

# Sex Differences Across the Life Course: A Focus On Unique Nutritional and Health Considerations among Women

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## ABSTRACT

In the United States, women, while having a longer life expectancy than men, experience a differential risk for chronic diseases and have unique nutritional needs based on physiological and hormonal changes across the life span. However, much of what is known about health is based on research conducted in men. Additional complexity in assessing nutritional needs within gender include the variations in genetics, body compositions, hormonal milieus, underlying chronic diseases, and medication usage, with this list expanding as we consider these variables across the life course. It is clear women experience nutrient shortfalls during key periods of their lives, which may differentially impact their health. Consequently, as we move into the era of precision nutrition, understanding these sex- and gender-based differences may help optimize recommendations and interventions chosen to support health and weight management. Recently, a scientific conference was convened with content experts to explore these topics from a life-course perspective at biological, physiological, and behavioral levels. This publication summarizes the presentations and discussions from the workshop and provides an overview of important nutrition and related lifestyle considerations across the life course. The landscape of addressing female-specific nutritional needs continues to grow; now more than ever, it is essential to increase our understanding of the physiological differences between men and women, and determine how these physiological considerations may aid in optimizing nutritional strategies to support certain personal goals related to health, quality of life, sleep, and exercise performance among women. *J Nutr* 2022;152:1597–1610.

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**Keywords:** women's health, life course nutrition, dietary supplements, precision nutrition, female health

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## Introduction

The Dietary Guidelines for Americans were recently updated with a life-course perspective recognizing the unique nutritional needs of individuals and population subgroups at various ages and life stages. Building on the social-ecological model, sex is identified as an individual characteristic that may modify the impacts of wider social and environmental influences on health-related behaviors, such as nutrition, physical activity, sleep, and the risk of chronic disease. Sex is a biological characteristic based on genetics, whereas gender can be described as “the array of socially constructed roles and relationships, personality traits, attitudes, behaviors, values, relative power and influence that society ascribes to the 2 sexes on a differential basis”

(1). To fully understand nutrition and health across the life course, both sex and gender must be taken into account (2). Women are fundamentally different from men physiologically and from a biobehavioral perspective. Therefore, accounting for sex as a biological variable is critical throughout the scientific process, from the development of research questions to the interpretation, validation, and generalizability of findings (3, 4). Systematically studying the differences between men and women can improve our understanding of how and why metabolic processes differ by sex, and thus enable clinicians to target and personalize therapies based on biological sex (3, 4).

While women tend to have a longer life expectancy at birth, differential patterns of health exist such that while living longer,

women generally have poorer health and more chronic disease than men (5). Given that nutrition is directly related to the chronic disease risk, it is critical to understand how this modifiable factor relates to health. The relationship of nutrition and health varies across the life span, with women having unique nutritional needs based on physiological and hormonal changes at various times (e.g., menstruation, pregnancy, lactation, menopause). Recently, a scientific conference was convened with content experts to explore these topics from a life-course perspective at biological, physiological, and behavioral levels. This publication summarizes the presentations and discussions from the workshop and provides an overview of important nutrition and related lifestyle considerations across the life course, considering sex as a biological variable and gender as a social construct.

## Nutritional Needs of Women Across the Life Span

Nutrition is crucially important for women across their life spans and is of particular importance during pregnancy and breastfeeding. The Developmental Origin of Health and Disease theory posits that nutritional and environmental exposures during the first 1000 days (i.e., from conception to 24 months of life), contribute more towards the risk of obesity and cardiometabolic disorders in adulthood than genetics alone (6). Thus, both prenatal and postnatal nutrition, particularly in the context of micronutrients for this review, have immediate and long-term implications for offspring health (7). However, it is challenging to accurately and reliably assess nutritional exposures from foods, beverages, and dietary supplements through self-report dietary assessment methods (8). The use of biomarkers of nutritional status can be equally challenging, given the relative lack of laboratory tests that exist with good sensitivity and specificity for many micronutrients (9). Concentration biomarkers of nutritional status can be influenced by many factors, such as inflammation (e.g., level of C-reactive protein), hydration status, medication use, body weight, and genetic background. Chief among understanding the unique nutritional and health needs across the life course is the diversity within sex and gender in terms of genetics, body composition, physical activity, stress, the gut microbiome,

the hormonal milieu, and life choices (i.e., to procreate, breastfeed, follow specific dietary patterns, exercise, etc.). Thus, the appropriate use of micronutrient testing and application of accurate cutoff points for determining risk based on nutritional biomarkers, especially during pregnancy, is a key issue and is reviewed elsewhere (10).

## Current Dietary Intakes and Biomarkers of Nutritional Status of US Women Across the Life Course

National data suggest that the diets and complementary feeding practices among infants provide the recommended amounts of micronutrients, with the exception of iron, among exclusively human milk-fed infants after 6 months of age. By age 1 year, the micronutrients of concern in young children are similar to those of the adult population (11), with the number of at-risk nutrients increasing across childhood and adolescence. Disparities in risks of micronutrient inadequacy begin to emerge in adolescence (12). Indeed, female adolescents in the United States were identified by the most recent Dietary Guidelines for Americans as a population subgroup at risk for low intakes of a constellation of food components (12), with differential risks for some nutrients and diet quality among adolescent girls living with food insecurity (13).

