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## Gender and Sex Differences in Adipose Tissue

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### Abstract

**Purpose of Review**—As the ongoing epidemic of adult and childhood obesity grows, it puts a greater burden on individuals and the healthcare system due to increased prevalence of obesity-associated diseases. An important area that has gained much attention recently is the sex and gender difference related to obesity and associated complications. Basic science and clinical studies have now improved our understanding of obesity and have discovered adipose tissue biology to be key in metabolism.

**Recent Findings**—There is evidence related to the sex dichotomy in obesity in a variety of areas including adipocyte function, sex hormone effects, genetics, and metabolic inflammation leading to critical differences in adipose tissue biology.

**Summary**—The sex and gender difference in adipose tissue is a factor that should be considered when studying an individuals' risk for obesity and metabolic dysfunction. This understanding is important for strategizing treatment and prevention measures.

### Keywords

Sex; Gender; Adiposity; Obesity; Sex hormones; Metabolism

### Introduction

Obesity is on the rise in many countries and in the USA, the incidence has almost tripled since the 1960s [1]. It is estimated that at least one third of the adult population is currently obese. The rise in obesity has led to an increase in obesity-associated complications such as diabetes mellitus, cardiovascular disease, hypertension, dyslipidemia, and non-alcoholic fatty liver disease. Studies have shown that adipose tissue dysfunction has a significant role in who obtains obesity-associated diseases [2•]. Adipose tissue was traditionally thought of as a storage site for lipids but is now recognized as an endocrine organ secreting signaling molecules and hormones that regulate metabolic homeostasis [3••]. This leads to obesity-associated comorbidities that are a burden on the individual and costly for the healthcare system [4]. Therefore, there is much interest in better understanding the pathophysiology of

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obesity such as identifying individuals with a greater risk for diseases. This knowledge is valuable in devising preventative measures and treatments. Many studies have shown significant differences in at-risk populations identified on the basis of sex, race, and environment [5]. For example, men have specifically been identified as a high-risk population due to increased metabolic and cardiovascular disease in young men compared to premenopausal women [3••, 6]. This finding along with other evidence highlights the importance of better understanding the mechanism behind the sex and gender difference of obesity and its biology. This review article provides an overview of factors contributing to the sex dichotomy in obesity providing a greater appreciation for its role in obesity-induced complications.

## Adipose Tissue Distribution and Characteristics

In humans and other mammals, body fat distribution is significantly different between males and females and is a strong predictor of disease risk [7•, 8]. Women have more subcutaneous adipose tissue (SAT), creating a “pear shape” distribution, while men have fat, predominantly distributed to the visceral adipose tissue (VAT) around the abdominal organs creating an “apple shape” body habitus [9–11]. Central/abdominal (subcutaneous upper body and visceral) fat deposition correlates with an increased susceptibility for metabolic complications, while gluteal–femoral (lower body) adipose tissue distribution is associated with reduced metabolic risk and may be protective against the adverse health effects of obesity in both sexes [12–14]. The higher visceral adiposity observed in men is associated with elevated postprandial insulin, free fatty acids (FFAs), and triglyceride (TG) level. Though women can also possess the upper-body obese phenotype, the reduced metabolic disease risk in women has been attributed to the propensity to store body fat in the gluteal–femoral region [15, 16]. In obesity, the rate of lipolysis is higher which leads to excessive fatty acid deposition in the liver giving rise to increased hepatic glucose production, hyperinsulinism, and other features of the metabolic syndrome [17]. Promoting sex differences, the rate of lipolysis in SAT is lower than that of VAT [18]. In addition, inflammatory changes within the VAT with leukocyte accumulation and activation have been strongly associated with metabolic disease [19]. The SAT is associated with very little inflammation during obesity and is more avid in absorption of circulating free fatty acids and triglycerides and can actually provide a protective effect against obesity-related diseases [20]. The factors and mechanisms that govern this sexual dimorphism in body fat are critical to the understanding of obesity and its complications.

## Animal Models Identify Sex Differences in Adipose Tissue Biology

Animal models have demonstrated that sex and sex hormones influence adipose tissue both in adipocyte development, adipogenesis, gene expression profiles regulating insulin resistance and lipolysis, as well as the inflammatory tone and remodeling responses to obesity.

