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Sex differences in metabolism and cardiometabolic disorders

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Abstract

Purpose of review—Sex differences are pervasive in metabolic and cardiovascular traits, yet they have often been ignored in human and animal model research. Sex differences can arise from reversible hormonal effects, from irreversible organizational (developmental) processes, and from gene expression differences from the X and Y chromosomes. We briefly review our current understanding of the impact of these factors in metabolic traits and disorders, with an emphasis on the recent literature.

Recent findings—Novel sex differences continue to be identified for metabolic and cardiovascular traits. For example, it is now clear that gut microbiota tend to differ between men and women, with potentially large implications for disease susceptibility. Also, tissue-specific gene regulation differs between men and women, contributing to differential metabolism. These new insights will open up personalized therapeutic avenues for cardiometabolic diseases.

Summary—Sex differences in body fat distribution, glucose homeostasis, insulin signaling, ectopic fat accumulation, and lipid metabolism during normal growth and in response to hormonal or nutritional imbalance are mediated partly through sex hormones and the sex chromosome complement. Most of these differences are mediated in a tissue-specific manner. Important future goals are to better understand the interactions between genetic variation and sex differences, and to bring an understanding of sex differences into clinical practice.

Keywords

genetic interactions; gonadal hormones; mitochondria; mouse models; sex chromosomes

INTRODUCTION

Sex differences in metabolic traits such as obesity, diabetes, and cardiovascular disease have been amply described in mice, humans, and other species, with females generally exhibiting more beneficial metabolic profiles [1–6,7,8]. While originally those differences were

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Conflicts of interest

There are no conflicts of interest.

attributed to the effect of sex hormones, recent studies suggest that both hormones and sex chromosome complement play a role [9,10[■]]. The effects of sex hormones can be either reversible or irreversible ('organizational'). Sex differences may be dependent upon the genetic background, environmental factors and the gut microbiome [11,12[■]]. Gene expression studies show a large proportion of genes differentially expressed in adipose, liver, brain, and other tissues [6,13[■]], and that sex hormones and also chromosome complement play a major role in modulation of gene expression [6,14–17]. It is important to understand sex differences for practical reasons. First, because sex affects the prevalence of most chronic diseases, in some cases as much as 10-fold, there is much to be learned about disease mechanisms. Second, as discussed below, disease symptoms and treatments will also differ between sexes, and sex differences are probably the most accessible target of the current Precision Medicine effort. An ultimate goal will be to understand sex differences at the level of biologic networks (the 'sexome') [18].

BODY COMPOSITION, ADIPOSE DISTRIBUTION AND OBESITY

Adipose tissue is now recognized as more than a mere fat storage organ. Through their secretion of several adipokines and cytokines such as leptin, adiponectin, tumor necrosis factor (TNF)- α and interleukin (IL)-6, adipose tissue plays a major role in regulating metabolic and energy homeostasis [19]. The major form of adipose tissue in adult mammals is the white adipose tissue, and it occurs either under the skin as subcutaneous adipose tissue (SAT) or in the deep abdominal region as visceral adipose tissue (VAT). Understanding how normal adipose physiology differs between men and women will be key to deciphering how sex differences affect the pathology of disrupted metabolic homeostasis. Under normal physiological conditions, premenopausal women have higher overall fat mass percentage, whereas men have higher lean mass percentage [20]. However, premenopausal women store more fat in their SAT depots surrounding hips and thighs (also known as gynoid fat distribution), whereas men store fat in their VAT depots in the deep abdominal region (also known as android fat distribution) [20]. Increasing evidence shows that higher VAT in men is significantly associated with cardio-metabolic risk, whereas higher SAT in women might be involved in cardiometabolic protection [21–24]. Postmenopausal women lose this protection, as there will be a shift from gynoid fat to android fat accompanied by increased cardiometabolic risk compared to men [25–27]. This signifies that increased VAT confers more cardiometabolic risk in women compared to men.

Sex differences in adipose distribution are attributed partly to adipose depot-specific differences in lipoprotein lipase (LPL) activity, and also adrenergic receptor and estrogen receptor distribution. LPL plays a key role in fat accumulation in adipose. Although LPL is highly active in SAT of women compared to VAT, the converse is true in men [28]. Apart from this, testosterone also suppresses LPL activity in SAT of men [29]. Adipose tissues express both lipolytic β 1–2-adrenergic receptor and antilipolytic α 2-adrenergic receptor, thereby regulating balance between lipolysis and lipogenesis leading to fat storage. However, in premenopausal women, estradiol increases α 2-adrenergic receptor only in SAT, thereby shifting the balance toward gynoid fat accumulation [30–32]. In contrast, men have higher α 2-adrenergic receptor in their VAT contributing to android fat [31]. Animal studies revealed that women are resistant to diet-induced obesity, whereas ovariectomy reverses this

protective effect [33,34]. Nevertheless, estrogens can rescue ovariectomized women from obesity in an estrogen receptor α -dependent manner [35–37]. Women have lower estrogen receptor α distribution in SAT, whereas men have lower estrogen receptor α in VAT, thereby partly contributing to their differential fat depot accumulation. Adipose-specific estrogen receptor α deletion increases diet-induced adiposity in both men and women, specifically increasing VAT deposition [38]. Estrogens mediate their antiobese effect by decreasing food intake and increasing energy expenditure in women [39–43].