Pregnancy and lactation are critical windows of the life stages to ensure adequate nutritional status both for the health of the mother and her offspring (Table 1). Much of what is known about maternal dietary intakes comes from national data repositories, like the NHANES and the National Environmental Influences On Child Health Outcomes (ECHO) Consortium. The majority of pregnant and lactating women in the United States use dietary supplements (14–17); however, the prevalence of use varies by maternal age and education, trimester of pregnancy, race and ethnicity, and income. During pregnancy, low risks of dietary inadequacy exist for thiamin, riboflavin, niacin, vitamin B12, phosphorus, and selenium. However, more than 10%–20% of pregnant women are at risk for inadequate intakes of choline, iron, magnesium, calcium, zinc, potassium, folate, and vitamins A, B6, C, D, E, and K. Most pregnant women also exceed recommendations for dietary sodium and, among supplement users, potentially excessive intakes of folic acid and zinc have been observed. In the ECHO consortium, disparities in total usual intakes exist by maternal factors that are associated with supplement use (14).

## Nutrients of Concern in Women Across the Life Course

Iron is the most common nutrient deficiency among young children, adolescents, and reproductive-aged females and during pregnancy, and can manifest with cognitive changes that affect memory and concentration and are linked to mood disorders, low energy levels, and difficulty with thermoregulation. Low iron is commonly paired with low intakes of several other micronutrients, especially B vitamins. While dietary supplement use is associated with a reduced risk of micronutrient inadequacy both from the diet and for biomarkers of nutrition status (18), many reproductive-aged females have a low iron status or iron deficiency (19). Approximately 1 in 10 women aged 12–49 years have iron deficiency, but racial disparities exist, with

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This article is based on information presented and ideas discussed at the Council for Responsible Nutrition ([www.crnusa.org](http://www.crnusa.org)) symposium “Women’s Health and Nutrition,” held in October 2021. The event was organized and supported by the Council for Responsible Nutrition (CRN; [www.crnusa.org](http://www.crnusa.org)), a trade association representing dietary supplement and functional food manufacturers and ingredient suppliers. CRN receives support primarily from its industry membership.

Author disclosures: All speakers received travel support and honorarium to add the participate in the meeting. Unrelated to this submission, RLB has served as a consultant in the past to the NIH Office of Dietary Supplements, Nestlé, the General Mills Bell Institute, RTI International, and Nutrition Impact; is a trustee of the International Food Information Council; is a former board member of International Life Sciences Institute-North America; has received travel support to present her research on dietary supplements from the Council of Responsible Nutrition, American Society of Nutrition, and the New York Academy of Sciences; and is an Editor for *The Journal of Nutrition*. All other authors report no conflicts of interest.

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Abbreviations used: CBT-I, cognitive behavioral therapy for insomnia; ECHO, Environmental Influences On Child Health Outcomes; HRT, hormone replacement therapy; iDIET, instinct diet; L, lutein; MPOD, macular pigment optical density; MVM, multivitamin-multimineral; Z, zeaxanthin; 5-methyl-THF, 5-methyl-tetrahydrofolate.

**TABLE 1** Key micronutrients and their role in women's health across the life course

Micronutrient	Life course relevance
Iron	<ul style="list-style-type: none"> <li>• Exclusively breastfed infants are at risk of inadequate intake when iron stores deplete (around 6 months of age).</li> <li>• Menstruating women have iron losses and may require supplementation to prevent anemia and other deleterious impacts on neurocognition and thermoregulation.</li> <li>• Pregnant women have higher iron requirements to support fetal growth and maternal red cell mass, and therefore may be at increased risk of inadequate iron intake during pregnancy.</li> <li>• Lactating women have lower iron requirements than nonpregnant, nonlactating women</li> </ul>
Vitamin B6	<ul style="list-style-type: none"> <li>• Reproductive-aged women using hormonal contraceptive agents may have higher requirements for vitamin B6</li> </ul>
Magnesium	<ul style="list-style-type: none"> <li>• Magnesium has been associated with reduced negative effects of menstruation among premenopausal women.</li> <li>• Plays a role in glucose metabolism and may be beneficial to those with altered glucose metabolism across the life course.</li> <li>• Women using proton pump inhibitors may have increased needs.</li> <li>• Associations of magnesium with risk of chronic diseases among adult women</li> </ul>
Folate	<ul style="list-style-type: none"> <li>• Folic acid before and during early gestation reduces the risk of neural tube defects.</li> <li>• Folate and folic acid have been associated with both positive and negative health outcomes from observational and animal lines of evidence</li> </ul>
Choline	<ul style="list-style-type: none"> <li>• Critical for optimal brain growth and development during pregnancy and early life.</li> <li>• Associations of low choline and impaired cognitive function and mood across the life course</li> </ul>
Vitamin B12	<ul style="list-style-type: none"> <li>• Related to maternal health (during pregnancy) and risk of neural tube defects.</li> <li>• B12 is limited to animal sources; individuals that limit intake of these food sources (i.e., vegans and vegetarians) may be at increased risk of low B12 status, especially during pregnancy.</li> <li>• Needs may be higher among women with inflammatory bowel disease, those who have undergone bariatric surgery, and those using certain medications.</li> <li>• Older adults may have increased needs if gastric acid secretion is compromised or if they use proton pump inhibitors</li> </ul>
Iodine	<ul style="list-style-type: none"> <li>• Increased requirements to support optimal pregnancy outcomes and for prevention of iodine deficiency disorders among the offspring</li> </ul>
Zinc	<ul style="list-style-type: none"> <li>• Critical for cellular metabolism and immunological function across the life course.</li> <li>• Mild and subclinical zinc deficiencies have been observed in older adults and nursing home residents.</li> <li>• Women using diuretics and angiotensin-converting enzyme inhibitors may have higher requirements</li> </ul>
Vitamin D and calcium	<ul style="list-style-type: none"> <li>• Essential for building peak bone mass in adolescence, and maintaining bone mineral density in adulthood.</li> <li>• Postmenopausal women have high risks of osteoporosis and bone fracture</li> </ul>