## Sex Hormone Programming of Adipose Tissue Expansion

Gonadal hormones, including estrogen, progesterone, and androgens, have receptors expressed in both VAT and SAT depots [21]. SAT has higher concentrations of estrogen

receptors (ER) and progesterone receptors compared to androgen receptors (AR) in females, and estrogen downregulates AR expression in subcutaneous fat [22, 23]. In contrast, VAT has a higher concentration of ARs [22, 24]. This differential expression of sex steroid receptors likely influences the differential function of adipose depots. Sex steroids specifically influence adipogenesis leading to male expansion of gonadal adipose tissue (GWAT); however, females expand both visceral GWAT and subcutaneous inguinal white adipose tissue (IWAT) [25, 26].

One potential contributor to sex differences in adipose tissue expansion is the number of adipocyte precursor cells in mouse gonadal or subcutaneous fat depots. On a low-fat chow diet, female C57BL/6J mice have more adipocyte precursor cells than males in GWAT and IWAT. When fed a high-fat diet (HFD), female mice showed increased adipocyte precursor cells and mature adipocytes in GWAT, but males did not increase mature fat cells in the GWAT [27]. HFD studies also show that male mice have greater overall weight gain, insulin resistance, and macrophage infiltration of both GWAT and IWAT when compared to females, although inflammatory markers in GWAT were similar between the sexes. These studies suggest protective benefits of estrogen in the obese state that appeared to improve the metabolic phenotype of adipose tissue.

Studies with rodent models of estrogen deficiency including ovariectomy, aromatase knockout, estrogen receptor  $\alpha$  knockout (ER- $\alpha$ KO), estrogen receptor  $\beta$  knockout (ER- $\beta$ KO), and double ER-KO mice show that the type and distribution of ER modulate fat distribution between the different depots. Primary studies using gonadectomy demonstrate that female mice who underwent ovariectomy had increased weight gain and impaired metabolism, but when estrogen is replaced, there is less weight gain and improved metabolism [28]. Deletion of ER- $\alpha$  from adipocytes specifically in both males and females led to increased adiposity of the visceral depot in mice and occurrence of metabolic syndrome [29, 30]. However, there were no differences in animals with ER- $\beta$ KO [31]. Replacement of 17 $\beta$ -estradiol prevents ovariectomized wild-type mice from developing obesity. Such protective effects are not observed in ovariectomized ER $\alpha$ -deficient mice [32]. Given the role of adipose tissue aromatase in estrogen levels within the adipose tissue, aromatase knockout animals have also been evaluated. These mice, regardless of sex, develop hypercholesterolemia, and male knockout mice exhibited elevated triglycerides and fatty liver disease [33, 34].

Androgens also play a role in depot- and gender-specific effects on adipose tissue distribution and have been studied with androgen deficiency models, such as the androgen receptor knockout (AR-KO) mouse and castrated mice. Castration studies have been conflicted showing decreased weight [35], improved glucose tolerance [36], increased insulin sensitivity [37], and improved triglycerides [38] even with increased fat mass, with other studies showing that castration impairs glucose tolerance and insulin resistance [39]. AR-KO mice also show increased adiposity [40] and improved insulin sensitivity consistent with a deleterious role for androgens in adipose tissue [41]. Consistent with this, testosterone replacement in castrated mice decreases energy expenditure, decreases adiposity, elevates triglyceride levels, and impairs metabolism. Collectively, these data demonstrate that both

circulating and local adipose tissue production of sex hormones may have important effects on adipose tissue distribution and function [42].

### Programming of Adipose Biology and Metabolism by Sex Chromosomes

Although intrinsic sex differences in adipose tissue distribution and inflammation have been attributed to sex hormones, it is notable that even prior to the differentiation of the gonads, human and mouse male embryos are larger than female embryos, suggesting that non-gonadal factors also exist [43]. Sex chromosomes may play a role in sex differences in adipose biology. A fundamental genetic difference that exists within every cell in the body of females compared to males is the presence of two X chromosomes in female cells, and an X and a Y chromosome in male cells [44–46]. The Y chromosome, and specifically the *Sry* gene located on it, initiates differentiation of the testes. To dissect the contributions of gonadal hormones and sex chromosome complement to sex differences, four core genotypes (FCG) mouse models have been used. The FCG model generates mice with four combinations of gonads and sex chromosomes: XX female, XX male, XY female, and XY male mice, through the translocation of the *Sry* gene [45]. With two X chromosomes, there is a twofold higher body fat independent of gonadal steroids [47]. FCG mice with *Sry* deletion on Y chromosome develop ovaries rather than testes. Conversely, an *Sry* transgene inserted onto autosome is sufficient to convert XX female mice to gonadal males [48]. In FCG mice that were gonadectomized as adults to remove acute effects of gonadal hormones, mice with XX versus XY chromosomes (regardless of male or female gonads present originally) gained weight more rapidly on a chow or HFD, and adiposity, particularly in the IWAT.