Apart from these mechanisms, adipose-mediated sex hormone metabolism also contributes in dimorphic adipose distribution. For instance, compared to VAT, SAT has higher levels of aromatase enzyme that converts androgens to estrogens [44,45]. In contrast, VAT has higher levels of 17 β -hydroxysteroid dehydrogenase (17 β HSD) that converts less active hormones to their more active counterparts, for example, androstenedione to testosterone [44,45]. As a consequence, higher VAT results in higher 17 β HSD-mediated local androgen production [44,45]. Furthermore, aromatase deletion in animal models leads to metabolic dysfunction such as increased adiposity, hyperinsulinemia and hepatic steatosis that can be partly rescued by estradiol treatment [46–48].

Genetic tools available in mouse models such as the four core genotypes (FCGs) enable better understanding of the role of sex chromosome complement in regulating obesity independent of sex hormones [49]. FCGs dissociate sex chromosome complement from sex hormones, and include XX men or women and XY men or women [49]. Studies on FCG mouse model revealed that X chromosome complement is positively associated with increased adiposity in a dose-dependent manner [50]. Comparing their observations with the most common human chromosomal anomaly (~1/600 live births), namely Klinefelter syndrome (XXY), revealed that compared to XY men, XXY men had higher incidence of visceral adiposity-associated metabolic abnormalities [51]. Genes that escape X inactivation, genes on Y chromosome and distinct epigenetic imprinting inherited from maternal or paternal parents are hypothesized to contribute to these differential chromosomal effects [9].

GLUCOSE HOMEOSTASIS, INSULIN RESISTANCE AND DIABETES

Glucose homeostasis is primarily regulated by skeletal muscle through basal and insulin-stimulated glucose uptake. Men have more muscle mass compared to women [52,53]; however, premenopausal women show similar insulin sensitivity compared to men. This difference was attributed to enhanced skeletal muscle-mediated glucose uptake in women compared to men [54]. Moreover, women tend to have increased insulin secretion compared to men as measured by postprandial insulin and C-peptide levels [55]. It is proposed that estradiol may partly mediate this mechanism [56■]. On the contrary, sex differences also affect prediabetic conditions such as impaired fasting glucose and impaired glucose tolerance. Population studies have shown that women have lower fasting glucose, but impaired glucose tolerance compared to men [57–60]. Estrogen therapy in menopausal women decreases fasting glucose, but impairs glucose tolerance [56■,59]. Sex differences also exist in diabetic prevalence. Population studies have shown that both type 1 and 2 diabetes have a male predominance [61–63]. Global survey on diabetic populations revealed that sex-specific diabetic prevalence reverses depending on the reproductive stages [64].

Specifically, more men have diabetes prepuberty, whereas more women have diabetes postmenopause [64].

Sex-specific adipose distribution is partly attributed to the observed differential glucose homeostasis between men and women. For instance, insulin resistance is associated with increased VAT through pro-inflammatory cytokines. Apart from this, increased VAT lipolysis results in higher free fatty acid flux delivered to liver leading to hepatic insulin resistance such as hyperinsulinemia and increased glucose production [65]. Moreover, insulin resistance and diabetes are improved by surgical removal of VAT in both animals and humans [66,67]. In contrast, selective SAT removal is associated with worse metabolic profiles in both animals and humans, indicating that SAT acts as a metabolic sink and protects against metabolic syndrome [68,69]. This is further exemplified by adipose redistribution from SAT to VAT following liposuction [70]. Studies in premenopausal women show that SAT through its highly active LPL takes up most of the fatty acids from circulation and meals, acting as a metabolic sink preventing ectopic fat accumulation in liver and muscle [71]. As a consequence, SAT adipocytes are larger, yet remain insulin-sensitive [72].

Studies have also shown that deregulated adipose expansion and their inability to store lipids lead to ectopic fat accumulation followed by insulin resistance [65]. Normal adipose tissue expansion happens through either increased cell number by recruitment of new adipocytes (hyperplasia) or increased cell size in pre-existing adipocytes (hyper-trophy). Hyperplastic expansion results in improved metabolic health, whereas hypertrophic expansion leads to systemic metabolic dysfunction [73,74]. Animal studies have shown that SAT expands predominantly via hyperplasia, whereas VAT expands primarily through hypertrophy following high-fat feeding [75,76]. A similar trend was observed in women as well [77]. It was proposed that estrogens play a role in this, but the precise mechanism for this differential fat expansion is unknown. Apart from this, vascular supply influences both hyperplasia and hypertrophy. Human samples have shown that SAT has increased capillary density and angiogenic growth compared to VAT [78]. Reduced vascular supply during fat expansion leads to hypoxia and activation of hypoxia inducible factor (HIF) that enhances adipose inflammation and fibrosis, leading to insulin resistance [79]. In contrast, estrogen through estrogen receptor α promotes HIF ubiquitination and degradation through transcriptional up-regulation of prolyl hydroxylase enzyme, thereby reducing adipose inflammation and fibrosis [80]. Apart from this, adipocyte-specific deletion of estrogen receptor α in mice has demonstrated its protective role against adipose inflammation, fibrosis, and insulin resistance in animal models [38].

