood as well as time of growth. On the other hand, a negative energy balance, where energy intake

is less than energy expenditure results in weight loss. Such a situation would be desirable under conditions of being overweight or obese, but would be undesirable, for example, during illness and anorexia.

Regulation of Energy Balance

Energy balance is controlled by the central nervous system and involves several intricate neural pathways, systems, and regions of the brain. Of these regions, the hypothalamus is considered principal in the homeostatic regulation of energy balance in response to peripheral energy stores and energy availability. The melanocortin system, consisting of agouti-related protein (AgRP)/neuropeptide Y (NPY)-expressing neurons and proopiomelanocortin (POMC)/cocaine and amphetamine regulated transcript (CART)-expressing neurons located in the arcuate nucleus, receives information regarding energy status via circulating hormones and relays this information to effector neurons in other areas of the hypothalamus that control energy intake and expenditure [8–10]. Although several hormones interact with this system, the two with the most influence are leptin and ghrelin. Leptin, a hormone produced by adipocytes in proportion to their size, promotes satiety and energy expenditure by activating POMC/CART neurons and inhibiting AgRP/NPY neurons [11]. Ghrelin, produced by endocrine cells in the stomach, triggers hunger and food intake by stimulating AgPR/NPY neurons [12]. Leptin signaling in the hypothalamus also increases energy expenditure through downstream effects on the sympathetic nervous system, heart rate, blood pressure, and brown adipose tissue thermogenesis [13]. Altered production and signaling of both leptin and ghrelin have been implicated in the development and maintenance of obesity [14]. Other hormones involved in regulation satiety and food intake include insulin, peptide YY, cholecystokinin, and glucagon-like peptide-1.

In addition to homeostatic regulation, hedonic mechanisms influence food intake, and can be powerful enough to override homeostatic regulation and promote energy intake in the absence of physiological hunger. Food cues, including the sight and smell of food, food advertisements, or triggered memories associated with pleasurable food experiences can elicit psychological and physiological responses, such as cravings, salivation, and hormone secretion, which enhance the desire to consume food and promote eating [15]. In the brain, the endocannabinoid and opioid systems within the nucleus accumbens reinforce the hedonic effects of food by stimulating dopamine release and triggering the reward system in response to enjoyable food [16]. Over-activity of the endocannabinoid system is thought to contribute to overeating and weight gain. However, recent research points to divergent effects of this system, with endocannabinoids also having a potential inhibitory effect on feeding behaviors [17].

Components of Energy Expenditure

Total energy expenditure (TEE) consists of basal energy expenditure (BEE), activity-induced energy expenditure (AEE), and diet-induced energy expenditure (DEE). BEE is the minimum energy required to sustain fundamental metabolic processes, including breathing, ion transport, and cardiovascular function, and constitutes anywhere from 60 to 75% of TEE [18]. Due to stringent measurement methods needed to accurately determine BEE, resting energy expenditure (REE) is used to estimate BEE, with REE being approximately 5–10% higher than BEE. REE is often expressed as resting metabolic rate (RMR), a measure of energy expenditure per minute. The two major factors accounting for variability in RMR are body size and body composition [18], with larger body size and higher lean body mass (brain, muscle, liver, blood, body fluids) proportional to RMR. Because of this, males generally have a higher RMR compared to females. Aging reduces RMR due to age-related loss of skeletal muscle mass, and can account for a 2–5% reduction in RMR for every decade after age 30 years [19]. Caloric restriction reduces RMR, with very low energy intake reducing RMR by as much as 10–20% [20]. Conversely, pregnancy, elevated body temperature caffeine, nicotine and thyroid hormone can increase RMR.

AEE is the most variable component of energy expenditure, with estimates ranging from 15–30% of BEE. However, given that AEE is a reflection of lifestyle, occupation, exercise duration and intensity, an accurate estimate is difficult to make. Energy expended for unintentional exercise is called non-exercise activity thermogenesis (NEAT). Generally, NEAT accounts for the majority of the energy expended for physical activity and varies enormously depending on an individual's daily activities [21]. Interestingly, high levels of spontaneous physical activity and therefore high NEAT appears to be protective against developing obesity [21].

Although food is consumed to yield energy, approximately 10% of TEE is required to digest, absorb, metabolize, and store nutrients derived from food [22]. This energy requirement, DEE, is also known as diet-induced thermogenesis due to the slight increase in body temperature observed for several hours after eating. DEE increases with meal size and is dependent on macronutrient composition, with dietary carbohydrate producing the highest DEE and dietary fat producing the lowest [23].

Genetic and Lifestyle Factors Affect Body Weight

It is estimated that genetic factors account for 40–75% of variation in BMI [24], with genome-wide association studies identifying more than 300 genes linked to BMI, waist-to-hip ratio, and adiposity [25]. Patterns and traits related to time spent in physical activity and sedentary behaviour are also influenced by genetic factors [26]. Several theoretical concepts have been developed to explain the genetics of

obesity. Set point theory suggests that body weight is genetically determined, and internal genetically-determined mechanisms defend against changes in weight [27]. The thrifty gene theory suggests that genetic variants cause some individuals to store energy from food more efficiently and expend less energy at rest and during physical activity than people who do not express this gene [24]. While such energy economy was evolutionarily advantageous during times of energy scarcity, energy thriftiness has become a disadvantage in the current environment where energy is readily available. Other proposed theories include the alternative thrifty hypothesis, the drifty genotype hypothesis, the climate adaptation hypothesis, and the aggression control hypothesis [28–31]. Recent studies confirm that genetically predisposed individuals are indeed at greater risk for higher BMI, and that genetic predisposition combined with environmental factors has contributed to increasing incidence of obesity. However, BMI has increased for both genetically predisposed and non-predisposed individuals, implying that environmental factors may have a larger influence on the development of obesity than genetic factors [32].

