

Review

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Review

Sex-Specific Variation in Metabolic Responses to Diet

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Abstract: Suboptimal nutrition is a leading cause of cardiometabolic disease and mortality. Biological sex is a variable that can play a role in individual response to nutritional factors and may modulate the impact of nutrition on disease. This narrative review explores the intricate interplay between sex, nutrition, and health outcomes, and the consequent importance of considering sex in nutrition research, dietary recommendations, and disease management. We examine the impact of sex on how various dietary patterns, including the Mediterranean diet, macronutrient content and quality, Western diet, and energy restriction associate with or affect metabolic health and disease risk. Understanding how sex influences the response to the diet can inform precision nutrition interventions and approaches for disease prevention and management.

Keywords: sexual dimorphism; dietary patterns; metabolic health; type 2 diabetes; insulin; glucose tolerance; body composition; cardiometabolic; sex difference; diet

1. Introduction

It is well recognized that inadequate nutrition plays a major contributing role in today's major chronic disease epidemics, accounting for an estimated 45% of cardiometabolic fatalities [1]. Dietary patterns have distinct impacts on metabolic health, particularly concerning insulin sensitivity, metabolic syndrome, obesity, and the risk of diabetes and other chronic diseases. The Western diet, typically high in refined sugars, saturated fats, and processed foods, is associated with increased insulin resistance and poor glucose tolerance, contributing significantly to the rising prevalence of type 2 diabetes [2–6]. In contrast, the Mediterranean diet, rich in fruits, vegetables, whole grains, and healthy fats like olive oil, has been shown to enhance insulin sensitivity and improve glucose metabolism [7,8], thereby reducing the risk of diabetes. Healthy plant-based diets, which emphasize the consumption of vegetables, legumes, nuts, and seeds while minimizing animal products, also promote better glycemic control and insulin sensitivity [9–11]. At the same time, caloric restriction, even without specific macronutrient adjustments or food group specifications, improves insulin sensitivity and lowers fasting glucose concentrations [12]. Additionally, intermittent fasting and time-restricted feeding patterns have been linked to reduced insulin resistance and better glucose regulation [13,14]. Though dietary modifications have the potential to improve metabolism in most people, evidence indicates that biological sex may affect response to diet-based interventions in clinical trials and preclinical models.

Sexual dimorphism, the phenotypic differences between males and females of the same species, extends beyond anatomical and physiological characteristics to include responses to dietary intake and metabolic processes [15]. It is established that some nutrient recommendations vary between males and females. For instance, iron requirements are higher in females due to menstrual losses [16]. The nutrient needs of females are significantly affected by pregnancy and lactation, requiring additional calories and nutrients such as folate, iron, iodine, and choline to support fetal development and breastfeeding [17]. Biological factors underpinning sexual dimorphism in nutrient needs and response to nutrient intake may include sex chromosome dosage [18], hormonal differences [19–21],

body composition [22], nutrient requirements [23,24], disease susceptibility [25,26], and reproductive stage [27,28], among others.

Understanding the sex-based differential effects of diet is crucial for developing precision dietary recommendations to optimize metabolic health and prevent or manage chronic disease. By examining sex-specific responses to different dietary patterns, and establishing the underlying mechanisms to differential responses, healthcare providers will be better prepared to advise patients considering the unique needs of men and women to improve health outcomes and disease prevention strategies. Here, we sought to describe how biological males and females have responded differently to the Mediterranean, variable macronutrient, Western, and energy restriction-based diets, with an emphasis on cardiometabolic outcomes. We include relevant clinical trials and prospective cohort studies conducted in primarily middle-aged to older adults with metabolic syndrome traits, while including animal work to support human study findings or highlight emerging diet components showing sexually dimorphic responses. We excluded studies relying on cross-sectional analyses. A comprehensive review of studies including preclinical models is outside the scope of this review, but for readers seeking more information on that topic, MacArthur and Mitchell recently published an excellent review of sex differences in healthspan and lifespan in response to several dietary interventions in model organisms [29].

2. Mediterranean Diet

While observational studies and clinical trials have demonstrated the potential of a Mediterranean diet to improve biomarkers of metabolic health and reduce risk of developing type 2 diabetes [30], some studies have also investigated whether men and women respond differently to this diet. Bedard et al. conducted a 4-week Mediterranean diet study where all meals were provided to 70 overweight and obese participants, including 38 men and 32 premenopausal women aged 24-53 years. The primary aim of the study was to document sex differences in the impact of the Mediterranean diet on cardiometabolic outcomes. After following the 4-week diet, men and women showed similar reductions in fasting blood glucose, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and circulating lipids [31]. The results of a 180-minute oral glucose tolerance test (OGTT), however, show that only men have significant reduction in plasma insulin iAUC, which included a significant sex-by-time interaction effect. These findings suggest that men have increased peripheral insulin sensitivity in response to a Mediterranean diet intervention. This possibility is supported by a significant increase in the Cederholm index, a measure of peripheral insulin sensitivity, in men only. That said, as is the case with most diet studies, the women were metabolically healthier at baseline when compared with the men, which may have limited their ability to respond to the intervention.