Apart from these mechanisms, mouse population studies revealed extensive gene-by-sex regulation in insulin resistance [3]. Furthermore, studies on FCG mice revealed that high fat/high carbohydrate feeding resulted in similar fasting glucose levels in all four genotypes; however, XX mice produced nearly twice as much insulin to maintain normal glucose levels compared to XY mice [50]. This suggests that, similar to adiposity, X chromosome complement contribute to insulin resistance and can lead to type 2 diabetes. Likewise, human studies have revealed that compared to XY men, XXY men have higher incidences of insulin resistance and type 2 diabetes [81–84].

HEPATIC STEATOSIS

Another major obesity complication is nonalcoholic fatty liver disease (NAFLD). NAFLD is the most common chronic liver disorder, which comprises of a spectrum of hepatic abnormalities ranging from simple steatosis (intrahepatic triglyceride accumulation) to steatohepatitis (NASH), fibrosis, and cirrhosis, in the absence of excessive alcohol consumption [85–87]. Population studies revealed that NAFLD is more prevalent in men than women, with men exhibiting more severe NAFLD symptoms [86,88–92]. Also, NAFLD was found to be more prevalent in postmenopausal compared to premenopausal women, suggesting hormonal regulation [93]. In addition, mouse population studies also revealed that, in response to high fat/high sucrose feeding, male mice generally had higher hepatic steatosis, and that genetic variation played a major role in sex differences [94]. Additionally, the FCG mice revealed that, similar to obesity and insulin resistance, X chromosome complement increased hepatic triglyceride accumulation in a dose-dependent manner [50]. The observed sex differences in both humans and animals were attributed partly due to genes escaping X inactivation and differences in genetic regulation, differential body fat distribution, and sex hormone metabolism between men and women. Nevertheless, the mechanisms underlying these sex differences in NAFLD prevalence are poorly understood.

Intrahepatic ceramide accumulation was implicated as one of the causal mechanisms for sex-specific differences observed in hepatic steatosis and insulin resistance. Using a mouse reference population, we observed that different ceramide species were prevalent between sexes, thereby differentially regulating hepatic steatosis and/or insulin resistance [95]. Follow-up gonadectomy studies on three different common inbred mouse strains revealed that these differences were partly due to testosterone-mediated inhibition of ceramide synthase 6 in the liver [95].

With no available pharmacological treatment, it is imperative that we need to understand the underlying sex-specific mechanisms modulating hepatic steatosis as it will lead to improved personalized therapeutics for NAFLD treatment and prevention.

CARDIOVASCULAR TRAITS

The prevalence of coronary heart disease (CHD) and myocardial infarction increases with age in both sexes, but is delayed by about 10 years in women as compared to men. Moreover, the symptoms, treatment, and outcomes of CHD differ between sexes [96,97]. The underlying causes of these differences are unclear. Blood lipoprotein levels are strongly associated with CHD, with LDL-cholesterol and triglyceride levels directly correlated, and disease and HDL-cholesterol levels inversely correlated. Men and women have similar levels of LDL-cholesterol, but women have about 20% higher HDL-cholesterol and about 15% lower triglyceride levels. Lp(a) is an LDL-like lipoprotein that is highly proatherogenic. A relatively small but potentially interesting recent epidemiologic study suggests that Lp(a) concentrations are correlated with angio-graphic scores in men but not women [98]. There are also sex differences in hypertension and thrombosis risk, two other CHD risk factors. The sex differences in hypertension are complex and age-dependent, being more prevalent in

men below 45 years of age, but more prevalent in women above 55 years of age. Women have elevated thrombosis risk as compared to men, which may be related to the fact that strokes comprise a larger fraction of cardiovascular events in women than men [99].

Differences in endogenous gonadal hormones have been hypothesized to play a role in CHD sex differences. In particular, the cardioprotection in women is lost once menopause occurs. Female sex hormones have been intensively investigated in the context of hormone replacement therapy, whereas male sex hormones have received less attention. Glisic *et al.* [100] recently examined the relationship of gonadal hormones with carotid plaque composition in 2100 older men and women. Men exhibited increased carotid atherosclerosis and increased likelihood of lipid cores and intraplaque hemorrhage. Both estrogen and testosterone levels were associated with carotid plaque composition. Increased estradiol was associated with a lipid core in both sexes, whereas testosterone was associated with reduced lipid cores in women, but was unrelated in men. Increased estradiol levels were also associated with stroke in women.

It has been hypothesized that some of the differences in metabolic and cardiovascular disorders could involve gut microbiota (collectively termed the ‘microbiome’). Studies over the last two decades have convincingly shown that gut microbiota play a significant role in many disorders, including obesity, inflammatory bowel disease, and cardiovascular disease. There are significant sex differences in gastrointestinal permeability and susceptibility to intestinal injury, and recent studies have also shown that the gut microbiome differs between sexes. In addition to intestinal properties, potential mechanisms include sex differences in bile acid metabolism and gut microbe effects on the levels and potency of estrogen metabolites [101].