An obesogenic environment is one where the availability, affordability, accessibility, and marketing of food, combined with lack of opportunities for physical activity and social norms surrounding food and physical activity, promotes excess energy intake, sedentary behavior, and weight gain [33]. Most environmental factors that contribute to the increased incidence of obesity have developed in response to a changing occupational landscape, societal norms, technological advances, and altered family dynamics. Historically, urban design has favored motorized transportation at the expense of active transportation, such as walking or cycling [34], and travel from suburban areas into the city for work often does not make active transportation feasible. Modern occupations are less physically demanding than in the past, with job-related energy expenditure now 100 kcal/day lower than in the past 50 years [35].

Changes in the amount and type of foods consumed also contribute to the rising incidence of obesity. Increasingly large portion sizes (both at home and restaurants) and value-size pricing have modified perceptions of normal and acceptable amounts to consume at an eating occasion [36–38]. Available portion size is directly related to the amount of food consumed at an eating occasion, and over-eating at one meal does not lead to compensatory reduction in food intake at future meals [36]. Interestingly, propensity to overeat in response to large portions does not appear to be affected by BMI, sex, dietary restraint, or socioeconomic status [39].

Convenience and fast foods, while time-saving and less expensive than unprocessed foods, are more energy dense, processed, and lacking in micronutrients [40]. Ultra-processed foods, defined as commercial foods produced from minimal or no whole food ingredients, have become increasingly prevalent and popular due to their ease of preparation, appealing taste, and extensive marketing. These foods tend to be more energy dense and higher in added sugars, salt, and artificial flavourings, colors, and preservatives compared to minimally processed foods [41]. Sales of ultra-processed foods have significantly increased over the past 30 years while those of unprocessed or minimally processed foods have gradually declined [42, 43], with energy intake from ultra-processed foods currently comprising up to

60% of total energy intake in U.S. adults [44]. Strong observational data supports the hypothesis that consuming ultra-processed foods has contributed to the high rates of excess weight and abdominal obesity in countries such as the U.S.A, Canada, the UK, Brazil, France, and Spain [45–49]. In a recent in-patient feeding study, participants consumed more calories when given ad libitum access to ultra-processed diet compared to ad libitum access to an diet composed of unprocessed foods, despite the two diets being matched for daily presented calories, sugar, fat, and macronutrients [50]. Additionally, participants on the ultra-processed diet gained weight, while those on the unprocessed diet lost weight, suggesting a direct role for consumption of ultra-processed foods on weight status.

Health Complications Due to Obesity

While 30 years ago the global focus was to combat childhood malnutrition and how to feed an increasing global population, today there is an additional challenge of managing obesity and concomitant non-communicable health complications [51]. There are several health complications that can develop as a consequence of being overweight or obese (summarized in Fig. 1.3). Since being obese increases the risk for developing hypertension and hypercholesterolemia, the risk for heart disease and occurrence of a stroke is elevated. Most individuals with type 2 diabetes are overweight or obese. Although diabetes and high blood pressure are the most common causes of chronic kidney disease, recent studies suggest that even in the absence of these risks, obesity itself may promote chronic kidney disease. Cancers of the colon, breast (post-menopausal women), endometrium (the lining of the

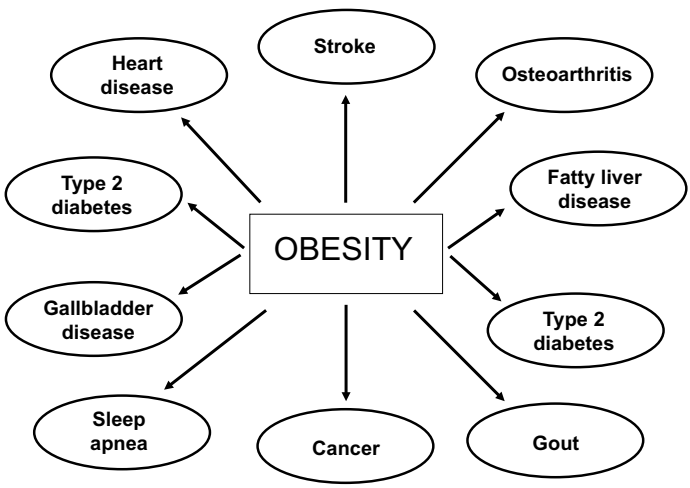

Fig. 1.3 Adverse health complications associated with obesity

uterus), kidney and esophagus have also been reported to be linked to obesity. Furthermore, some studies have reported an association between obesity and cancers of the gallbladder, ovaries, and pancreas. The incidence of gallbladder disease and gallstones are known to be more common in overweight and obese individuals. Osteoarthritis is a common joint condition that most often affects the knee, hip, or back.

With an excessive bodyweight, there is added pressure on joints, which degenerates the cartilage at a faster rate. On the other hand, gout, which is a condition that also affects the joints is caused by deposition of excessive uric acid crystals and is prevalent in overweight individuals. Sleep apnea is a breathing condition associated with being overweight that can lead to a brief interruption in normal breathing during sleep. In fact, sleep apnea can increase the risk for heart disease and stroke. Non-alcoholic fatty liver disease (NAFLD) due to fat accumulation in the liver causes liver injury. Fatty liver disease may lead to severe liver damage, cirrhosis, or even liver failure. Taken together, it is evident that understanding the cause of excessive weight gain as well as implementing measures that can prevent or treat it can result in a sustained weight reduction and normalization that would subsequently reduce the risk for obesity induced health complications.