In another investigation of the Mediterranean diet, Leblanc et al. studied sex-specific differences in response to a 12-week intervention in mid-aged, overweight, and obese participants meeting at least one metabolic syndrome criterion and having elevated LDL-c or total to HDL ratio (n=64 men and 59 premenopausal women). In contrast to the controlled feeding study above, these participants self-selected diet foods with support from group, on-on-one and phone counseling sessions based on motivational interviewing. There were no differences in Mediterranean diet score [34] at baseline, after the 12-wk diet, or at 6-month follow up between men and women, and both sexes reverted to baseline Mediterranean diet scores at the 6-month follow up. Despite similar adherence to the study diet, only men showed reductions in body weight, body fat %, LDL-C, and diastolic blood pressure at the conclusion of the study or 6 months post-intervention. While both sexes showed a significant reduction in waist circumference immediately after the dietary intervention, only men maintained a smaller waist circumference through the 6-month follow-up. Though Mediterranean diet score did not significantly vary between the sexes at any point, only men showed greater long-term reductions in energy intake and increases in fiber intake, so it is unclear whether the study's outcomes are resulting from these sustained dietary changes or intrinsic metabolic differences between the sexes.

Jennings et al. conducted a 12-month RCT of a Mediterranean-style diet in 1128 healthy participants aged 65-79 years from locations across Europe to determine how this diet affects vascular

health [35]. The intervention group received tailored dietary advice and received whole grain pasta, extra virgin olive oil, low-fat low-salt cheese, high polyunsaturated fat margarine, and vitamin D supplements (10 µg/d) to support compliance with the intervention, while the control group followed their habitual diet with general dietary guidance. After a year on the Mediterranean diet, only males showed a significant reduction in systolic blood pressures (SBP; about 9 mm Hg less than controls) and pulse pressure (about 6mm Hg less than controls). In contrast, in a subset of participants (n=225), only women showed a significant decrease in arterial stiffness following the intervention. Participants were permitted to continue antihypertensive therapies as prescribed at study baseline, and there were no differences in medication use between the control and intervention groups; however, it is not clear whether rates of antihypertensive use were different between men and women in the diet intervention group. This is relevant because SBP was only significantly improved in non-medicated groups in analyses testing the effect of antihypertensive therapy on diet efficacy. Moreover, only men showed significant reductions in 24-h urinary sodium with concomitant increases in 24-h potassium. Since urinary sodium and potassium are indirect measures of sodium and potassium ingestion [36], these findings suggest that men adhered more closely to the assigned diet because whole plant foods are high in potassium and generally low in sodium. It is also possible that women had baseline diets that were more like the Mediterranean diet intervention. That said, baseline antihypertensive use and dietary compliance, as indicated by food records, were covariates in statistical modeling of sex-based differences in primary outcomes. Sex was also a covariate when modeling the effect of antihypertensives on diet response. Moreover, a report from the 4-week controlled feeding study detailed above also reported reduced systolic blood pressure in men only [31].

It is possible that the emphasis on seafood in the Mediterranean diet may be especially important for men. An analysis of the Japan Public Health Center-based Prospective Study shows that fish intake reduced risk of developing type 2 diabetes in men, but not women [32]. Taken together, men tend to show greater improvements cardiometabolic outcomes after following a Mediterranean-style diet for up to 12 months.