There have also been genetic studies that show increased number of X chromosomes rather than the Y chromosome leads to differences in adiposity [47]. XO and XXY chromosome complements revealed that the differences between XX and XY mice are due to dosage of the X chromosome, rather than effects of the Y chromosome [47]. Results show that the presence of two X chromosomes (XX and XXY mice) led to higher body weight/fat than one X chromosome (XY and XO) while the presence of the Y chromosome did not have an influence [47]. These studies thus show the influence of the X chromosome on adipose tissue biology, which plays a role in the gender difference in humans.

### Modulation of Adipose Tissue Biology by Sex Differences in Gene Expression

Global gene expression analysis has identified thousands of sexually dimorphic genes in adipose tissue in HFD-fed male and female mice [49, 50]. These genes were enriched in functional categories such as immune response, lipid metabolism, and insulin signaling. Interestingly, only approximately 100 genes were differentially expressed between ovariectomized females and gonadally intact females, suggesting that circulating gonadal hormones do not regulate most sexually dimorphic genes [49].

Genes regulating the cytochrome 450 superfamily, including aromatase cytochrome P450 (product of the *Cyp 19* gene), and hydroxysteroid dehydrogenases are among the sexually dimorphic genes [50]. Some other interesting pathways of interest that have been altered by sex are developmental genes. In male mice, genes such as *Nr2f1*, *Thbd*, *HoxA5*, and *HoxC8*

showed higher expression in GWAT than females [9, 51]. Consistent with a sex-specific difference, FCG mouse models show that inactivation of one X chromosome in each non-germline XX cell greatly reduces the sex difference in level of expression of X genes that is predicted based on the number of copies of X genes [52]. However, a finite set of genes on both mouse and human X chromosomes escape inactivation and would therefore be expected to exhibit higher expression levels in XX compared to XY cells [53, 54]. Recent studies indicate that genes escaping X chromosome inactivation exhibit elevated expression in metabolic tissues from XX compared to XO mice and could potentially contribute to sex differences in metabolic phenotypes [55].

Gene expression itself can be regulated epigenetically. miRNAs are endogenous, small non-coding RNAs that are abundant in many cell types and tissues including the adipose tissue [56]. miRNAs are now known to modulate gene expression levels by interacting with specific mRNA species to increase their degradation or interfere with translation. These are also influenced by sex [57–59]. The X chromosome is enriched in miRNAs and there is a possibility that miRNAs may escape X-linked inactivation [53, 54]. This could result in the suppression of miRNA target genes involved in immunosuppressive pathways, leading to a heightened autoimmune response in females and their predisposition to autoimmune diseases [60]. This same change in gene expression by sex may lead to changes in genes for metabolism. miRNAs are reported to stimulate or inhibit the differentiation of adipocytes and to regulate specific metabolic and endocrine functions [61]. Some miRNAs with distinct sex-biased patterns in expression have been implicated in adipogenesis [62, 63]. However, most of what is known about miRNAs in regulating adipocyte differentiation, trafficking, insulin resistance, and adipocyte function has only been studied in male animals. In the future, understanding the sex differences in miRNAs will be critical because, like adipokines, miRNAs can also be secreted from adipocytes into the blood circulation and function in inter-tissue or organ communication in an endocrine fashion. This may serve as markers of dysregulated adipose tissue function [64, 65, 66].