Since the prevalence of being overweight and obesity among men and women varies greatly, more women are obese than men. Indeed, more than 2 of 3 women in the US are overweight or obese. Women, compared to men, have higher percent body fat and deposit it in a different pattern, with relatively more adipose tissue in the hips and thighs in women and central obesity typical of men [52]. Severe obesity is more prevalent in women than men worldwide, and obesity

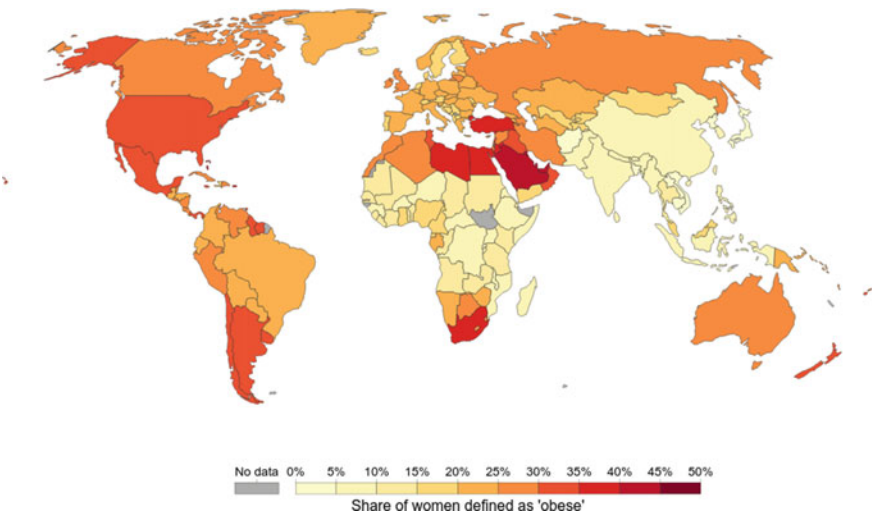

Fig. 1.4 Prevalence of obesity in adult females in 2014. The share of adult women defined as obese, measured as the percentage of women with a BMI value >30. *Source* Prevalence of weight categories in females, NCD Risk Factor Collaboration

pathophysiology and the resultant obesity-related disease risks differ in women and men. Although the underlying mechanisms are largely unknown, pre-clinical and human studies indicate that ovarian hormones may play a major role [53]. The underlying mechanisms are largely unknown. Pre-clinical and clinical research indicate that ovarian hormones may play a major role. Figure 1.4 shows the share of the global prevalence of obesity by women.

Consequences of Obesity in Women

Bodyweight is a major issue for women, however ethnicity and race as well as socioeconomic status can also have an effect on weight levels—which further affect the health status of the woman [54]. Central obesity seems to have a stronger impact in African-American women than general adiposity as measured by BMI [55]. There has been a global increase of obesity in women that are of reproductive age that has resulted in infertility/reduced fertility as well as an increase in the time taken to conceive [56, 57]. In addition, the development of obesity associated co-morbidities (i.e. type 2 diabetes and hypertension) increase the risk of adverse outcomes for both mother and child. Indeed, children of obese gravida are at a greater risk for the development of cardiometabolic disease in childhood and throughout adulthood [58].

Obese pregnant women are at a greater risk of premature pregnancy loss, increased risk of congenital fetal malformations, delivery of large for gestational age infants, spontaneous and premature birth, and stillbirth [59, 60]. During late stage of pregnancy the risk for gestational diabetes and pre-eclampsia are increased. Women with obesity can also experience difficulties during labor and delivery, and are more at risk of post-partum hemorrhage. With respect to long-term health complications in obese women, weight retention after delivery, and difficulties in subsequent pregnancy can occur [56]. It should be mentioned that aside from the physical complications of obesity, obesity has negative psychological consequences particularly in women including impaired body image, low self-esteem, eating disorders, stress, depression and poor quality of life [61]. In addition, it is interesting to note that emotional problems such as depression, anxiety, and stress are associated with an increase in BMI during pregnancy have also been reported to occur [62]. It is evident that women with obesity need support to lose weight before they conceive, and to minimize their weight gain in pregnancy to reduce the risk of complications for both mother and offspring [56]. It should also be noted that polycystic ovary syndrome is a common endocrine disorder that results in polycystic ovaries and is often seen concomitantly with obesity [63]. This condition also represents an increase in the risk in the development of cardiovascular, metabolic syndrome and diabetes.

It is known that there are large variations in obesity and breast cancer rates worldwide and across racial/ethnic groups, however; most studies evaluating the impact of obesity on breast cancer risk and survival have been conducted in

non-Hispanic white women in the US or Europe [55]. Since there are differences in tumor hormone receptor subtype distribution, obesity prevalence, and risk factor profiles, among women of different racial/ethnic groups, it would be expected that differences also exist in breast cancer risk. Indeed, obesity and a sedentary lifestyle may be two important modifiable risk factors for breast carcinoma and thus may have a significant public health impact in women from various racial and ethnic backgrounds [64]. Despite the paucity of data, current evidence suggests a stronger adverse effect of obesity on breast cancer risk and survival in women of Asian ancestry. For African Americans and Hispanics, the strength of the associations appears to be more comparable to that of non-Hispanic whites, particularly when accounting for subtype and menopausal status [55]. In the US, African American women are more likely than non-Hispanic European women to be obese and to be diagnosed with triple-negative breast cancer [65]. With respect to other specific women's health issues during obesity, despite extensive research examining adiposity (BMI), a weak positive correlation has been observed between the risk of ovarian cancer, the most fatal gynecological cancer, and adiposity [66].

The prevalence of obesity is rapidly increasing in the US, particularly among women. Approximately 60–70% of hypertension in adults may be directly attributed to obesity. In addition, maternal obesity is a major risk factor for hypertensive disorders during pregnancy [67]. The underlying mechanisms for the association between obesity and cardiovascular disease (CVD) risk are multifactorial, but activation of the sympathetic nervous system is one significant contributing factor. Sex may influence the association between hypertension and sympathetic overactivity in obese people. Chronic hyperinsulinemia due to insulin resistance, high plasma levels of leptin, and obstructive sleep apnea may be responsible for sympathetic overactivity in obesity-related hypertension [67]. It is pointed out that weight gain in women in mid-life is related to an increase in central fat distribution as a consequence of diminishing levels of estrogen [68]. Central obesity results in dysglycemia, dyslipidemia, hypertension and CVD. Since CVD is the leading cause of death in postmenopausal women, the importance of weight management cannot be overstated.