3. Macronutrients

3.1. Carbohydrate Quality

Some evidence indicates that women are especially susceptible to chronic disease associated with high glycemic index (GI) dietary pattern [33,34]. One group sought to determine if 8-hour average plasma glucose and insulin profiles of men and women are different when provided either a low or high GI Mediterranean diet [35]. Using data from the MEDGI-Carb trial, a 12-wk RCT comparing high and low GI Mediterranean diets, 156 adults having a BMI ≥ 25 and a high waist circumference were included in a secondary analysis. The two diets called for equal amounts of carbohydrates (270 g/day) and fiber (35 g/day), differing only in starch sources. In both diet groups, half of the carbohydrates (135 g) were from fruits, vegetables, and dairy. The low-GI group (<55 GI) additionally consumed pasta, brown rice, and whole grain breads, while the high-GI group (>70 GI) had jasmine rice, potatoes, and whole grain bread. Energy intake was eucaloric to maintain stable body weight. At the end of the intervention participants underwent two meal challenges with subsequent observation for 8 hours, and investigators determined average plasma glucose and insulin concentrations over that time. While there were no notable differences in insulin secretion post-intervention compared with baseline, women on the high GI diet showed considerably higher mean glucose concentrations in response to the meal challenges when compared baseline values. While these findings suggest that women may be especially susceptible to intolerance to rapidly absorbed dietary carbohydrates when compared with men, the women assigned to the high GI diet were less metabolically healthy at baseline when compared with the women assigned to the low GI group as evidenced by their significantly higher baseline mean glucose and insulin meal challenge responses. The assignment to a high GI diet in less metabolically healthy women may have amplified refined carbohydrate intolerance in these women. On the other hand, a recent meta-analysis

evaluating the effect of GI and glycemic load on cardiometabolic health concluded that both sexes show greater risk of type 2 diabetes development with a high GI diet independent of overall dietary pattern [36]. That said, women, when compared with men, showed greater type 2 diabetes risk in association with a high GI diet after controlling for the dietary instruments' correlation coefficients for carbohydrate, ethnicity, and duration of follow-up [36].

Additional evidence indicates that women may be especially susceptible to cardiovascular disease when consuming diets high in refined plant foods, i.e., white grains, potatoes, sugar-sweetened beverages, and other sweetened foods. Use of diet indices is a common method for measuring diet quality and adherence to healthy dietary patterns [37]. These tools allow a comparative assessment of diet quality, which is generally applicable across most population categories. Using food-frequency questionnaires from the Nurses Health Study (NHS 1 and NHS2; female participants) and the Health Professionals Follow-Up Study (male participants), study authors created three plant-food index scores to define plant-based diets (plant-based diet index; PDI), healthy plant-based diets (hPDI), and unhealthy plant-based diets (uPDI) [11,38]. All plant-based foods contribute positively to the PDI, only healthful/whole plant foods contribute positively to hPDI, and unhealthful plant foods contribute positively to the uPDI. Any dietary component that doesn't "fit" the defined diet contributes negative scores, i.e., animal foods for all versions of the PDI, processed plant foods for the hPDI, and whole plant foods for the uPDI. Authors then modeled how compliance to each of the dietary patterns associated with risk of developing coronary heart disease (CHD) later in life [38]. Based on fully adjusted multivariable models, women in the highest versus lowest deciles of the uPDI were at a 49% (NHS1) and 77% (NHS2) greater risk of CHD, while male counterparts showed a 21% increased risk for CHD. Though analysis of both sexes together showed an inverse association between hPDI and CHD and a positive association with CHD for uPDI, the risk of developing CHD while following a dietary pattern high in refined carbohydrates appeared greater in women.

Similarly, using dietary data from a large cohort study conducted in Japan (Japan Public Health Center-Based Prospective Study), investigators sought to determine whether intake of several common dietary grain products, including rice, noodles, and bread, affected risk of Type 2 diabetes development in men ($n=25,666$) and women ($n=33,622$) 45-75 years of age [39]. Women who consumed 3 bowls (420g) or more of rice each day showed an increased risk for type 2 diabetes; however, the men did not show increasing diabetes risk with greater rice intake. The relationships remained consistent significant after adjusting the models. The observed risk increase in women was greater among non-obese women, lending credibility to the idea that the dietary factor, rather than overall weight, affected diabetes risk. Since most rice consumed in Japan is the white or refined version, this study further supports the ideas that refined grain products are more deleterious to women's metabolic health when compared with men. The risk in women was attenuated among those with high levels of physical activity, showing the importance of considering the impact of physical activity on diet-disease relationships. Another analysis of the same cohort study showed high intakes of total sugar, fructose, and starch were associated with risk of developing type 2 diabetes in women, but men did not show increased diabetes risk with high consumption of these dietary components [40]. On the other hand, recent meta-analysis of cohort data from 8 Asian countries ($n=256,818$) showed a higher relative risk of diabetes development in women (1.58) with high rice intake when compared with men (1.30); however, the interaction effect was not significant [41]. That said, this meta-analysis did not consider the potential impact of physical activity on the relationship.