### Sex Differences in Adipose Remodeling and Inflammation

During HFD exposure and obesity, a large change is the expansion and remodeling of the adipose tissue depot. While male animal models demonstrate that there is enhanced adipocyte death promoting macrophage infiltration with obesity and secondary fibrosis [67, 68], female animals are specifically protected from this response with a greater ability to expand adiposity [67, 68]. Metabolic inflammation of the adipose tissue leads to metabolic disturbances such as glucose intolerance. VAT has a greater number of adipose tissue resident macrophages. These immune cells produce more proinflammatory cytokines like tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6) and less adiponectin. These cytokines can induce insulin resistance and cause endothelial dysfunction and subsequent atherosclerosis [69]. This inflammation occurs less in SAT which is the predominant fat depot in women.

Several factors may regulate inflammation and fibrosis in adipose tissue such as sex hormones, chemokines, cytokines, and inflammatory regulators such as hypoxia-inducible factor (HIF-1) [70, 71]. Estrogen and ER- $\alpha$  can increase Phd3 transcription which reduces

HIF-1 activity, thus leading to reduction of metabolic inflammation [72]. Estrogen possibly regulates other factors since ovariectomy itself leads to an increase in inflammation with the number of crown-like structures of macrophages [49]. This concept of gender differences in immune system activation has been clinically seen with an increase in autoimmunity in women and reduced responsiveness to LPS [73–75]. Further evidence that there is an inherent effect of sex on the immune system, comes from female mice fed a HFD that have lower myeloid progenitor expansion, with fewer activated circulating monocytes and less recruited CD11c<sup>+</sup> proinflammatory adipose macrophages [76].

In addition to inflammation-induced remodeling, a sex difference in sympathetic activity results in female-specific induction of brown adipocytes in GWAT, which could be involved in the protection of female mice against metabolic disease [77]. Estrogen can also influence brown adipose tissue (BAT) activity by upregulating thermogenesis. The rise in activity of BAT increases the body temperature, which has a negative association with body weight [78]. This is yet another adipose tissue that likely develops in a sexually dimorphic way leading to a systemic metabolic difference between men and women.

## Clinical Studies of Gender Differences in Adipose Tissue Biology

### Sex Hormone Programming of Adipose Tissue Expansion in Clinical Studies

In the clinical settings, gender differences in adiposity and metabolism vary by stages of life. Prior to puberty, there is little difference in adipose distribution, but during early puberty, the differences in weight trajectory and body composition become more apparent. For example, men tend to develop more central distributed fat during the transition from adolescence to young adult [79]. Premenopausal women have higher levels of estrogen which has a protective effect against weight gain by increasing energy expenditure and distributing adipose tissue in subcutaneous regions [80]. Part of this increased energy expenditure comes from the estrogen effect of the “browning” or metabolic activity of adipose tissue. BAT is metabolically more active because of increased number of mitochondria [81]. This has been demonstrated in biopsy samples and increased gene expression for mitochondrial function [81, 82]. Postmenopausal women gain weight due to the natural decrease in endogenous estradiol during menopause. This reduction in energy expenditure can be prevented by estrogen replacement therapy; however, the risk for metabolic disease does not appear to improve [83]. This estrogen response may be sexually dimorphic as estrogen in vitro upregulates the expression of both ER $\alpha$  and ER $\beta$  in subcutaneous adipocytes from women, but only upregulates ER $\alpha$  in subcutaneous and visceral adipocytes from men [84, 85].

Along with estrogen protection, there is a role for male androgen hormones in regulating adiposity and metabolism. Obese men, compared to obese women, have lower insulin sensitivity, elevated glucose levels, and lower adiponectin levels promoting intraabdominal adiposity and insulin resistance [86]. This ability for increased adiponectin concentrations in women stands true even when men and women are pair-matched for age, BMI, intraabdominal fat, and insulin sensitivity [86]. This effect has been shown in vitro with androgens directly decreasing adiponectin even in 3T3-L1 adipocytes [87]. Circulating testosterone levels are readily converted to estrogen via aromatase. Studies blocking conversion of testosterone to estrogen resulted in decreased insulin sensitivity and