deficiency being more common among Mexican-American and non-Hispanic Black females compared to non-Hispanic White females (19). Nevertheless, low iron and anemia can cause long-term neurobehavioral damage that may not be reversible, even with iron treatment. Unfortunately, iron supplementation can prove challenging, given the well-known gastrointestinal side effects.

Many clinicians and consumers are unaware that commonly prescribed medications can influence the micronutrient status. Moreover, nearly 65% of women ages 15–49 years in the United States utilize a form of contraception (e.g., oral contraceptive, implants, intrauterine device), with oral conception reported as the most common, followed by intrauterine devices (20). The use of oral contraceptive agents can alter the absorption of many B vitamins, particularly vitamin B6 (21). Approximately 20% of younger US women (ages 15–29 years) report use of oral contraceptive agents (20), often for years, in addition to other prescription medications (22). Given that oral contraceptive use is associated with lower concentrations of 5-plasma pyridoxal phosphate, the vitamin B6 status should be periodically monitored among those who use oral contraceptives. Thus, even with a healthy baseline diet, medication use must be considered in the context of evaluating the nutritional status of women, as well as the likelihood of fertility.

Magnesium plays a key role in many health issues that pertain to women, such as the prevention of dysmenorrhea, premenstrual syndrome, and menstrual migraine in premenopausal women (23), and may ease climacteric symptoms during menopause (24). The role of magnesium in women's health extends across the life course, and low magnesium in older women has been related to increased incidences of

cardiovascular disease, stroke, and mortality (25, 26). Given the role of magnesium in the glucose metabolism, various lines of evidence suggest that magnesium can be beneficial for improving insulin resistance and slowing the progression of diabetes-related complications (27). Proton pump inhibitors can interfere with passive and active magnesium absorption, and several systematic reviews have confirmed hypomagnesemia among individuals using these medications (28); close to 9% of American adults routinely use these medications (29).

The term folate is used to represent forms of the vitamin that occur naturally in food, while folic acid and 5-methyltetrahydrofolate (5-methyl-THF) are the forms present in fortified foods and many dietary supplements. Folic acid supplementation (but not other forms) in the periconceptional and early gestational time periods has been associated with a reduced risk of the occurrence and reoccurrence of neural tube defects (30, 31). Folic acid clearly has a beneficial role in the prevention of birth defects and may reduce the risk of certain cancers and heart disease, and observational data suggest that increased folate intake is also beneficial for prevention of some cancers and cardiovascular disease; however, high folic acid intake may also increase the risks for colorectal cancers (32, 33) and cognitive impairment (34–36) among certain individuals in the nonreproductive years, and may be associated with autism spectrum disorders (37). The intake of folic acid is associated with unmetabolized folic acid being present in the serum. It is currently unknown whether this poses any harm to human health (38, 39). As of late, researchers are looking more closely at the active form of folate, 5-methyl-THF, as an alternative to folic acid, as it does not result in elevated levels of unmetabolized folic acid and is not affected

by genetic polymorphisms in 5,10-methylenetetrahydrofolate reductase. A growing number of dietary supplements contain 5-methyl-THF; however, less is known about its ability to prevent birth defects or whether it is a safer alternative to folic acid supplementation.

Choline is another essential B vitamin that is critically important during pregnancy and early childhood to support normal brain development (40). Choline is important for neurotransmitter synthesis (e.g., acetylcholine), cell-membrane signaling, and methyl-group metabolism (41). In pregnancy, choline may play a role in protecting the fetus from neural and metabolic insults (42). During gestation and early life there appear to be critical windows when adequate choline is necessary for optimal cognitive development (43). Choline deficiency has been previously associated with poor concentration, memory loss, and mood changes.