CONCLUSION

In reviewing the current literature, we find that there are many reports of sex differences in cardiovascular and metabolic traits, but relatively few basic studies directed at understanding the underlying mechanisms. For example, as yet very little is known about the epigenetic differences in men and women, and few genome-wide association studies examine the sexes separately. Such basic studies will be critical for the implementation of Precision Medicine. We summarize some important questions for the future in Table 1. Also, quite surprising, given the attention that has been raised about sex differences in recent years, is that many animal model studies include only one sex, most often males.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest

1. Kenney-Hunt JP, Wang B, Norgard EA, et al. Pleiotropic patterns of quantitative trait loci for 70 murine skeletal traits. *Genetics* 2008; 178: 2275–2288. [PubMed: 18430949]
2. Mittelstrass K, Ried JS, Yu Z, et al. Discovery of sexual dimorphisms in metabolic and genetic biomarkers. *PLoS Genet* 2011; 7:e1002215. [PubMed: 21852955]
3. Parks BW, Sallam T, Mehrabian M, et al. Genetic architecture of insulin resistance in the mouse. *Cell Metab* 2015; 21:334–347. [PubMed: 25651185]
4. Varlamov O, Bethea CL, Roberts CT, Jr. Sex-specific differences in lipid and glucose metabolism. *Front Endocrinol (Lausanne)* 2014; 5:241. [PubMed: 25646091]
5. White UA, Tchoukalova YD. Sex dimorphism and depot differences in adipose tissue function. *Biochim Biophys Acta* 2014; 1842:377–392. [PubMed: 23684841]
6. Yang X, Schadt EE, Wang S, et al. Tissue-specific expression and regulation of sexually dimorphic genes in mice. *Genome Res* 2006; 16:995–1004. [PubMed: 16825664]
7. Karp NA, Mason J, Beaudet AL, et al. Prevalence of sexual dimorphism in mammalian phenotypic traits. *Nat Commun* 2017; 8:15475. [PubMed: 28650954] ■■ Authors analyzed up to 234 traits from 14 250 wild-type and 40 192 mutant mice to quantify how often sex influences phenotype. They demonstrated that sex must be considered as a biological variable irrespective of research field or biological system.
8. Ober C, Loisel DA, Gilad Y. Sex-specific genetic architecture of human disease. *Nat Rev Genet* 2008; 9:911–922. [PubMed: 19002143]
9. Link JC, Chen X, Arnold AP, Reue K. Metabolic impact of sex chromosomes. *Adipocyte* 2013; 2:74–79. [PubMed: 23805402]
10. Traglia M, Bseiso D, Gusev A, et al. Genetic mechanisms leading to sex differences across common diseases and anthropometric traits. *Genetics* 2017; 205:979–992. [PubMed: 27974502] ■■ Analyzing multiple datasets, authors demonstrated that sex-specific gene regulation, X-chromosomal genes, gene-by-sex and gene-by-environment interactions contribute to sexual dimorphisms seen in common diseases and anthropometric traits.
11. Org E, Mehrabian M, Parks BW, et al. Sex differences and hormonal effects on gut microbiota composition in mice. *Gut Microbes* 2016; 7:313–322. [PubMed: 27355107]
12. Fields CT, Chassaing B, Paul MJ, et al. Vasopressin deletion is associated with sex-specific shifts in the gut microbiome. *Gut Microbes* 2017; 9:1–13. [PubMed: 28686482] ■ Authors demonstrated that the arginine-vasopressin (Avp) gene regulated sex-specific microbiota composition.
13. Kwekel JC, Vijay V, Han T, et al. Sex and age differences in the expression of liver microRNAs during the life span of F344 rats. *Biol Sex Differ* 2017; 8:6. [PubMed: 28174625] ■ Authors demonstrated sex-specific differential miRNA expression profiles exist in liver tissues that are associated with cell death, cell proliferation, and cell cycle.
14. Kukurba KR, Parsana P, Balliu B, et al. Impact of the X Chromosome and sex on regulatory variation. *Genome Res* 2016; 26:768–777. [PubMed: 27197214]
15. Mozhui K, Lu L, Armstrong WE, Williams RW. Sex-specific modulation of gene expression networks in murine hypothalamus. *Front Neurosci* 2012; 6:63. [PubMed: 22593731]
16. Rinn JL, Snyder M. Sexual dimorphism in mammalian gene expression. *Trends Genet* 2005; 21:298–305. [PubMed: 15851067]
17. Vieira Potter VJ, Strissel KJ, Xie C, et al. Adipose tissue inflammation and reduced insulin sensitivity in ovariectomized mice occurs in the absence of increased adiposity. *Endocrinology* 2012; 153:4266–4277. [PubMed: 22778213]