decrements in metabolism [88]. Women affected by aromatase deficiency develop a phenotype that includes metabolic co-morbidities such as obesity, steatohepatitis, insulin resistance with acanthosis nigricans, and dyslipidemia [89]. In reverse, an individual affected by severe androgen deficiency can acquire more VAT [90, 91]. This may be related to how testosterone can enhance catecholamine-induced lipolysis and reduce lipoprotein lipase activity and triglyceride uptake in human abdominal adipose tissue [92]. Men with prostate cancer receiving 12 months of androgen deprivation therapy had a 22% increase of abdominal VAT mostly within 6 months [93]. Another study that suggests severe sex steroid deficiency can rapidly increase fat mass involved the induction of hypogonadism in healthy young men with gonadotropin-releasing hormone analogue treatment. The affected men had a 20% increase in fat mass within 10 weeks from the initiation of treatment [94]. Aging men who have declining levels of testosterone also develop an increase in fat mass and decreased insulin sensitivity [95]. When aging men receive testosterone therapy, this decreases visceral fat mass, increases lean muscle mass, and improves insulin sensitivity [96, 97]. Contrary to this, women with high androgen levels have increased body weight and VAT, hyperinsulinemia, and higher cardio-metabolic risk such as in polycystic ovarian syndrome (PCOS) [15, 98] and female to male transgender individuals [99].

In summary, there are gender differences in adiposity, metabolism, and predisposition for metabolic dysfunction that are driven partially by sex hormones such as androgens and estrogen. Depending on the sex of the individual, the level of specific sex hormones can improve or worsen adiposity and metabolic dysfunction. Estrogen generally provides a protective effect in females while atypical elevation of androgens is detrimental. In males, adequate androgen levels are important in promoting appropriate adiposity and metabolic status but the overall impact of excess androgens on metabolism in males is unclear.

### **Gender Differences in Adipose Remodeling and Inflammation**

Clinical studies confirm gender differences in fat storage, adipocyte modeling/remodeling, lipolytic responses, and secondary inflammation responses [100]. For example, cross-sectional comparisons of adipocyte morphology in the abdominal and femoral SAT depots belonging to men and premenopausal women with normal weight gain show that women have a greater abundance of small adipocytes especially in the femoral depot, indicating a gender difference in the morphology of adipose tissue at baseline [101, 102]. In the context of obesity, there are depot-specific differences in adipogenesis, fatty acid storage, and adipocyte morphology where VAT is more susceptible to detrimental adipose remodeling and is a poorer storage for fatty acid compared to SAT depots [103]. However, men have more hypertrophic type of WAT expansion compared to women and less small adipocytes, indicating a gender difference in adipose tissue remodeling and fatty acid storage [103]. Women with increased adiposity and SAT, when compared to men, have more efficient triglyceride fatty acids uptake via LPL and from circulation, leading to better insulin sensitivity [104]. The consequence of having free fatty acids is that some end up in the liver, causing an increase in glucose production and insulin production. Eventually, insulin resistance and metabolic syndrome can occur if there is prolonged and excessive fatty acid exposure [17].

The complex and integrated adipose tissue immune system that responds to HFD exposure includes an inflammatory response likely serving as an adaptive mechanism to allow healthy adipose tissue expansion and efficient lipid storage [105]. The inflammatory response is a result of adipose tissue macrophage (ATM) accumulation [100] that forms around dead or dying adipocytes. Studies remain controversial about the gender differences in these ATMs and are limited by predominant sampling of subcutaneous adipose tissue in clinical sampling. Clinical studies implicate more ATMs in men and women with PCOS compared to premenopausal women [106•, 107].

### **Clinical Implications of Sex Differences in Adiposity**

With all of these findings of gender differences in obesity and metabolic dysfunction, it is important to think of the clinical implications of this. One implication is identification of at-risk populations. Interestingly, race in addition to gender is a critical factor to assess. Black populations are at higher disease burden for diabetes, hypertension, and cardiovascular mortality [108]. One possible factor for why certain racial population is inherently at greater risk for obesity and metabolic dysfunction may be due to racial differences in androgenic sex steroids [109]. However, there is a sexual dichotomy. Women with markedly lower sex hormone-binding globulin (SHBG) and high bioavailable testosterone had increased abdominal and visceral adipose tissue. In men, increased bioavailable testosterone decreased abdominal obesity and metabolic risk profile [110]. The SWAN study showed that Black women had higher SHBG compared to White women, while both Black and Hispanic women had lower free androgen index (FAI) compared to White women, which is consistent with Black and Hispanic women having higher prevalence of obesity. Chinese women had significantly lower SHBG and higher FAI than White women which is consistent with Chinese women having lower prevalence of obesity [109]. Having an awareness of the influences of race and gender on adiposity can be helpful in identifying an individual's own risk.