Ethnic Differences in Obesity-Related Disease

Strategies for the treatment and prevention of obesity-related health complications may need to understand and address ethnic related differences in the occurrence of co-morbidities due to obesity as well as lifestyle factors that predispose ethnic groups to obesity [69]. Indeed, ethnic minorities are disproportionately affected by overweight and obesity that increases the risk for adverse health outcomes including CVD and diabetes [70].

An association between vitamin D status and obesity and obesity-induced co-morbidities has been proposed [71]. In this regard, ethnic minorities have higher rates of vitamin D insufficiency, which is correlated to obesity-related chronic

diseases i.e. type 2 diabetes, CVD and metabolic syndrome. There is a high prevalence of obesity in American Indians of all ages and in both men and women [72] that has been linked to high rates of complications including type 2 diabetes, hypertension, dyslipidemia and respiratory problems. Such observations have been attributed to a high-fat, high-calorie diet coupled with a sedentary lifestyle. NAFLD has been reported to exist in approximately 30% of the world's population [73]. Epidemiological studies have concluded that ethnicity plays a role in complications and treatment response. The highest NAFLD prevalence is observed in Hispanic populations, exhibiting a worse disease progression. Interestingly, it has been reported that the Hispanic American population is at higher risk for obesity as well as diabetes and end-stage renal disease [74]. In contrast, African-Caribbean exhibit the lowest risk, with less severe steatosis and inflammation, lower levels of triglycerides, and less metabolic derangement, but conversely higher prevalence of insulin resistance. The prevalence of NAFLD in Asian cohorts is considered to be of epidemic proportions in these populations [73].

As already mentioned in the previous section, obese women experience higher rates of infertility and other pregnancy complications. Obese women have a lower chance of pregnancy following in vitro fertilization (IVF), which also appear to be related to racial/ethnic background. In this regard, compared with normal-weight women, failure to achieve a clinical intrauterine gestation is significantly more likely among obese women overall, normal-weight and obese Asian women, normal-weight Hispanic women, and overweight and obese Black women. Among women who do conceive, compared with normal-weight women, failure to achieve a live birth is significantly more likely among overweight and obese women overall, and among overweight and obese Asian women, overweight and obese Hispanic women, and normal-weight and obese Black women. Although weight loss should theoretically be the first line of therapy for obese women, other lifestyle factors, such as regular physical exercise, elimination of tobacco use and alcohol consumption, and stress management, may be of more immediate benefit in achieving conception [60].

South Asians are at higher risk than white Caucasians for the development of obesity and obesity-related non-communicable diseases, including insulin resistance, the metabolic syndrome, type 2 diabetes and coronary heart disease (CHD) [75]. Rapid nutrition and lifestyle transitions have contributed to acceleration of obesity-related non-communicable diseases in South Asians. Differences in determinants and associated factors for obesity-related non-communicable diseases between South Asians and White Caucasians include body phenotype (high body fat, high truncal, subcutaneous and intra-abdominal fat, and low muscle mass), biochemical parameters (hyperinsulinemia, hyperglycemia, dyslipidemia, hyperleptinemia, low levels of adiponectin and high levels of C-reactive protein), procoagulant state and endothelial dysfunction. Higher prevalence, earlier onset and increased complications of type 2 diabetes and CHD are often seen at lower levels of BMI and waist circumference in South Asians than white Caucasians.

Imbalanced nutrition, physical inactivity, perinatal adverse events and genetic differences are also important contributory factors. Other differences between South

Asians and white Caucasians include lower disease awareness and health-seeking behavior, delayed diagnosis due to atypical presentation and language barriers, and religious and sociocultural factors. All these factors result in poorer prevention, less aggressive therapy, poorer response to medical and surgical interventions, and higher morbidity and mortality in South Asians. During 2011 and 2012, more than a third of the US population was obese [76]. Significant racial and ethnic variations exist in the prevalence of obesity and diabetes. Generally, non-Hispanic blacks and Mexican Americans appear to be at higher risk for developing obesity as well as diabetes as compared to the non-Hispanic white population for both adults and children [76].

Although the prevalence of chronic kidney disease (CKD) is similar or slightly less in Hispanics than non-Hispanic whites, the prevalence of end-stage renal disease is almost 50% higher in Hispanics compared to non-Hispanic whites [77] that may be related to the greater prevalence of obesity in the US Hispanic population. It should be mentioned that since blood pressure is strongly related to body weight, the control of obesity is a key component in the prevention and control of hypertension [78]. Given the high prevalence of obesity in the African American population, especially among women [79], interventions for weight reduction would be highly beneficial as even a modest weight loss can not only prevent or reverse blood pressure elevations, but would also be seen to reduce the risk of obesity induced CVD, diabetes and hyperlipidemia [78].

Approaches for Obesity Management and Weight Reduction

Management of obesity as a chronic disease focuses on improving physical health, mental health, and overall wellbeing [80]. While preventing further weight gain may be the first goal of obesity management, weight reduction is indicated to improve obesity-related conditions such as hypertension, dyslipidemia, and type 2 diabetes. The first approach to obesity management focuses on lifestyle changes aimed at reducing energy intake and increasing physical activity to achieve fat loss [81]. Although seemingly straightforward, success of such lifestyle interventions relies heavily on behavioural change, which can be hampered by factors such as lack of time for physical activity or meal preparation, societal, social and family pressures, emotional state, physical limitations or injuries, socioeconomic status, limited knowledge on nutrition and physical activity, and lack of motivation [82]. Lifestyle interventions are more likely to be effective if individualized, with a patient's personal barriers considered before making specific dietary and exercise recommendations. Factors such as successful initial weight loss, lower starting BMI, better mental outlook at the start of weight loss, being male, and older age have been linked to higher adherence to and success with lifestyle interventions [83]. Maintaining initial weight loss can be challenging and often difficult for

patients, with many experiencing cycles of weight loss and weight re-gain. Therefore, attention should be given to ensuring weight loss goals, and the methods used to achieve them, are realistic and sustainable. Specific lifestyle factors associated with sustained weight loss include one hour of physical activity per day, consuming a low calorie, low fat diet, eating breakfast regularly, consistency in weekly eating patterns, and self-monitoring of body weight [84, 85]. If weight loss can be maintained for 2 to 5 years, the likelihood of longer-term success, even after 10 years, significantly increases [84].