Low maternal serum vitamin B12 levels during the first trimester of pregnancy are a risk factor for neural tube defects and poor maternal outcomes (e.g., preeclampsia, macrocytic anemia, neurological impairment). Like choline, vitamin B12 is concentrated in animal sources, so individuals that limit their intake of these foods (i.e., vegans, vegetarians) may be at an increased risk for low B12 status, especially during pregnancy (44). Additional at-risk population subgroups include those with inflammatory bowel disease, those who have undergone bariatric surgery, and those taking certain medications (e.g., metformin, proton pump inhibitors), particularly long-term users. Older adults are also at increased risk for low B12 status, as gastric acid secretion naturally declines with age. Symptoms of B12-deficiency anemia include muscle weakness, numbness or tingling in the hands and feet, a decreased appetite, irritability, fatigue, and trouble walking, all of which can easily be confused with signs of aging. The crystalline form of the vitamin in fortified foods and dietary supplements is much more bioavailable than protein-bound sources, and the National Academy of Medicine recommends that all adults 50 years and older receive the majority of their vitamin B12 intake from these sources (45). Given the high proportion of Americans at risk for clinical or subclinical B12 deficiency, targeted screening of vitamin B12 status should be performed by health and nutrition professionals.

Iodine, another crucial micronutrient, is important for fetal and early childhood brain development (46). Iodine needs increase during pregnancy due to increased maternal demand for thyroid hormones, transfer of iodine to the fetus, and increased renal clearance. To prevent iodine insufficiency, the American Thyroid Association recommends that all women who are pregnant, lactating, or planning to become pregnant supplement their diet with 150  $\mu\text{g}$  of iodine a day (47, 48). Despite its vital role, the use of iodine-containing supplements is very low among pregnant and lactating women (49–51), and urinary iodine concentrations of pregnant women in the United States are below the WHO recommendations for sufficiency (49, 52, 53). Inadequate iodine intake can lead to a spectrum of iodine-deficiency disorders, some of which can result in irreversible harm to the infant (54).

Zinc is an essential mineral involved in multiple aspects of the cellular metabolism and immunological function across the life course (55). While much of the focus has been on severe deficiency in children, mild and subclinical zinc deficiencies have also been observed in older adults and nursing home residents. An observational study of 420 nursing home residents in Boston found that those with normal plasma zinc levels ( $\geq 70 \mu\text{g/dL}$ ) had a lower incidence and duration of pneumonia, lower use

and duration of use of antibiotics, and a reduction of all-cause mortality compared with the group with lower plasma zinc levels ( $< 70 \mu\text{g/dL}$ ) (56). Some prescription medications can decrease zinc levels, including diuretics and angiotensin-converting enzyme inhibitors, both of which are routinely prescribed to older adults for managing hypertension.

Women are disproportionately impacted by osteoporosis, which affects roughly 20% of women over age 50 years, compared to 4.4% of men (57). Vitamin D is essential for bone health, as well as preventing muscle weakness, protecting against falls, and providing immune support (58). Obtaining adequate levels in the diet is difficult, as there are limited food sources of vitamin D. Both vitamin D and calcium are identified as micronutrients of public health concern, given that low intakes are ubiquitous in the United States and are directly related to risks of osteoporosis and bone fracture. As women transition to menopause, there are dramatic increases in chronic disease risks. Most peri- and postmenopausal women are deficient in or have low levels of vitamin D and magnesium. Iron, calcium, folate, riboflavin, vitamin B12, and vitamin K2 are also important during menopause. Thus, across the life course, females have unique nutritional needs that must be met within the context of energy balance in order to promote adequate nutrition and healthy body weights (Table 1).

## Metabolism and Weight

The biological processes in men and women differ considerably, specifically with respect to metabolism and the distribution of adipose tissue in the human body. Men tend to accrue more visceral fat (i.e., fat located intra-abdominally and closer in proximity to organs), leading to the classic android distribution of fat (4), which has previously been highly correlated with an increased cardiovascular risk (4). In contrast, women accrue more fat in the subcutaneous depot (i.e., under the skin) prior to menopause, a feature that affords protection from the negative consequences associated with cardiovascular disease, obesity, and metabolic syndrome (4). Therefore, these sex-specific differences in body composition must be considered when developing successful and sustainable weight-loss strategies. Moreover, to achieve an optimal body weight, the beneficial effects of sex-specific differences and body composition characteristics that differentiate men and women must be harnessed in such a way as to promote “healthy” adiposity (4).