Recent evidence indicates that female mice increase hepatic triglyceride content significantly more than male mice in response to the addition of sucrose to the drinking water [42]. This phenotypic change was accompanied by a dramatic increase in transcription for both genes encoding for hepatic acetyl-CoA carboxylase (ACC; *Acaca* and *Acacb*) in females, which was not observed in males. ACC is the rate-limiting step of de novo fatty acid synthesis. Its product, malonyl-CoA, reduces activity of carnitine palmitoyltransferase 1 (CPT1), which is a protein needed to transport and metabolize fatty acids in the mitochondria. While dysregulation of adipocyte lipolysis was

requisite for the development of sucrose-induced steatosis in both sexes, only female mice showed a contribution from de-novo hepatic lipogenesis following sucrose intake.

The combined human and preclinical findings suggest that women are more susceptible to glucose intolerance and excess fatty acid synthesis in response to large amounts of rapidly absorbed and refined carbohydrates.

3.2. Lipids

Women may better tolerate less healthful dietary sources of dietary lipids. In order to evaluate whether biological sex affects postprandial lipemia, investigators instructed young, healthy participants (n=10) to consume self-selected low-fat/low-cholesterol diet and after another two weeks on the self-selected high-fat/high-cholesterol diet [43]. Participants' food records showed significant shifts when comparing the low- and high-fat diets. On the high-fat diet, when compared with the low-fat diet, both men and women showed comparable and substantial increases energy, cholesterol, and total fat intake (approximately 40% increase in total kcal, 1000mg increase in daily cholesterol, and shift in fat from 30% to 40% of total energy). While fasting circulating cholesterol concentrations increased similarly for both sexes following the high-fat diet, only men showed a significant postprandial increase in triglycerides following a weight-adjusted challenge meal of tea, rolls, ham, and liquid cream.

Similarly, men may respond more favorably to a diet that is reduced in atherogenic dietary lipids. In one cross-over study, mid-aged to older men (n=19) and postmenopausal women (n=14) with high total blood cholesterol (LDL-C concentrations of ≥ 4.14 mmol/L) were provided a diet consistent with Therapeutic Lifestyle Changes (TLC, diet: 26% of energy as fat, 4% as saturated fat, and 45 mg cholesterol/4.2 MJ), which was compared with a typical Western diet (35% of energy as fat, 14% as saturated fat, and 147 mg cholesterol/4.2 MJ) [44]. Following a 6-week period on the TLC diet, men generally showed significantly more pronounced changes in both fasting and post-prandial lipids. The TC/HDL-C ratio was reduced by 5% in men yet increased 5% in women following the TLC diet. Unfortunately, baseline diet and indicators of carbohydrate quality in the diet provided are not reported. Overall, the impact of sex on lipid response to low-fat/high-carbohydrate diet are equivocal with some showing greater benefits for men [45,46] and others showing no differences between the sexes [47,48]. As outlined above, the impact of dietary carbohydrate quality may also be sex dependent. That said, most of these studies were performed at a time when refined carbohydrate was less broadly recognized as injurious to metabolic health and less often reported in manuscripts. Having been published primarily in the 90s, these studies are "old news," but since the diets tended to show benefits on average, they were touted as beneficial for everyone. With the immense interest in precision nutrition at present, the field of nutrition needs powered trials to test sex-specific diet responses to various dietary patterns and macronutrient shifts to better support individualized dietary recommendations.

While women's ability to metabolize fat is often attributed to actions of higher circulating estrogen [49], there is evidence that boys and girls may respond differently to modulations in dietary fat even before overt sex hormones concentrations are different between the sexes. The STRIP baby trial team implemented a low-saturated fat, low-cholesterol randomized diet intervention in children from birth to three years of age and compared these children to a control group (n=1062) [50]. The intervention group's family received continuous dietary counseling, which resulted in significantly lower serum cholesterol concentrations without adverse effects on growth or development. The investigators noted a significant interaction between sex and treatment group in serum cholesterol (p=.011) and non-HDL cholesterol (p=.017) then followed up with an analysis of data disaggregated by sex. The intervention had a more pronounced effect on boys and showed serum cholesterol and non-HDL cholesterol concentrations that were approximately 6% lower than the control group (p<0.0001). The girls in the intervention, despite having a significantly higher baseline cholesterol than the boys, showed approximately 3% less circulating lipids than the control group, and the difference was not statistically different from the control group (p=0.089). Since boys and girls show

significantly different responses to low-fat diet at an early age, perhaps the sex-based differences in dietary response are not entirely explained by differences in sex hormones.