18. Arnold AP, Lusis AJ. Understanding the sexome: measuring and reporting sex differences in gene systems. *Endocrinology* 2012; 153:2551–2555. [PubMed: 22434084]
19. Cao H Adipocytokines in obesity and metabolic disease. *J Endocrinol* 2014; 220:T47–T59. [PubMed: 24403378]
20. Lemieux S, Prud'homme D, Bouchard C, et al. Sex differences in the relation of visceral adipose tissue accumulation to total body fatness. *Am J Clin Nutr* 1993; 58:463–467. [PubMed: 8379501]
21. Björntorp P Metabolic abnormalities in visceral obesity. *Ann Med* 1992; 24:3–5. [PubMed: 1575959]
22. Ohlson LO, Larsson B, Svärdsudd K, et al. The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes* 1985; 34:1055–1058. [PubMed: 4043554]
23. Snijder MB, Visser M, Dekker JM, et al. Low subcutaneous thigh fat is a risk factor for unfavourable glucose and lipid levels, independently of high abdominal fat. The Health ABC Study. *Diabetologia* 2005; 48:301–308. [PubMed: 15660262]
24. Fox CS, Massaro JM, Hoffmann U, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. *Circulation* 2007; 116:39–48. [PubMed: 17576866]
25. Svendsen O, Hassager C, Christiansen C. Age- and menopause-associated variations in body composition and fat distribution in healthy women as measured by dual-energy x-ray absorptiometry. *Metabolism* 1995; 44:369–373. [PubMed: 7885283]
26. Nakhjavani M, Imani M, Larry M, et al. Metabolic syndrome in premenopausal and postmenopausal women with type 2 diabetes: loss of protective effects of premenopausal status. *J Diabetes Metab Disord* 2014; 13:1–6. [PubMed: 24393631]
27. Piché M-È, Lapointe A, Weisnagel JS, et al. Regional body fat distribution and metabolic profile in postmenopausal women. *Metabolism* 2008; 57:1101–1107. [PubMed: 18640388]
28. Arner P, Lithell H, Wahrenberg H, Brönnegård M. Expression of lipoprotein lipase in different human subcutaneous adipose tissue regions. *J Lipid Res* 1991; 32:423–429. [PubMed: 2066672]
29. Ramirez ME, McMurry MP, Wiebke GA, et al. Evidence for sex steroid inhibition of lipoprotein lipase in men: comparison of abdominal and femoral adipose tissue. *Metabolism* 1997; 46:179–185. [PubMed: 9030826]
30. Pedersen SB, Kristensen K, Hermann PA, et al. Estrogen controls lipolysis by up-regulating alpha2A-adrenergic receptors directly in human adipose tissue through the estrogen receptor alpha. Implications for the female fat distribution. *J Clin Endocrinol Metab* 2004; 89(4):1869–1878. [PubMed: 15070958]
31. Richelsen B Increased alpha 2- but similar beta-adrenergic receptor activities in subcutaneous gluteal adipocytes from females compared with males. *Eur J Clin Invest* 1986; 16:302–309. [PubMed: 3019701]
32. Gavin KM, Cooper EE, Raymer DK, et al. Estradiol effects on subcutaneous adipose tissue lipolysis in premenopausal women are adipose tissue depot specific and treatment dependent. *Am J Physiol Endocrinol Metab* 2013; 304:E1167–E1174. [PubMed: 23531620]
33. Stubbins RE, Holcomb VB, Hong J, et al. Estrogen modulates abdominal adiposity and protects female mice from obesity and impaired glucose tolerance. *Eur J Nutr* 2012; 51:861–870. [PubMed: 22042005]
34. Hong J, Stubbins RE, Smith RR, et al. Differential susceptibility to obesity between male, female and ovariectomized female mice. *Nutr J* 2009; 8:11. [PubMed: 19220919]
35. Meli R, Pacilio M, Raso G, et al. Estrogen and raloxifene modulate leptin and its receptor in hypothalamus and adipose tissue from ovariectomized rats. *Endocrinology* 2004; 145:3115–3121. [PubMed: 15059958]
36. Heine PA, Taylor JA, Iwamoto GA, et al. Increased adipose tissue in male and female estrogen receptor-alpha knockout mice. *Proc Natl Acad Sci* 2000; 97:12729–12734. [PubMed: 11070086]
37. Lindberg MK, Weihua Z, Andersson N, et al. Estrogen receptor specificity for the effects of estrogen in ovariectomized mice. *J Endocrinol* 2002; 174:167–178. [PubMed: 12176656]