Men and women also differ in their energy requirements across the life course. In prepubescent children, beginning as early as age 3, there are clear differences in energy requirements for girls and boys, with differences in energy expenditure ranging from 50 to 75 kcal per day. These differences continue through prepubescence, where boys and girls differ by approximately 200 kcal in energy expenditure per day by age 9. Similar findings are also observed among adolescents and adults; in adolescents (i.e., 10–18 years), the discrepancy in energy requirements becomes larger, and is amplified to nearly a 1000-kcal difference (59). This large difference ( $\geq 1000$  kcal) in energy needs translates to adulthood as well, where men have at least a 500-kcal higher energy requirement when compared with women (58). A recent study evaluating energy requirements in men and women using energy expenditure measurements via doubly labeled water confirmed that energy requirements are sex specific and differ between men and women across all age groups (60). Even in the resting state, the body needs a certain

amount of energy to maintain the body's cellular activities (i.e., basal metabolism). Data from adults in the United States show that resting energy needs are very different for men and women, with men needing approximately 200–400 more kcals per day across all age groups (61).

Women also face very different physiological challenges when compared with men. Menarche, pregnancy, perimenopause, and postmenopause are critical windows in the female life course, where challenges to weight management are particularly enhanced. In adolescence, 50% of a girl's adult body weight is gained, in an unprecedented rate of growth second only to that in infancy (62, 63). For this reason, adolescence is a critical period for ensuring that weight gain is healthy and optimal. In addition, weight gain among girls closely corresponds with the age of menarche, which has been previously associated with a variety of factors, including mental health, fertility-related conditions, cardiovascular disease, and bone health. Perturbations in the timing of menarche (i.e., early or late onset) has been shown to increase the disease burden for women in these 4 areas (i.e., mental health, fertility, cardiovascular disease, and bone health) (62, 63).

Female sex-steroid hormones and hormone fluctuations throughout the menstrual cycle also significantly affect weight and the body composition among girls and women of reproductive age. The menstrual cycle has critical implications for appetite and energy requirements; sex hormones interact to modulate the energy balance, resulting in higher energy requirements (kcal/d) during the luteal phase as compared to the follicular phase of the menstrual cycle (4, 64). In addition to higher energy requirements (kcal/d), women also experience a higher appetite and more cravings during the luteal phase, suggesting that physiology related to each phase of the menstrual cycle may be worth considering as part of strategies to optimize weight loss in this population (4, 64).

Pregnancy is another life stage in which women experience challenges related to weight management. Optimal gestational weight gain is a critical determinant of both fetal health and pregnancy outcomes, and therefore can have a multigenerational impact on both the mother and the offspring (65, 66). Despite this, only 32% of expectant mothers are within optimal gestational weight gain recommendations; nearly half (48%) of the population is above recommendations (65, 66). Excess weight gain during pregnancy can result in a large-for-gestational-age baby that is predisposed to excessive weight gain, perpetuating a cycle of metabolic resistance and therefore perpetuating obesity (67). Therefore, achieving optimal gestational weight gain is key to the health of the mother and the offspring.

Several weight-loss and dietary interventions have been conducted during pregnancy; however, these interventions have been challenged by low recruitment, poor compliance, high attrition, modest outcome improvements, and a lack of direct physician or provider involvement (68, 69). Therefore, it remains unclear whether lifestyle interventions can reliably reduce gestational weight gain in pregnant women, particularly in those with overweight or obesity. Difficulties in intervening during pregnancy suggest that programs targeted at optimal weight gain during pregnancy need to be initiated pre-pregnancy in women of reproductive age, ideally when they begin planning for parenthood (68, 69).

The final stage in which weight-related issues may arise is during the transition from perimenopause to postmenopause. These menopausal states are marked with physiological changes that affect energy requirements in women. Prior to menopause,

women accrue more fat in the subcutaneous depot, and therefore receive some protection from the negative consequences associated with obesity and metabolic syndrome (4). However, after menopause, fat deposition and accrual shift to favor the visceral depot, which is accompanied by a parallel increase in the metabolic risk, similar to that observed in men (4).

Other lifestyle factors, such as sleep and cravings, influence weight and weight-related challenges among women. Craved foods that are calorie rich and high in energy density can further exacerbate challenges with weight loss. Men and women differentially experience and view food cravings. Women are significantly more likely to be food cravers (28% compared with 13% of men) and report negative feelings or guilt for indulging in cravings, whereas men are less likely to crave foods and report positive feelings associated with the same activity (70). Food energy density is thought to be the strongest predictor of cravings in adults with overweight and obesity, and in an energy-restriction study, 75% of craved foods were chocolate, salty snacks, ice cream, or sweetened bakery products (71). Consuming large quantities of energy-dense foods is not only problematic in terms of nutrient intake, but also with regard to energy balance. Despite our knowledge of lifestyle factors, physiological states, and the challenges that women face, energy balance and weight management are directly influenced by the ratio of energy expenditure to energy intake. Additionally, exercise can improve metabolic health and contribute to successful weight maintenance. However, exercise in general has a small average effect on body fat (72). Studies suggest that getting enough sleep may be just as crucial to losing weight as diet and exercise, given that sleep deprivation is associated with increased body weight and higher levels of ghrelin, the hormone responsible for stimulating hunger (73).