Studies including rodents testing high-fat diets typically show that male rodents exhibit hyperphagia, increased body weight, and poor metabolic outcomes when compared with females [51–53]. Estrany et al. conducted a trial that investigated the impact of a high-fat diet on glucose tolerance, insulin signaling and lipid catabolism in rats [51]. Male and female rats were assigned to either a standard diet (2.9% w/w fat) or a high-fat diet (30% w/w fat) for 14 weeks. Male rats consuming a high-fat diet showed greater adiposity and impaired glucose tolerance and concomitant decrease in PPAR- γ when compared with male rats consuming a standard diet. PPAR- γ is a nuclear receptor with regulation activity promoting insulin sensitivity and reducing inflammation associated with type 2 diabetes and atherosclerosis. When female rats consumed a high-fat diet, they remained glucose tolerant and showed higher expression of PPAR- γ transcripts and CPT1 protein, which is responsible for transporting fatty acids into the mitochondria for beta-oxidation. Elzinga et al. investigated the effects of a high-fat (60% fat) or a standard diet (10% fat) diet on insulin resistance and peripheral neuropathy in male and female mice and found similar sex-based variation [53]. While both sexes experienced similar nerve-conduction deficits and nerve fiber loss, male mice gained weight more rapidly than females throughout the course of the study up until 36 weeks, and females also displayed delayed insulin resistance [53]. Huang et al. fed young mice either a standard diet (10% fat) or high-fat diet (45% fat) for 5 weeks and measured food intake, energy expenditure, weight, and fat mass over this period [52]. Males on the high-fat diet had significantly higher weight and adipose tissue after 5 weeks compared to males assigned to the standard diet, while females consuming the high-fat diet had significantly greater weight, but not fat mass, compared to females on a low-fat diet. Males on the high-fat diet had lower energy expenditure during the light [sleeping/inactive] phase compared with high-fat diet consuming females. While both male and female mice consuming the high-fat diet showed a lower RER than their same-sex low-fat diet counterparts, the AUC difference over 24-hours appears more substantial in the females when compared with the males, but the statistics were not completed to test that difference. These RER data appear to reinforce the molecular observations showing that female rodents consuming a high-fat diet show greater expression of enzymes associated with lipid catabolism when compared with females consuming a typical chow.

3.3. Protein

The role of dietary protein in metabolic health is under great scrutiny [54]. While some dietary intervention studies show benefits protein or amino acids for improved metabolic outcomes [55], energy expenditure [56], retention of lean mass during weight loss and enhanced satiety [57–59], others have associated protein intake with higher risk for morbidity and mortality from common cardiometabolic diseases [54,60]. Recently, convincing preclinical data has shown that high-protein and amino acid intake causes metabolic impairment in rodents, while dietary restriction of protein and certain amino acids (e.g., isoleucine and valine) promote improved metabolic outcomes mimicking calorie restriction [60,61]. Reliable human data on the metabolic effects of protein intake is difficult to identify for several reasons. Many human studies tend to focus on modifying carbohydrate or fat while keeping protein consistent around 10-16% of overall energy intake. The 10% value is the bottom of the protein Dietary Reference Intakes Acceptable Macronutrient Distribution Range while the 2017-2020 pre-pandemic *What We Eat in America* data shows that 14-16% of energy consumed is sourced from protein in various US sub-groups, which has been consistent in recent decades.

The effect of protein intake on health is further complicated by the difficulty of standardizing intake in an appropriate way, particularly in cohort and cross-sectional studies. Though protein needs are often given standardized to weight (e.g., the RDA of 0.8 g/kg), standardizing protein intake to weight in cross-sectional or cohort studies often results in reporting of spurious relationships between high protein intake and good metabolic health [62]. Analyses using protein intake standardized to weight are often published, but methods standardizing to total energy intake, or

ideal or fat-free body weight are preferred [62]. Protein research is further complicated by a lack of consistency in the definition of high, moderate, or low protein and the level of compliance with the assigned diet [63]. Finally, studies of protein modulation on lower energy diet are complicated by the fact that absolute protein intake on a weight maintenance diet and a higher protein diet, defined as a percent of macronutrients, may be the same when defined as a number of grams of protein [63]. Consequently, lower protein weight loss diets could preferentially induce negative nitrogen balance due to an absolute decrease in participants' protein intake.