Very low energy diets (VLED) are the most aggressive form of caloric restriction used in obesity management, limiting caloric intake to 450–800 kcal per day. Because the volume of food associated with such a low caloric value is small, commercially available products fortified with vitamins and minerals are often used to prevent micronutrient deficiencies with this dietary approach. VLED should be undertaken with medical supervision to monitor micronutrient status, and also to adjust medications used for treating co-morbidities as they improve with weight loss. Initially weight loss may be significant with VLED. However, adherence to such a low energy diet can be challenging for patients and their usefulness for long-term sustained weight loss has been questioned. A recent systematic review and meta-analysis suggests that, if coupled with adequate support and behavioural programs, VLED can be well-tolerated and used more widely than is currently practiced [86]. Additional concerns regarding severe caloric restriction include loss of fat free mass, metabolic adaptations, and reduction in energy expenditure accompanying rapid and drastic weight loss that can oppose sustained weight loss [87]. However, fat free mass can be maintained with VLED with adequate protein intake and resistance exercise [88].

When lifestyle strategies alone are insufficient to elicit weight loss, complementary therapies may be initiated. Pharmacological agents for obesity management are generally only prescribed for patients with a BMI of ≥ 30 kg/m^2, or ≥ 27 kg/m^2 in the presence of one or more weight related co-morbidities, such as hypertension, dyslipidemia, or type 2 diabetes. Weight loss medications that were commonly prescribed for weight loss in the past, such as fen-phen and sibutramine, have been withdrawn from the market due to increased risk of serious cardiovascular complications [89, 90]. Five anti-obesity medications are currently approved by the American Food and Drug Administration, each with differing mechanisms of action: Orlistat (Xenical, Ali), Lorcaserin (Belviq), Phentermine/topiramate (Qsymia), Naltrexone/bupropion (Contrave), and Liraglutide (Saxenda). All of these medications induce weight loss (average of 5–10 kg lost) and are associated with improved cardiometabolic risk factors [91].

Orlistat, the oldest of these approved drugs, is available in a non-prescription version known as Ali, and both versions work by inhibiting pancreatic lipase and digestion of dietary triglycerides (TG). Undigested TG move through the intestinal tract and cause the side effects commonly reported with this medication, including abdominal pain, oily discharge, inability to hold or sudden urge to have a bowel movement, increased number of bowel movements, and malabsorption of fat soluble vitamins. The remaining four approved anti-obesity medications act on the

central nervous system and/or neuroendocrine pathways to regulate energy intake and expenditure. Prescribing these newer medications in combination at lower doses can maximize effectiveness while minimizing side effects of each [82, 92]. These medications have favourable safety profiles, but have been associated with side effects including dry mouth, paresthesia, constipation, insomnia, dizziness, and dysgeusia, nausea, headache, and increased lipase enzymes [93].

The most effective medical intervention for sustained weight loss is bariatric surgery. Although specific eligibility criteria may vary, generally patients with a BMI >40 kg/m^2 or >35 kg/m^2 with co-morbidities such as type 2 diabetes, dyslipidemia, hypertension, sleep apnea or renal disease are eligible for this intervention [94]. The ultimate outcome of bariatric surgery is to reduce the size of the stomach, with different surgical procedures achieving this via different methods. The most commonly performed bariatric procedures are gastric banding, sleeve gastrectomy, and gastric bypass. Gastric banding involves surgically placing an adjustable and removable band around the upper stomach to create a small stomach pouch, while sleeve gastrectomy creates a small stomach pouch by surgically removing a large portion of the stomach. In Roux-en-y gastric bypass, the stomach is permanently divided to make a small pouch, which is then attached directly to the jejunum, and the remaining portion of the stomach and duodenum are bypassed. Each of these surgeries reduces stomach capacity and the amount of food that can be eaten, thereby reducing caloric intake. However, changes to circulating gastrointestinal hormones and the gut microbiome may also contribute to restoration of energy homeostasis, weight loss, and improvements in cardiometabolic risk factors observed after these surgical procedures [95, 96].

Bariatric surgeries carry risks common to any surgery. However, these surgeries have additional complications including abdominal hernias, stretched stomach pouches, gallstones, and dumping syndrome, where premature gastric emptying of hyperosmolar stomach contents into the small intestine leads to nausea, weakness, sweating, faintness, and diarrhea [97]. Due to the malabsorptive nature of these surgeries, nutrient deficiencies can be common, and supplementation is vital for these patients [98]. Deficiencies in calcium and vitamin D, combined with changes in gastrointestinal hormones, circulating adipokines, and decreased mechanical load from weight loss can compromise bone health [99]. Anemias are also a common complication of bariatric surgeries due to an increased susceptibility to vitamin B_{12}, folate, and iron deficiencies. In addition, bioavailability of oral medications may be impacted by bariatric surgery and medication doses must be closely monitored in the immediate post-surgery period [100]. As a result of the magnitude and speed of weight loss post-surgery, REE and the REE to fat free mass ratio may decrease, hindering sustained weight loss [101], which may account for the plateau or increase in weight that is often observed after the initial weight loss post-surgery [102, 103]. As such, lifestyle interventions are an important adjunct to surgery if weight loss is to be sustained.

Conclusions

It is evident that obesity and its related co-morbidities have become major threats to world health. Greater risks for adverse health complications occur during obesity are associated with ethnic backgrounds and sex differences. Effective strategies are required for obesity prevention and treatment that will also reduce the burden of obesity associated non-communicable diseases. Indeed, to be effective, educational and environmental interventions are required that are culture and gender specific. Although weight loss is the first line of therapy, there are of course, other lifestyle factors including regular physical activity and stress management that can reduce obesity and associated health complications and the global epidemic of obesity.