The instinct diet (iDIET) (74) is a behavioral weight-loss program developed based on 20 years of research and focuses on instinct control by targeting hunger, availability, calorie density, familiarity, and variety. To target hunger, the iDIET recommends eating 3 balanced meals and snacks every day. These meals and snacks should be comprised of satiating foods that are moderately high in fiber, protein, and total volume. The iDIET is also designed to keep calories low without sacrificing taste by using portion-appropriate healthy fats and liberally seasoning vegetables and protein. Eating timing and familiarity are also very important when engaging in a weight-loss program; establishing regular eating times, eating healthy and satiating foods when hungry, and substituting nutrient-dense foods for energy-dense foods are suggested ways to introduce familiarity when on the iDIET. Lastly, variety often leads to overconsumption. Rebalancing the variety of foods available (i.e., transitioning towards an increased, healthy variety of foods) can reduce unconscious overeating and improve the development of healthy eating behaviors. The iDIET aims to address these biological drives and instincts and eliminate hunger. To date, the results from the iDIET have been extremely successful and may have broad applicability across the life course for women.

## Nutritional Considerations for Active Women

Important physiological, sex-based considerations include differences in brain, cognitive, and respiratory functions and in bone, musculoskeletal, and neuromuscular processes (75, 76). Substrate utilization, fatigability, muscle recovery and

soreness, and the body composition are additional aspects that differ between men and women, and are related to bone, musculoskeletal, and neuromuscular processes. Recent evidence suggests that men and women may have varied responses to fatigue, with women demonstrating lower fatigability when compared to men. Metabolically, reduced fatigability among women is thought to be associated with greater vasodilation and muscle perfusion, meaning that blood is transported to the muscle and metabolites are excreted at an increased rate. Additionally, women also have a greater proportion of type I muscle fibers in several muscle groups; this mechanism may be associated with reduced fatigability among women during isometric contractions (77). Despite this, women have smaller blood vessels when compared with men and face delayed recovery times, impeded by hormonal fluctuations from the menstrual cycle. Thus, nutritional recommendations and dietary supplements for women should consider physiological differences to maximize performance and recovery.

The potential impacts of the menstrual cycle and menstrual hormones on health, exercise performance, and metabolic demand are also critical to understanding nutritional needs. Additional studies investigating the menstrual cycle in relation to nutrient and energy intakes and energy expenditure are needed; however, it is known that a menstrual cycle is associated with increased energy expenditure, resulting in potential differences in caloric and macronutrient needs, especially in the presence of exercise. While the range for macronutrient needs may vary according to the menstrual cycle, body composition goals, energy demands, and specific phases of the menstrual cycle increase energy demands across all women (78, 79).

In terms of chronic disease, women face increased risks of heart disease and arthritis with aging and of overweight or obesity throughout adulthood, all of which can be directly targeted through dietary modifications. Currently, over 60% of women in the United States are overweight, and nearly one-third of those women are obese. Even among those that are of normal weight, 75% believe they are overweight and 90% overestimate their body size. Taken together, these findings suggest that women consistently have certain personal goals related to leanness and desires to lose weight (80, 81). As a result, women tend to be underfueled due to desires to reduce their body size, which significantly exacerbates metabolic and macronutrient implications. Active women, in particular, are at an even greater risk of underconsuming calories; a recent study reported only 9% of active women met their energy needs (82). Thus, opportunities for education and tailored interventions should be considered as a potential strategy to encourage maintaining caloric needs and maximizing muscle in this population.

Carbohydrate recommendations for active women should be driven by the frequency and longevity of exercise performance. The intensity, duration, and volume of physical activity are all important factors that play a role in carbohydrate needs. Active women tend to underconsume carbohydrates, which in turn can impact aerobic exercise performance and recovery. However, due to a woman's maximized ability to utilize fat for fuel, a moderate-carbohydrate diet is optimal for women, as it increases the opportunity for more effective carbohydrate loading and the utilization of fat for fuel. The amount of carbohydrate intake that is needed from a diet is directly dependent on the frequency and longevity of exercise performance. For women that complete longer durations of exercise ( $\geq 90$  minutes of exercise), sex-specific

recommendations for carbohydrate loading and carbohydrate quality may be warranted.

Active women may also require a higher level of protein intake per day due to increased protein oxidation and differences in their ability to rebuild protein into muscle and recover when compared with men (83). Data suggest that women have a lower ability to uptake and utilize amino acids for protein synthesis, which supports the need for higher baseline protein requirements. More recent evidence suggests that women need a baseline of approximately 1.5–1.6 g per kg of body weight per day of protein (84); nevertheless, additional studies are needed to draw further inferences regarding protein requirements for women, particularly across the menstrual cycle. Essential amino acid supplementation may enhance absorption and amino acid availability and, in turn, aid in protein turnover across the life span for women (85).

Adequate fat intake is essential for maintaining menstrual hormone concentrations, sustaining normal menstrual cycles, and absorbing fat-soluble vitamins (86, 87). Women tend to restrict fat intake due to certain personal goals related to leanness and desires to lose weight; however, restricted fat intake can have critical implications for sex hormones, fat-soluble vitamin absorption, immune functions, and recovery. For active women, diets that do not meet the recommendations for adequate fat intake and do not incorporate high-quality, unprocessed fats (as opposed to processed fats) can negatively impact restoration and recovery of intramyocellular lipid stores after extended exercise performances, and subsequently hinder performance in future exercise bouts (88). Additionally, recent data highlight the potential impact of omega-3 fatty acid supplementation in support of muscle anabolism (and decreased catabolism), and targeting those differences between men and women in terms of skeletal muscle (89, 90).