There is, however, some evidence that protein and amino intake affects health and metabolism differently in males and females [64–67]. Investigators used data from 27,799 men and 36,875 women aged 45–75 from the Japan Public Health Center-Based Prospective Study to investigate the association between a low-carbohydrate diet and the risk of type 2 diabetes among Japanese men and women, taking into consideration plant and animal sources of protein [68]. Over a 5-year period, 1,191 new cases of type 2 diabetes were reported. Findings indicated that a high low-carbohydrate diet score, particularly one high in animal protein and fat, was associated with a decreased risk of type 2 diabetes in women, while men with greater plant fat intake showed lower type 2 diabetes risk. The authors posit that the unexpected relationship between reduced diabetes risk and animal protein and fat in women likely stems from the high consumption of fish and seafood in the Japanese population. Nonetheless, the protective effect of these foods was not observed in the men and conflicts with another study reported above where high fish intake was associated with better metabolic health in men [32]. However, like those studies reported above [39], women showed a significantly increased risk of diabetes with higher carbohydrate consumption. This association was partially attributed to the high intake of white rice. Similarly, another prospective cohort study of older Australian men ($n=794$) showed that total protein intake was associated with increased all-cause mortality, whereas plant protein showed an inverse relationship with all-cause mortality in these men [69], warranting further investigation into the differing impacts of animal-based and plant-based proteins and diets in men and women.

Some evidence indicates that protein intake affects energy metabolism differently in males and females [64–67]. Using a randomized cross-over design, investigators used a whole room calorimeter to determine the effects of dietary macronutrient distribution difference on energy metabolism, satiety, and associated hormones [67]. Ten metabolically healthy, young men were recruited to compare findings to a previous study that included only similarly healthy women [70]. Thirty-six hour, eucaloric diet interventions contained 10% or 30% protein, 30% fat, and the remainder as carbohydrate for the low and high protein diets, respectively. Investigators reported that men showed a greater increase in energy expenditure in response to the higher protein diet, while women showed a greater satiety response to the higher protein diet.

Particularly in the context of energy-restricted diets, dietary interventions testing the efficacy of higher protein diets during weight loss show generally better body composition outcomes when women follow a hypocaloric diet higher in protein, rather than carbohydrate, when fat remains constant [58,59,71]. One group tested the effect of a higher protein diet including 30% of energy from protein at $1.5 \text{ g}/(\text{kg} \cdot \text{d})$ compared with a higher carbohydrate diet restricting protein to $0.8 \text{ g}/(\text{kg} \cdot \text{d})$ in overweight and obese mid-aged women ($n=24$). Both diets provided consistent fat intake at 30% of energy consumption. During the 10-week diet intervention period, women consumed food in a laboratory setting for the first 4 weeks combined with intensive diet instruction. Women prepared food themselves during the final 6 weeks. After 10 weeks, the women assigned to the carbohydrate intervention had significantly lower fasting blood glucose, which was not observed in the high protein group [31]. Nonetheless, by showing a greater ratio of fat/lean loss, the women in the higher protein intervention spared fat-free mass when compared with women in the carbohydrate group [58]. In lieu of a standard oral glucose tolerance test, the investigators chose to use isocaloric test meals mirroring the assigned intervention diet; hence, carbohydrate load was different during the meal challenge, making meaningful carbohydrate metabolism group comparisons difficult [72]. The same research group later conducted a 12-month study randomizing overweight and male and female participants with obesity ($n=130$) to similar diet groups [59]. While the protein diet group

showed greater fat loss when compared with the carbohydrate group, there was no tendency for the protein group to retain more fat-free mass in the mixed sex trial [59], contrasting with the studies that only included females. Similarly, a 16-week trial comparing the effects of a high protein vs. lower protein diet in men and women showed that women retained fat-free mass better than men with the high protein diet, whereas men showed a greater loss of abdominal fat [55]. On the other hand, a study of leucine supplementation during a controlled 8-wk diet showed that leucine better supported fat-free mass retention in male participants [57].

Green et al. examined the impact of low-protein diets on metabolic health in different strains and sexes of mice [65]. The findings showed that the benefits of a low-protein diet, such as improved glucose tolerance and increased energy expenditure, were influenced by both sex and genetic background. For instance, mirroring results of the calorimeter study above, male mice on a low-protein diet showed a significant increase in energy expenditure ($p < 0.05$), whereas female mice did not. Additionally, changes in adiposity and insulin sensitivity varied significantly between male and female mice, with males showing a greater reduction in adiposity ($p < 0.01$) and females displaying improved insulin sensitivity ($p < 0.05$). These findings highlight the importance of considering sex and genetic background in dietary interventions for metabolic health. Several compelling protein and sex-related studies using pre-clinical models have been published in recent years [54,60,61,66,73,74].

4. Western Diet

The Western diet pattern is characterized by chronic consumption of meats, high-fat dairy, processed foods, fried foods, and sweets. The Western diet is associated with chronic inflammation [75] and a sequela of metabolic disorders including obesity [76], type 2 diabetes [77], and CVD [78]. Evidence from human and animal studies indicates that the effects of a Western-style diet on the inflammatory response, postprandial lipid profile [43], glucose tolerance [79], weight gain [79], and metabolic enzyme mRNA expression are sex-specific [80,81].