Acknowledgements Infrastructural support was provided by the St. Boniface Hospital Research Foundation and the University of Winnipeg.

References

1. World Health Organization (2019) https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accesed 11 July 2019
2. Wagner KH, Brath H (2012) A global view on the development of non communicable diseases. Prev Med 54(Suppl):S38–S41
3. Taherogorabi Z, Khazaei M, Moodi M, Chamani E (2016) From obesity to cancer: a review on proposed mechanisms. Cell Biochem Funct 34:533–545
4. Dugani S, Gaziano TA (2016) 25 by 25: achieving global reduction in cardiovascular mortality. Curr Cardiol Rep 18:10
5. Jagannathan R, Patel SA, Ali MK, Narayan KMV (2019) Global updates on cardiovascular disease mortality trends and attribution of traditional risk factors. Curr Diab Rep 19:44
6. Berry DC, Jiang Y, Graff JM (2016) Emerging roles of adipose progenitor cells in tissue development, homeostasis, expansion and thermogenesis. Trends Endocrinol Metab 27:574–585
7. Cuthbertson DJ, Steele T, Wilding JP, Halford JC, Harrold JA, Hamer M, Karpe F (2017) What have human experimental overfeeding studies taught us about adipose tissue expansion and susceptibility to obesity and metabolic complications? Int J Obes 41:853–865
8. Aponte Y, Atasoy D, Sternson SM (2011) AGRP neurons are sufficient to orchestrate feeding behavior rapidly and without training. Nat Neurosci 14:351–355
9. Fan W, Boston BA, Kesterson RA et al (1997) Role of melanocortinergic neurons in feeding and the agouti obesity syndrome. Nature 385:165–168
10. Krashes MJ, Koda S, Ye C et al (2011) Rapid, reversible activation of AgRP neurons drives feeding behavior in mice. J Clin Invest 121:1424–1428
11. Oswal A, Yeo GS (2007) The leptin melanocortin pathway and the control of body weight: lessons from human and murine genetics. Obes Rev 8:293–306
12. Shaw AM, Irani BG, Moore MC et al (2005) Ghrelin-induced food intake and growth hormone secretion are altered in melanocortin 3 and 4 receptor knockout mice. Peptides 26:1720–1727
13. Pandit R, Beerens S, Adan RAH (2017) Role of leptin in energy expenditure: the hypothalamic perspective. Am J Physiol Regul Integr Comp Physiol 312:R938–R947
14. Cui H, López M, Rahmouni K (2017) The cellular and molecular bases of leptin and ghrelin resistance in obesity. Nat Rev Endocrinol 13:338–351

15. Belfort-DeAguiar R, Seo D (2018) Food cues and obesity: overpowering hormones and energy balance regulation. Curr Obes Rep 7:122–129
16. Lutter M, Nestler EJ (2009) Homeostatic and hedonic signals interact in the regulation of food intake. J Nutr 39:629–632
17. Lau BK, Cota D, Cristino L, Borgland SL (2017) Endocannabinoid modulation of homeostatic and non-homeostatic feeding circuits. Neuropharmacology 124:38–51
18. Westerterp KR (2017) Control of energy expenditure in humans. Eur J Clin Nutr 71:340–344
19. St-Onge MP, Gallagher D (2010) Body composition changes with aging: the cause or the result of alterations in metabolic rate and macronutrient oxidation? Nutrition 26:152–155
20. Keys A, Brozek J, Henschel A et al (1950) The biology of human starvation. University of Minnesota Press, Minneapolis, USA
21. Teske JA, Billington CJ, Kotz CM (2008) Neuropeptidergic mediators of spontaneous physical activity and non-exercise activity thermogenesis. Neuroendocrinology 87:71–90
22. van Baak MA (2008) Meal-induced activation of the sympathetic nervous system and its cardiovascular and thermogenic effects in man. Physiol Behav 94:178–186
23. Tappy L (1996) Thermic effect of food and sympathetic nervous system activity in humans. Reprod Nutr Dev 36:391–397
24. Reddon H, Patel Y, Turcotte M et al (2018) Revisiting the evolutionary origins of obesity: lazy versus peppy-thrifty genotype hypothesis. Obes Rev 19:1525–1543
25. Goodarzi MO (2018) Genetics of obesity: what genetic association studies have taught us about the biology of obesity and its complications. Lancet Diabetes Endocrinol 6:223–236
26. den Hoed M, Brage S, Zhao JH et al (2013) Heritability of objectively assessed daily physical activity and sedentary behavior. Am J Clin Nutr 98:1317–1325
27. Farias MM, Cuevas AM, Rodriguez F (2011) Set-point theory and obesity. Metab Syndr Relat Disord 9:85–89
28. Stöger R (2008) The thrifty epigenotype: an acquired and heritable predisposition for obesity and diabetes? BioEssays 30:156–166
29. Speakman JR (2007) A nonadaptive scenario explaining the genetic predisposition to obesity: the "predation release" hypothesis. Cell Metab 6:5–12
30. Sellayah D, Cagampang FR, Cox RD (2014) On the evolutionary origins of obesity: a new hypothesis. Endocrinology 155:1573–1588
31. Belsare PV, Watve MG, Ghaskadbi SS, Bhat DS, Yajnik CS, Jog M (2010) Metabolic syndrome: aggression control mechanisms gone out of control. Med Hypotheses 74:578–589
32. Brandkvist M, Bjørngaard JH, Ødegård RA et al (2019) Quantifying the impact of genes on body mass index during the obesity epidemic: longitudinal findings from the HUNT Study. BMJ 366:l4067
33. World Health Organization (2016) Report of the commission on ending childhood obesity. http://apps.who.int.uml.idm.oclc.org/iris/bitstream/10665/204176/1/9789241510066_eng.pdf?ua=1 Version current 1 2016. Accessed 12 July 2019
34. Garfinkel-Castro A, Kim K, Hamidi S, Ewing R (2017) Obesity and the built environment at different urban scales: examining the literature. Nutr Rev 75:51–61
35. Church TS, Thomas DM, Tudor-Locke C et al (2011) Trends over 5 decades in U.S. occupation-related physical activity and their associations with obesity. PLoS ONE 6: e19657
36. Livingstone MB, Pourshahidi LK (2014) Portion size and obesity. Adv Nutr 5:829–834
37. Nielsen SJ, Popkin BM (2003) Patterns and trends in food portion sizes, 1977–1998. JAMA 289:450–453
38. Zheng M, Rangan A, Meertens B, Wu JHY (2017) Changes in typical portion sizes of commonly consumed discretionary foods among Australian adults from 1995 to 2011–2012. Nutrients 9. pii: E577
39. Ello-Martin JA, Ledikwe JH, Rolls BJ (2005) The influence of food portion size and energy density on energy intake: implications for weight management. Am J Clin Nutr 82:236S–241S