In addition to the macronutrient composition, the timing of nutrient consumption also influences the metabolism in women. To date, 95% of our nutrient timing recommendations originate from research conducted in men. The timing of nutrient consumption around exercise directly influences performance, recovery, fat oxidation, and energy expenditure (91). Women often exercise in a fasted state, driven by gastrointestinal distress and a desire to “burn fat.” However, evidence indicates that for women specifically, exercising in a fasted state can blunt fat oxidation (92). Alternatively, exercising in a fed state will result in a greater total daily energy expenditure and increased fat oxidation and, indirectly, improve the body composition. A recent analysis suggests that consuming a bolus of protein prior to exercise, as opposed to consuming a bolus of carbohydrate, significantly augments energy expenditure and enhances fat oxidation postexercise for aerobic exercise, high-intensity interval training, and resistance training (93). When this approach is combined with resistance training, it appears that pre-exercise nutrition may be more efficacious for women to see improvements in strength and lean body mass, compared to postexercise nutrition (94).

Due to unique physiological requirements, there are key areas where dietary supplements may be advantageous for active women: in body composition and lean body mass, energy and fatigue, mental health, and physical health and wellness. A primary reason females purchase a dietary supplement is to address feelings of fatigue (95). Key effective ingredients that may help improve energy, delay fatigue, or improve other parameters related to athletic performance include beta-alanine (96), caffeine (91), teacrine (97, 98), and creatine monohydrate (99).

Mental health differences exist between men and women. Women are significantly more susceptible to depression and stress, which can also have physical implications on the body. With increased mental demands and high levels of multitasking among women, intake of specific supplement ingredients aimed at improving focus may be advantageous. A few ingredients that may provide benefits include rhodiola, theanine, and citicoline. Rhodiola may help active women reduce fatigue and may also improve mood as well (100); theanine, often combined with caffeine, has the potential to improve relaxation and attention (101); and citicoline may help to improve memory (102). When evaluating the use of dietary supplements for active women, consideration should be given to the supplement's potential for improving fatigue and targeting memory, attention, and focus (103).

## Optimizing Women's Sleep Health

Sleep is 1 of the 3 pillars of women's health, along with nutrition and physical activity. Sleep health encompasses a cycle of timing, efficiency of sleep while in bed, duration of sleep, regularity, satisfaction with sleep, and alertness during the day (104). The amount of sleep required for optimal health varies based on sex, differences across the life span, and differences among individuals.

Normal sleep patterns differ by sex. Women report a greater need for sleep and longer sleep durations (105). Men and women interpret the meaning of sleep quality differently, with daytime dysfunction and sleep disturbances influencing sleep quality ratings in women, whereas sleep efficiency and sleep duration influence ratings in men (106). Women are more likely to be morning types, experience a shorter circadian period, and experience an earlier circadian phase than men (107). Further sex differences are evident when examining polysomnographic recordings, and there are considerable differences in relation to age; as men age, their slow-wave sleep declines to a greater extent than that of women (108). Further, women have less light sleep and less wakefulness after sleep onset than men as they age.

The prevalence of sleep disorders differs by sex. Sleep apnea is more common in men than in women, with women experiencing protection from obstructive sleep apnea, at least until postmenopause, when their risk for sleep apnea increases (109). Throughout the life span, women are more prone to insomnia than men, which is driven by many interacting factors, including women being more likely to seek help for their insomnia symptoms; increased risks for depression and anxiety and for painful syndromes, where insomnia is comorbid; and differences in physiological risk factors, such as stress reactivity (110). Changes in sex steroids also play a role; sex differences emerge after puberty, and insomnia is more prevalent at certain reproductive stages, such as premenstrually and during menopause. When considering treatment options for insomnia, cognitive behavioral therapy for insomnia (CBT-I) is the gold-standard treatment, and is as effective and acts similarly in men and women (110). When compared to the effectiveness of CBT-I, alternative interventions for insomnia, such as melatonin, light exposure, exercise, and complementary and alternative medicine, did not have superior effects (111). However, there is support for melatonin being effective for treating sleep-onset difficulties and daytime sleepiness (111).

Some women report reductions in sleep quality and increases in sleep disturbances premenstruation and during menstruation (112). The most robust change in physiological sleep across

the menstrual cycle is evident in electroencephalograms, with increased sleep spindles during the luteal phase, potentially due to the presence of progesterone (113). There was also a small, but consistent decline in rapid eye movement sleep in the luteal phase (114). Women who suffer from menstrual-associated disorders, including polycystic ovary syndrome, premenstrual syndrome, and dysmenorrhea, may be more likely to experience sleep problems (112).