38. Davis KE, Neinast MD, Sun K, et al. The sexually dimorphic role of adipose and adipocyte estrogen receptors in modulating adipose tissue expansion, inflammation, and fibrosis. *Mol Metab* 2013; 2:227–242. [PubMed: 24049737]
39. Brown LM, Clegg DJ. Central effects of estradiol in the regulation of food intake, body weight, and adiposity. *J Steroid Biochem Mol Biol* 2010; 122:65–73. [PubMed: 20035866]
40. Eckel LA. The ovarian hormone estradiol plays a crucial role in the control of food intake in females. *Physiol Behav* 2011; 104:517–524. [PubMed: 21530561]
41. Tarttelin MF, Behavior G-RA. Variations in food and water intake in the normal and acyclic female rat. *Physiol Behav* 1971; 7:847–852. [PubMed: 5167385]
42. Xu Y, Nedungadi TP, Zhu L, et al. Distinct hypothalamic neurons mediate estrogenic effects on energy homeostasis and reproduction. *Cell Metab* 2011; 14:453–465. [PubMed: 21982706]
43. Musatov S, Chen W, Pfaff DW, et al. Silencing of estrogen receptor α in the ventromedial nucleus of hypothalamus leads to metabolic syndrome. *Proc Natl Acad Sci* 2007; 104:2501–2506. [PubMed: 17284595]
44. Bélanger C, Luu-The V, Dupont P, Tchernof A. Adipose tissue intracrinology: potential importance of local androgen/estrogen metabolism in the regulation of adiposity. *Horm Metab Res* 2002; 34:737–745. [PubMed: 12660892]
45. Meseguer A, Puche C, Cabero A. Sex steroid biosynthesis in white adipose tissue. *Horm Metab Res* 2002; 34:731–736. [PubMed: 12660891]
46. Jones ME, Thorburn AW, Britt KL, et al. Aromatase-deficient (ArKO) mice accumulate excess adipose tissue. *J Steroid Biochem Mol Biol* 2001; 79:3–9. [PubMed: 11850201]
47. Jones ME, Thorburn AW, Britt KL, et al. Aromatase-deficient (ArKO) mice have a phenotype of increased adiposity. *Proc Natl Acad Sci USA* 2000; 97:12735–12740. [PubMed: 11070087]
48. Misso ML, Murata Y, Boon WC, et al. Cellular and molecular characterization of the adipose phenotype of the aromatase-deficient mouse. *Endocrinology* 2003; 144:1474–1480. [PubMed: 12639931]
49. Arnold AP. Mouse models for evaluating sex chromosome effects that cause sex differences in non-gonadal tissues. *J Neuroendocrinol* 2009; 21:377–386. [PubMed: 19207816]
50. Chen X, McClusky R, Chen J, et al. The number of x chromosomes causes sex differences in adiposity in mice. *PLoS Genet* 2012; 8:e1002709. [PubMed: 22589744]
51. Bojesen A, Kristensen K, Birkebaek NH, et al. The metabolic syndrome is frequent in Klinefelter's syndrome and is associated with abdominal obesity and hypogonadism. *Diabetes Care* 2006; 29(7):1591–1598. [PubMed: 16801584]
52. Gallagher D, Visser M, Meersman RE, et al. Appendicular skeletal muscle mass: effects of age, gender, and ethnicity. *J Appl Physiol* 1997; 83:229–239. [PubMed: 9216968]
53. Janssen I, Heymsfield SB, Wang ZM, Ross R. Skeletal muscle mass and distribution in 468 men and women aged 18–88 yr. *J Appl Physiol* (1985) 2000; 89(1):81–88. [PubMed: 10904038]
54. Nuutila P, Knuuti MJ, Mäki M, et al. Gender and insulin sensitivity in the heart and in skeletal muscles. Studies using positron emission tomography. *Diabetes* 1995; 44:31–36. [PubMed: 7813811]
55. Basu R, Dalla Man C, Campioni M, et al. Effects of age and sex on postprandial glucose metabolism: differences in glucose turnover, insulin secretion, insulin action, and hepatic insulin extraction. *Diabetes* 2006; 55:2001–2014. [PubMed: 16804069]
56. Mauvais-Jarvis F, Manson JE, Stevenson JC, Fonseca VA. Menopausal hormone therapy and type 2 diabetes prevention: evidence, mechanisms, and clinical implications. *Endocrine Rev* 2017; 38:173–188. [PubMed: 28323934] ■■ A comprehensive review on how menopause affects body composition, glucose homeostasis, insulin resistance, and diabetes. It also discussed how menopausal hormone therapy, despite its complex risk–benefit balance, could be considered as a potential therapeutic for menopausal women.
57. Glümer C, Jørgensen T, Borch-Johnsen K, Study I. Prevalences of diabetes and impaired glucose regulation in a Danish population: the Inter99 study. *Diabetes Care* 2003; 26:2335–2340. [PubMed: 12882858]