40. Wellard L, Havill M, Hughes C et al (2015) Energy-dense fast food products cost less: an observational study of the energy density and energy cost of Australian fast foods. Aust N Z J Public Health 39:544–545
41. Moubarac JC, Parra DC, Cannon G, Monteiro CA (2014) Food classification systems based on food processing: significance and implications for policies and actions: a systematic literature review and assessment. Curr Obes Rep 3:256–272
42. Marrón-Ponce JA, Tolentino-Mayo L, Hernández-F M, Batis C (2018) Trends in ultra-processed food purchases from 1984 to 2016 in Mexican households. Nutrients 11:2018
43. Solberg SL, Terragni L, Granheim SI (2016) Ultra-processed food purchases in Norway: a quantitative study on a representative sample of food retailers. Ultra-processed food purchases in Norway: a quantitative study on a representative sample of food retailers. Public Health Nutr 19:1990–2001
44. Martínez Steele E, Baraldi LG, Louzada ML et al (2016) Ultra-processed foods and added sugars in the US diet: evidence from a nationally representative cross-sectional study. BMJ Open 6:e009892
45. Adams J, White M (2015) Characterization of UK diets according to degree of food processing and associations with socio-demographics and obesity: cross-sectional analysis of UK National Diet and Nutrition Survey (2008–12). Int J Behav Nutr Phys Act 12:160
46. Julia C, Martinez L, Allès B et al (2018) Contribution of ultra-processed foods in the diet of adults from the French NutriNet-Santé study. Public Health Nutr 21:27–37
47. Louzada ML, Baraldi LG, Steele EM et al (2015) Consumption of ultra-processed foods and obesity in Brazilian adolescents and adults. Prev Med 81:9–15
48. Mendonça RD, Pimenta AM, Gea A, de la Fuente-Arrillaga C et al (2016) Ultra-processed food consumption and risk of overweight and obesity: the University of Navarra Follow-Up (SUN) cohort study. Am J Clin Nutr 104:1433–1440
49. Canella DS, Levy RB, Martins AP et al (2014) Ultra-processed food products and obesity in Brazilian households (2008–2009). PLoS ONE 9:e92752
50. Hall KD, Ayuketah A, Brychta R et al (2019) Ultra-processed diets cause excess calorie intake and weight gain: an inpatient randomized controlled trial of ad libitum food intake. Cell Metab 30:67–77.e3
51. Prentice AM (2006) The emerging epidemic of obesity in developing countries. J Epidemiol 35:93–99
52. Lee MJ, Fried SK (2017) Sex-dependent depot differences in adipose tissue development and function; role of sex steroids. J Obes Metab Syndr 26:172–180
53. Leeners B, Geary N, Tobler PN, Asarian L (2017) Ovarian hormones and obesity. Hum Reprod Update 23:300–321
54. Bowen DJ, Tomoyasu N, Cauce AM (1991) The triple threat: a discussion of gender, class, and race differences in weight. Women Health 17:123–143
55. Bandera EV, Maskarinec G, Romieu I, John EM (2015) Racial and ethnic disparities in the impact of obesity on breast cancer risk and survival: a global perspective. Adv Nutr 6:803–819
56. Poston L, Caleyachetty R, Cnattingius S et al (2016) Preconceptional and maternal obesity: epidemiology and health consequences. Lancet Diabetes Endocrinol 4:1025–1036
57. Kelly-Weeder S, Cox CL (2006) The impact of lifestyle risk factors on female infertility. Women Health 44:1–23
58. Chandrasekaran S, Neal-Perry G (2017) Long-term consequences of obesity on female fertility and the health of offspring. Curr Opin Obstet Gynecol 29:180–187
59. Marchi J, Berg M, Dencker A et al (2015) Risks associated with obesity in pregnancy, for the mother and baby: a systematic review of reviews. Obes Res 16:621–638
60. Luke B (2017) Adverse effects of female obesity and interaction with race on reproductive potential. Fertil Steril 107:868–877
61. Chu DT, Minh Nguyet NT, Nga VT et al (2019) An update on obesity: mental consequences and psychological interventions. Diabetes Metab Syndr 13:155–160