In the transgender population, cross-sex hormone therapy is commonly used in the transition process [111•]. For feminization, estrogen is given in combination with antiandrogen drugs to decrease testosterone and minimize masculine physical characteristics [112]. In parallel, masculinization is achieved with testosterone esters [113]. One retrospective study showed that cross-sex hormone therapy did not induce any changes in fasting plasma glucose in male to female subjects but that it lowered them in female to male subjects [114]. A Dutch study showed that 250 mg testosterone esters every 2 weeks led to slightly decreased fasting glucose level after 12 months of therapy [115]. There was no significant difference between the body mass index from baseline to being on cross-sex hormone therapy for both male to female individuals and female to male individuals. However, this study was limited by sample size and a limited follow-up period (up to 30 months) [116•]. In addition, estradiol treatment increased protective HDL cholesterol [116•].

There is also a growing area of research trying to understand the clinical impact of parental obesity on offspring health, specifically on obesity and metabolism. When examining the association between maternal and paternal body mass index with offspring outcomes, there is a stronger association for maternal obesity, likely due to the direct intrauterine relationship



[117]. This is particularly relevant since there are more women of reproductive age who are now overweight or obese. The prevalence of macrosomia among neonates of obese women is almost double compared to those born to women of normal weight [118]. Children born to overweight women prior to or early in pregnancy developed greater BMI and adiposity compared to the children born to women of normal weight [119]. However, it may not entirely be the excess adiposity itself that increases their risk but rather the onset of metabolic health abnormalities during the pregnancy, particularly gestational diabetes [120]. The diabetogenic environment of the fetus results in maternal glucose crossing the placenta, thus causing the fetus to increase its insulin production. Insulin itself has growth properties and stimulates adipogenesis [121].

It is thought that metabolic inflammation also has an influence on the offspring phenotype. Maternal obesity causes elevated levels of proinflammatory cytokines both in the adipose tissue and systemically [122]. This likely exposes the fetus to an inflammatory environment during development [123] which can lead to systemic inflammation even within the first few postnatal days, based on laboratory testing [124]. There is a sexual dimorphism on placental oxidative stress under different conditions. In the setting of maternal obesity, there is higher oxidative and nitrative stress for the male fetus when compared to the female fetus [125]. The increased level of stress and inflammation is thought to drive adipogenesis and adiposity later on in the affected child's life [126]. While clinical studies do not show clear sex dichotomy, animal models show that maternal obesity or HFD exposure during pregnancy creates an obese phenotype in both sexes, while other studies show only the male offspring being affected [127, 128]. Due to the inconsistencies across studies, more work still needs to be done to better understand the underlying mechanisms governing the sexual dimorphism of maternal obesity programming on the affected offspring.

Conversely, the association between paternal obesity and offspring outcome is not as strong. In offspring of diabetic fathers but non-diabetic mothers, the excessive fetal growth did not occur [129]. However, there are animal studies that suggest paternal overweight/obesity may still influence the offspring phenotype through genetic and epigenetic changes in spermatozoa [130]. The paternal obesity influence may also be related to the shared family-based influences of the fathers on their children's lifestyle [131]. There still needs to be more population-based study to better determine the association between paternal obesity and offspring risk for obesity and metabolic disease [130].

## Conclusion

There are strong sex differences in adipose tissue biology and subsequently sex differences in metabolism. Males and females show anatomical differences in adipose tissue distribution and level of risk for developing obesity and its complications. For women who are premenopausal, they are more protected compared to males and postmenopausal females, partially due to the higher levels of estrogen. However, higher levels of androgen can sometimes be beneficial for men while detrimental for females. Animal models have provided information that has deepened our understanding of the sex dichotomy related to obesity. There are differences in sex hormone production, receptor activity, genetic influences, and gene expressions (related to adipocyte formation, inflammation, etc.), but

more mechanistic studies are needed to fully understand the sex dimorphism. Clinically, there are gender differences in how adipose responds to obesity leading to altered levels of lipolysis, inflammation, and metabolism. Certain medical conditions that affect sex hormone production and exposure provide more evidence of the sex dichotomy. Sex differences not only influences the current generation but also future generations that are born to individuals affected by obesity. It is important that we better understand the influence of sex on obesity and the development of metabolic dysfunction so that more personalized care can be created to prevent or treat those affected.

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