58. Sicree RA, Zimmet PZ, Dunstan DW, et al. Differences in height explain gender differences in the response to the oral glucose tolerance test- the AusDiab study. *Diabetic Med* 2008; 25:296–302. [PubMed: 18307457]
59. van Genugten RE, Utzschneider KM, Tong J, et al., Group A. Effects of sex and hormone replacement therapy use on the prevalence of isolated impaired fasting glucose and isolated impaired glucose tolerance in subjects with a family history of type 2 diabetes. *Diabetes* 2006; 55:3529–3535. [PubMed: 17130501]
60. Williams JW, Zimmet PZ, Shaw JE, et al. Gender differences in the prevalence of impaired fasting glycaemia and impaired glucose tolerance in Mauritius. Does sex matter? *Diabetic Med* 2003; 20:915–920. [PubMed: 14632717]
61. Gale EA, Gillespie KM. Diabetes and gender. *Diabetologia* 2001; 44:3–15. [PubMed: 11206408]
62. Mauvais-Jarvis F, Sobngwi E, Porcher R, et al. Ketosis-prone type 2 diabetes in patients of sub-Saharan African origin: clinical pathophysiology and natural history of beta-cell dysfunction and insulin resistance. *Diabetes* 2004; 53:645–653. [PubMed: 14988248]
63. Louet JF, Smith SB, Gautier JF, et al. Gender and neurogenin3 influence the pathogenesis of ketosis-prone diabetes. *Diabetes Obes Metab* 2008; 10(10):912–920. [PubMed: 18093211]
64. Wild S, Roglic G, Green A, et al. Global prevalence of diabetes estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27:1047–1053. [PubMed: 15111519]
65. Shulman GI. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. *N Engl J Med* 2014; 371:1131–1141. [PubMed: 25229917]
66. Gabriely I, Ma XH, Yang XM, et al. Removal of visceral fat prevents insulin resistance and glucose intolerance of aging: an adipokine-mediated process? *Diabetes* 2002; 51:2951–2958. [PubMed: 12351432]
67. Thorne A, Lonnqvist F, Apelman J, et al. A pilot study of long-term effects of a novel obesity treatment: omentectomy in connection with adjustable gastric banding. *Int J Obes Relat Metab Disord* 2002; 26:193–199. [PubMed: 11850750]
68. Weber RV, Buckley MC, Fried SK, Kral JG. Subcutaneous lipectomy causes a metabolic syndrome in hamsters. *Am J Physiol Regul Integr Comp Physiol* 2000; 279:R936–R943. [PubMed: 10956251]
69. Klein S, Fontana L, Young VL, et al. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *N Engl J Med* 2004; 350:2549–2557. [PubMed: 15201411]
70. Hernandez TL, Kittelson JM, Law CK, et al. Fat redistribution following suction lipectomy: defense of body fat and patterns of restoration. *Obesity (Silver Spring)* 2011; 19:1388–1395. [PubMed: 21475140]
71. Shadid S, Koutsari C, Jensen MD, et al. Direct free fatty acid uptake into human adipocytes in vivo: relation to body fat distribution. *Diabetes* 2007; 56:1369–1375. [PubMed: 17287467]
72. Johnson JA, Fried SK, Pi-Sunyer FX, Albu JB. Impaired insulin action in subcutaneous adipocytes from women with visceral obesity. *Am J Physiol Endocrinol Metab* 2001; 280:E40–E49. [PubMed: 11120657]
73. Gustafson B, Hedjazifar S, Gogg S, et al. Insulin resistance and impaired adipogenesis. *Trends Endocrinol Metab* 2015; 26(4):193–200. [PubMed: 25703677]
74. Lessard J, Laforest S, Pelletier M, et al. Low abdominal subcutaneous preadipocyte adipogenesis is associated with visceral obesity, visceral adipocyte hypertrophy, and a dysmetabolic state. *Adipocyte* 2014; 3:197–205. [PubMed: 25068086]
75. Faust IM, Johnson PR, Stern JS, Hirsch J. Diet-induced adipocyte number increase in adult rats: a new model of obesity. *Am J Physiol* 1978; 235:E279–E286. [PubMed: 696822]
76. Wang QA, Tao C, Gupta RK, Scherer PE. Tracking adipogenesis during white adipose tissue development, expansion and regeneration. *Nat Med* 2013; 19:1338–1344. [PubMed: 23995282]
77. Drolet R, Richard C, Sniderman AD, et al. Hypertrophy and hyperplasia of abdominal adipose tissues in women. *Int J Obes (Lond)* 2008; 32:283–291. [PubMed: 17726433]
78. Gealekman O, Guseva N, Hartigan C, et al. Depot-specific differences and insufficient subcutaneous adipose tissue angiogenesis in human obesity. *Circulation* 2011; 123(2):186–194. [PubMed: 21200001]