62. Faria-Schützer DB, Surita FG, Nascimento SL et al (2017) Psychological issues facing obese pregnant women: a systematic review. J Matern Fetal Neonatal Med 30:88–95
63. Meier RK (2018) Polycystic ovary syndrome. Nurs Clin North Am 53:407–420
64. McTiernan A (2000) Associations between energy balance and body mass index and risk of breast carcinoma in women from diverse racial and ethnic backgrounds in the U.S. Cancer 88:1248–1255
65. Dietze EC, Chavez TA, Seewaldt VL (2018) Obesity and triple-negative breast cancer: disparities, controversies, and biology. Am J Pathol 188:280–290
66. Tworoger SS, Huang T (2016) Obesity and ovarian cancer. 208:155–176
67. Fu Q (2019) Sex differences in sympathetic activity in obesity and its related hypertension. Ann NY Acad Sci 1454:31–41
68. Kapoor E, Collazo-Clavell ML, Faubion SS (2017) Weight gain in women in midlife: a concise review of the pathophysiology and strategies for management. Mayo Clin Proc 92:1552–1558
69. Abate N, Chandalia M (2003) The impact of ethnicity on type 2 diabetes. J Diabetes Complic 17:39–58
70. Nesbitt SD, Ashaye MO, Stettler N et al (2004) Overweight as a risk factor in children: a focus on ethnicity. Ethn Dis 14:94–110
71. Renzaho AM, Halliday JA, Nowson C (2011) Vitamin D, obesity, and obesity-related chronic disease among ethnic minorities: a systematic review. Nutrition 27:868–879
72. Story M, Stevens J, Himes J et al (2003) Obesity in American-Indian children: prevelance, consequences, and prevention. Prev Med 37:S3–S12
73. Szanto KB, Li J, Cordero P, Oben JA (2019) Ethnic differences and heterogeneity in genetic and metabolic makeup contributing to nonalcoholic fatty liver disease. Diabetes Metab Syndr Obes 12:357–367
74. Yracheta JM, Alfonso J, Lanaspa MA et al (2015) Postgrad Med 127:503–510
75. Misra A, Khurana L (2011) Obesity-related non-communicable diseases: South Asians vs white Caucasians. Int J Obes 35:167–187
76. Bhupathiraju SN, Hu FB (2016) Epidemiology of obesity and diabetes and their cardiovascular complications. Circ Res 118:1723–1735
77. Desai N, Lora CM, Lash JP, Ricardo AC (2019) CKD and ESRD in US Hispanics. Am J Kidney Dis 73:102–111
78. Kumanyika SK (1997) The impact of obesity on hypertension management in African Americans. J Health Care Poor Underserved 8:352–364
79. Kumanyika S (1987) Obesity in black women. Epidemiol Rev 9:31–50
80. Obesity Canada (2019) https://obesitycanada.ca/managing-obesity/. Accessed 10 July 2019
81. Semlitsch T, Stigler FL, Jeitler K et al (2019) Management of overweight and obesity in primary care-A systematic overview of international evidence-based guidelines. Obes Rev 20:1218–1230
82. Sweeting AN, Caterson ID (2017) Approaches to obesity management. Intern Med J 47:734–739
83. Burgess E, Hassmén P, Pumpa KL (2017) Determinants of adherence to lifestyle intervention in adults with obesity: a systematic review. Clin Obes 7:123–135
84. Wing RR, Phelan S (2005) Long-term weight loss maintenance. Am J Clin Nutr 82:222S–225S
85. Thomas JG, Bond DS, Phelan S et al (2014) Weight-loss maintenance for 10 years in the National Weight Control Registry. Am J Prev Med 46:17–23
86. Parretti HM, Jebb SA, Johns DJ et al (2016) Clinical effectiveness of very-low-energy diets in the management of weight loss: a systematic review and meta-analysis of randomized controlled trials. Obes Rev 17:225–234
87. Fothergill E, Guo J, Howard L et al (2016) Persistent metabolic adaptation 6 years after "The Biggest Loser" competition. Obesity (Silver Spring). 24:1612–1619

88. Hansen TT, Hjorth MF, Sandby K et al (2019) Predictors of successful weight loss with relative maintenance of fat-free mass in individuals with overweight and obesity on an 8-week low-energy diet. Br J Nutr 27:1–12
89. Connolly HM, Crary JL, McGoon MD et al (1997) Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med 337:581–588
90. James WP, Caterson ID, Coutinho W et al (2010) Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med 363:905–917
91. Daneschvar HL, Aronson MD, Smetana GW (2016) FDA-approved anti-obesity drugs in the United States. Am J Med 129(879):e1–e6
92. Sweeting AN, Hocking SL, Markovic TP (2015) Pharmacotherapy for the treatment of obesity. Mol Cell Endocrinol 418:173–183
93. Krentz AJ, Fujioka K, Hompesch M (2016) Evolution of pharmacological obesity treatments: focus on adverse side-effect profiles. Diabetes Obes Metab 18:558–570
94. International Federation for the Surgery of Obesity and Metabolic Disorders (2019) Are you a candidate. https://www.ifso.com/are-you-a-candidate/. Accessed 11 July 2019
95. Madsbad S, Dirksen C, Holst JJ (2014) Mechanisms of changes in glucose metabolism and bodyweight after bariatric surgery. Lancet Diabetes Endocrinol 2:152–164
96. Tremaroli V, Karlsson F, Werling M et al (2015) Gastroplasty induce long-term changes on the human gut microbiome contributing to fat mass regulation. Cell Metab 22:228–238
97. Ahmad A, Kornrich DB, Krasner H et al (2019) Prevalence of dumping syndrome after laparoscopic sleeve gastrectomy and comparison with Laparoscopic Roux-en-Y gastric bypass. Obes Surg 29:1506–1513
98. Stroh C, Manger T, Benedix F (2017) Metabolic surgery and nutritional deficiencies. Minerva Chir 72:432–441
99. Gregory NS (2017) The effects of bariatric surgery on bone metabolism. Endocrinol Metab Clin North Am 46:105–116
100. Angeles PC, Robertsen I, Seeberg LT et al (2019) The influence of bariatric surgery on oral drug bioavailability in patients with obesity: a systematic review. Obes Rev 20:1299–1311
101. Lamarca F, Melendez-Araújo MS, Porto de Toledo I et al (2019) Relative energy expenditure decreases during the first year after bariatric surgery: a systematic review and meta-analysis. Obes Surg 29:2648–2659
102. Chang SH, Stoll CR, Song J et al (2014) The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012. JAMA Surg 149:275–287
103. Gloy VL, Briel M, Bhatt DL et al (2013) Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. BMJ 347: f5934