One study assessed the association between overall diet quality and the risk of impaired fasting glucose and type 2 diabetes in older adults. Overall diet quality was assessed with the Healthy Eating Index for Australians Total Diet Score using dietary data collected from 2,564 participants aged 49 and older. After adjusting for various factors, men in the highest with lowest tertile of total diet score showed a 75% decrease in the risk of impaired fasting glucose when compared with men in the lowest tertile of in Total Diet Score. Each two-point increase in Total Diet Score was associated with a 52% reduction in impaired fasting glucose risk in men. No significant associations were found in women or with the incidence of diabetes in either sex group. The study authors concluded that better diet quality was linked to a reduced risk of pre-diabetes in men.

Some studies have investigated whether responses to comprehensive lifestyle change, which includes a shift away from a Western diet, affect men and women differently. A prospective study examined sex differences in diabetes risk factors among participants in the Diabetes Prevention Program [82]. While intensive lifestyle modification significantly correlated with diabetes prevention overall, men achieved more ILS goals than women throughout the intervention but had a similar diabetes incidence. Over the first year of the Diabetes Prevention Program, weight loss of 3-7% body weight led to greater improvements in certain risk factors for diabetes in men compared to women, and weight loss exceeding 7% showed similar trends. Despite these differences, baseline risk factors in men may have masked a potential sex disparity in incident diabetes.

DeGroef et al. investigated the sexual dimorphism in metabolic responses to a Western Diet in fruit flies utilizing standard diets supplemented with up to 30% sugar and 30% coconut oil [81]. While female flies on all diets containing added sugar gained more weight when compared with females consuming a standard diet, no such weight differences were observed in the male flies with added sugar or fat. That said, male flies consuming any diet having added fat showed greater body TAG storage when compared with male flies on the standard diet, but dietary fat-induced TAG differences were attenuated in female flies. Female flies displayed a twofold higher glycogen concentration compared to males under normal conditions and much more diet-associated variability in glycogen storage when compared with males. In females, most groups receiving fat-supplemented

diets showed a significant decrease in glycogen content. On the other hand, sugar supplementation alone induced a substantially higher glycogen storage in female flies, a response not observed in males. Perhaps the female propensity to store, rather than metabolize, glucose could reduce glycogen disposal capacity at later eating occasions and contribute to glucose intolerance with high consumption of refined carbohydrates. Moreover, mRNA abundance of several genes encoding proteins critical for lipid and carbohydrate metabolism showed sexual dimorphism in their expression patterns. This study demonstrated that a Western-style diet induces metabolic changes and metabolism-related gene expression in a sex-specific manner in fruit flies, shedding light on potential metabolic mechanisms underlying the sex-dietary interactions.

5. Restriction and Fasting

Recent research has increasingly considered the influence of sex as a biological variable in responses to energy-restricted diets. A large multinational study including 2020 overweight individuals with prediabetes (PREVIEW lifestyle intervention study) examined the sex-specific responses to an energy-restricted diet (810 calories/day) [83]. While men and women experienced similar improvements in insulin resistance, men lost 16% more weight after 8 weeks on an energy-restricted diet, which could be explained a difference in absolute energy deficit between the sexes given the same energy prescription for all participants. That said, women experienced significantly greater reductions in fat-free mass, hip circumference, and HDL concentrations. Women were also significantly more likely to experience adverse reactions during and immediately following the low-energy diet, including constipation, diarrhea GI symptoms (nausea, pain, vomiting), sore throat, headaches and migraines, muscular weakness and pain, hair loss, and infections.

Investigations into the effects of low-energy diets have revealed sexual dimorphism in weight loss and cardiometabolic risk factors. Trowbourn and colleagues conducted a randomized controlled trial where 782 participants with BMI ≥ 25 (65% women) followed an 8-week 800 kcal/day diet and then were randomized to either a control or four different *ad libitum* diets that varied in protein content and glycemic index [84]. The study found sex-specific effects of a low-energy diet among participants. Men experienced greater weight loss during the low-calorie diet period when compared with the women (-12.8 kg vs. -10.1 kg, $p < 0.001$), but regained more weight during the follow-up period (1.5 kg vs. -0.5 kg, $p < 0.001$). Men also showed more pronounced improvements in various cardiometabolic risk factors, such as insulin sensitivity, cholesterol levels, and blood pressure, after weight loss, even after adjusting for weight change. Conversely, women demonstrated a smaller rebound in HDL-cholesterol, triacylglycerol, and diacylglycerol concentrations during the weight maintenance phase, independent of weight changes. These differences suggest that metabolic responses to weight loss and maintenance are influenced by sex-specific factors, which may include body fat distribution and baseline metabolic status.