79. Palmer BF, Clegg DJ. Oxygen sensing and metabolic homeostasis. *Mol Cell Endocrinol* 2014; 397:51–58. [PubMed: 25132648]
80. Kim M, Neinast MD, Frank AP, et al. ERα upregulates Phd3 to ameliorate HIF-1 induced fibrosis and inflammation in adipose tissue. *Mol Metab* 2014; 3(6):642–651. [PubMed: 25161887]
81. Jiang-Feng M, Hong-Li X, Xue-Yan W, et al. Prevalence and risk factors of diabetes in patients with Klinefelter syndrome: a longitudinal observational study. *Fertil Steril* 2012; 98:1331–1335. [PubMed: 22940087]
82. Bardsley MZ, Falkner B, Kowal K, Ross JL. Insulin resistance and metabolic syndrome in prepubertal boys with Klinefelter syndrome. *Acta Paediatr* 2011; 100:866–870. [PubMed: 21251059]
83. Gravholt CH, Jensen AS, Høst C, Bojesen A. Body composition, metabolic syndrome and type 2 diabetes in Klinefelter syndrome. *Acta Paediatr* 2011; 100:871–877. [PubMed: 21342256]
84. Han S, Kim K-S, Kim W, et al. Obesity and hyperglycemia in Korean men with Klinefelter syndrome: The Korean Endocrine Society Registry. *Endocrinol Metab* 2016; 31:598.
85. Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005; 129:113–121. [PubMed: 16012941]
86. Browning JD, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004; 40:1387–1395. [PubMed: 15565570]
87. Kopec KL, Burns D. Nonalcoholic fatty liver disease: a review of the spectrum of disease, diagnosis, and therapy. *Nutr Clin Pract* 2011; 26:565–576. [PubMed: 21947639]
88. Pan J-J, Fallon MB. Gender and racial differences in nonalcoholic fatty liver disease. *World J Hepatol* 2014; 6:274. [PubMed: 24868321]
89. Ruhl CE, Everhart JE. Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. *Gastroenterology* 2003; 124:71–79. [PubMed: 12512031]
90. Clark JM, Brancati FL, Diehl A. The prevalence and etiology of elevated aminotransferase levels in the United States. *Am J Gastroenterol* 2003; 98(5):960–967. [PubMed: 12809815]
91. Ioannou GN, Boyko EJ, Lee SP. The prevalence and predictors of elevated serum aminotransferase activity in the United States in 1999–2002. *Am J Gastroenterol* 2006; 101:76–82. [PubMed: 16405537]
92. Lazo M, Hernaez R, Eberhardt MS, et al. Prevalence of nonalcoholic fatty liver disease in the United States: The Third National Health and Nutrition Examination Survey, 1988–1994. *Am J Epidemiol* 2013; 178:38–45. [PubMed: 23703888]
93. Ryu S, Suh B-S, Chang Y, et al. Menopausal stages and nonalcoholic fatty liver disease in middle-aged women. *Eur J Obstet Gynecol Reproduct Biol* 2015; 190:65–70.
94. Norheim F, Hui ST, Kulahcioglu E, et al. Genetic and hormonal control of hepatic steatosis in female and male mice. *J Lipid Res* 2017; 58:178–187. [PubMed: 27811231] ■ This study demonstrated extensive gene-by-sex regulation in hepatic steatosis using mouse reference population. These differences were attributed partly due to body fat distribution, plasma HDL and genetic regulation.
95. Norheim F, Bjellaas T, Hui ST, et al. Genetic, dietary, and sex-specific regulation of hepatic ceramides and the relationship between hepatic ceramides and IR. *J Lipid Res* 2018; 59:1164–1174. [PubMed: 29739864] ■ This study demonstrated that both gene-by-sex and gene-by-environment interactions were involved in regulating hepatic ceramide metabolism. These differences were attributed partly due to testosterone mediated inhibition of hepatic ceramide synthase 6 (Cers6) enzyme.
96. Robinet P, Milewicz DM, Cassis LA, et al. Consideration of sex differences in design and reporting of experimental arterial pathology studies-statement from ATVB Council. *Arterioscler Thromb Vasc Biol* 2018; 38:292–303. [PubMed: 29301789] ■■ A brief review on animal models of arterial pathology studies. Authors have also suggested guidelines for designing and inclusion of sex as a biological variable while reporting these data.
97. Kawamoto KR, Davis MB, Duvernoy CS. Acute coronary syndromes: differences in men and women. *Curr Atheroscler Rep* 2016; 18:73. [PubMed: 27807732]

98. Málek F, Dvořák J, Skalníková V, et al. Correlation of lipoprotein(a) with the extent of coronary artery disease in patients with established coronary atherosclerosis: gender differences. *Eur J Prev Cardiol* 2015; 22(5):603–605. [PubMed: 24618477]
99. Leening MJ, Ferket BS, Steyerberg EW, et al. Sex differences in lifetime risk and first manifestation of cardiovascular disease: prospective population based cohort study. *Br Med J* 2014; 349:g5992. [PubMed: 25403476]
100. Glisic M, Mujaj B, Rueda-Ochoa OL, et al. Associations of endogenous estradiol and testosterone levels with plaque composition and risk of stroke in subjects with carotid atherosclerosis. *Circ Res* 2018; 122:97–105. [PubMed: 29097437] ■ Using population studies on postmenopausal women and elderly men, the authors demonstrated that estradiol was positively correlated with carotid plaque composition and risks of stroke. No associations were observed for testosterone in either sex.
101. Cross TL, Kasahara K, Rey FE. Sexual dimorphism of cardiometabolic dysfunction: gut microbiome in the play? *Mol Metab* 2018; doi: 10.1016/j.molmet.2018.05.016 [Epub ahead of print]■■■ A comprehensive review on sex differences in cardiometabolic disease and gut microbiome composition. It also discussed that sex-specific gut microbiome composition can alter disease susceptibility and further elaborate studies are warranted.

KEY POINTS

- Sex differences contribute to majority of cardiometabolic traits and are mediated mostly in a tissue-specific manner.
- Sex differences are mediated through reversible sex hormones, irreversible developmental processes, and sex chromosome complement.
- Gene-by-sex interactions must be understood for a better understanding of sex differences and development of personalized treatment.

Table 1.

Key questions in understanding sex differences in metabolic and cardiovascular traits

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1. How do different tissues and cell types differ in hormonal responses between sexes?
 2. What genes on the X or Y chromosomes are involved in sex differences?
 3. How do tissues differ in epigenetic organization during sexual development?
 4. Are sex-specific differences well conserved between humans and animal models?
 5. How do men and women differ in drug responses? For example, statin use is associated with diabetes, but more so in women than men.
 6. How prevalent are gene-by-sex interactions?
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