Tremblay et al. examined the profiles of individuals who had been successful or unsuccessful losing weight on a calorie-restricted diet [85]. The study found that 10.2% of women and 7.9% of males were unsuccessful at losing weight on an energy-restricted diet and that males experienced greater changes in fat mass, percent body fat, and waist circumference when compared with women. Additionally, the differences between unsuccessful and successful responders were more pronounced in men. However, men weighed more at baseline, and men who were successful and unsuccessful had greater average energy deficits (1,659 and 815 kcal) compared to their female counterparts (1,299 and 656 kcal), which likely explains these differences. Researchers point to less favorable changes in appetite and hunger sensations among unsuccessful responders and suggest that these individuals display a "behavioral vulnerability" which may reduce their ability to lose weight during a weight loss program.

Lin et al. conducted a secondary analysis of three 12-week studies that compared the effect of alternate-day fasting on weight loss, dietary adherence, and metabolic disease risk reduction in premenopausal women, postmenopausal women, and men [86]. Despite the hypothesis that postmenopausal women would exhibit greater compliance with alternate-day fasting, leading to

more substantial reductions in body weight and insulin resistance, no significant differences were observed among the groups.

Calubag and colleagues examined calorie restriction in mice, focusing on the role of the hormone FGF21, known for regulating energy balance and improving metabolic health [87]. Researchers compared mice with and without the *Fgf21* gene, feeding them either a normal diet or a 30% energy restricted diet for 15 weeks. Results indicated that *Fgf21* is not essential for energy restriction-induced improvements in body composition and energy balance in both male and female mice; however, there were sex-specific responses in adapting to calorie restriction. Female mice without *Fgf21* showed poorer glucose regulation and insulin sensitivity when compared with female mice consuming food ad libitum, a group difference not observed in male mice. On the other hand, when compared with male mice on an ad libitum diet, energy-restricted male mice without *Fgf21* showed less being of white fat, a process that increases energy expenditure. This study demonstrates that males and females may show biologically different responses when adapting to known efficacious treatments, like energy restriction.

6. Future Directions and Research Gaps

Sexual dimorphism in nutrition manifests in multiple organs and metabolic pathways, driven by factors such as sex hormones, body composition, XY chromosome dosage effects, and gut microbiota composition [15]. These biological differences contribute to divergent responses to dietary components and patterns, highlighting the need for sex-specific considerations in nutritional recommendations. Despite this, many studies do not include both sexes [88].

Sex hormones such as estrogen¹⁸ and testosterone¹⁷ are known to influence metabolism and nutrient utilization. For instance, studies have demonstrated that circulating concentrations of most metabolites and micronutrients vary significantly at different points throughout the menstrual cycle with many metabolic pathways changing in rhythm with the female cycle [89]. Hormonal fluctuations throughout the menstrual cycle can affect dietary intake [90], nutrient metabolism [91], and appetite in women [92–94]. For example, during the luteal phase of the menstrual cycle, women report an increase in protein intake and food cravings [95]. Evidence suggests that luteal phase cravings and eating habits may be modulated by the estradiol-leptin axis [20]. Conversely, food choice can impact how women experience symptoms associated with the menstrual cycle [96]. Significant alterations in ghrelin and the metabolically active adipocytokines are linked to menopause phases and basal follicle-stimulating hormone (FSH) shifts, and these variations may be linked to mid-life obesity in women [97]. Nutrition studies that include female participants without controlling for the menstrual cycle phase, hormonally induced variations in nutrient intake and food selection could mask the impact of interventions with small effect sizes.

A potential limitation for nutrition studies assessing dietary response variation between the sexes is the difference in reporting intake between men and women [98]. Other potential considerations include diet adherence, food preferences and other lifestyle factors. Future research should continue to elucidate the intricate mechanisms underlying sexual dimorphism in nutrition and health while considering additional biological and psychosocial factors, paving the way for personalized dietary interventions tailored to individual needs.

7. Conclusion

Sexual dimorphism significantly influences nutrient requirements, metabolic processes, and disease susceptibility. Incorporating sex-specific considerations into nutrition research, dietary recommendations, and public health strategies is imperative for greater quality evidence, optimal health outcomes, and advancement toward precision nutrition approaches. Considering the influence of sex as a biological variable in nutrition research ensures the development of precise diet guidelines and treatments that consider the distinct needs of men and women.

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