Physiological changes occur during the menopausal transition, and are associated with reproductive aging, including declining estrogen levels and increasing follicle-stimulating hormone levels that affect sleep (115). The Study of Women Across the Nation, a longitudinal study that follows women from premenopause through postmenopause, observed that the most common sleep difficulty during menopause is sleep maintenance, which involves having trouble going back to sleep after waking during the night (116). However, not all women experience changes in sleep as they transition into menopause; about 40% of women had a low prevalence of sleep maintenance issues (116). Approximately 15% of women showed an increasing prevalence of sleep maintenance issues across the menopausal transition, whereas the remaining women showed a moderate to high prevalence of sleep problems during premenopause that persisted across the transition.

In addition to hormonal changes, other factors contributing to sleep difficulties in women entering midlife include hot flashes; psychosocial, stress, and socioeconomic factors; depression and anxiety; medical comorbidities; and aging (117). Sleep diaries indicate perimenopausal women with insomnia, on average, wake up more frequently and stay awake longer during the night, along with experiencing more variability in the sleep pattern for nights of wakefulness, compared to women without insomnia (118). Perimenopausal women with insomnia are more likely to experience hot flashes during the night compared to women without insomnia (118–120). Interestingly, variability between women was observed in the extent to which hot flash-associated wakefulness contributed to the total wake time across the night, with some being more disturbed than others.

Just as CBT-I is effective for treating insomnia at other life stages, strong evidence suggests it is also effective for women in the perimenopausal and postmenopausal stages who have insomnia (121–123). These clinical trials support that changing a woman's behaviors and negative thoughts and concerns about their sleep can contribute to long-term improvements in sleep. Because every woman is different, there is a need to treat each woman individually (124). For some women with severe and persistent hot flashes, hormone therapy may be a good approach, following guidance for its use (125). Nonhormonal pharmacological and nonpharmacological options beyond CBT-I (e.g., soy isoflavones), have been shown to be effective for sleep problems in postmenopausal women (126).

## Estrogen and Women's Health

Estrogens are important for the development and maintenance of reproductive and nonreproductive tissues. Loss of estrogens during menopause causes a major change in the systemic metabolism and results in increased central obesity, decreased insulin sensitivity, and increased inflammation that predisposes postmenopausal women to type 2 diabetes, cardiovascular disease, and cancer. Estrogens are the primary regulators of the reproductive system for males (e.g., epididymis and testis) and females (e.g., uterus, ovary, and vagina; development of the

mammary glands). Estrogens are essential for brain function, the immune system, the cardiovascular system, liver health, and bone health in both sexes. At the same time, estrogens have adverse effects; for example, they are drivers of breast cancer and uterine cancer.

Postmenopausal women have increased risks of diabetes, cardiovascular disease, metabolic syndrome, and certain cancers, including estrogen receptor (+) breast cancer. Hormone replacement therapy (HRT) improves the metabolic health of postmenopausal women; however, HRT increases breast and uterine cancer risks. There is still a critical need to find safer alternatives to HRT to improve postmenopausal metabolic syndrome. Botanical estrogens are components that share similar structures with estrogen and are relevant throughout the life cycle. Botanical estrogens have been used to treat urinary tract infections, are used during pregnancy and lactation to improve milk production during lactation, and are used during menopause; they include black cohosh, red clover, and soy (127). Botanical estrogens share a similar chemical structure, which is the main determinant in interactions with estrogen receptors and dictates in which tissues chemical activity will occur (128). Mechanistically, botanical estrogens were shown to activate classical estrogen receptor genomic activity, which is mainly dominant in the reproductive tissue, as well as in nonclassical pathways (127). Botanical estrogens effectively activate those critical pathways (i.e., classical and nonclassical) for many different tissues, and research is exploring whether they mitigate not only symptoms in menopause, but risks of chronic diseases like breast cancer and metabolic syndrome.

Licorice root, wild yam, and epimedium are some of the plants encapsulated in dietary supplements used by postmenopausal women. In animal models, botanical estrogens are very effective in normalizing weight gain associated with an ovariectomy under normal and high-fat diets, particularly with licorice root (129). Botanical estrogens were able to prevent some of the excessive weight gain due to the excess calories from the high-fat diet. More specifically, botanical estrogens reduced the weight of various fat depots without increasing the weight of the uterus, and without increasing the weight or changing the structure of the mammary gland. These findings suggest that botanical estrogens from licorice root do not impose any of the potential risks to the reproductive tissues or the mammary gland (e.g., breast and/or uterine cancer risks). Consistently, no increase in uterine weight was noted with licorice root extracts. This finding is promising in terms of providing alternative approaches that might be useful for alleviating symptoms of postmenopausal women. Botanical estrogens may also modulate the gut microbiota, which metabolizes estrogens (130), and animal models have demonstrated an impact on metabolic outcomes and weight (131, 132).

Weight maintenance is an important component of the risk of chronic disease. Indeed, an adverse weight status can increase the risk of cancer by 50% (133). For a woman with breast cancer, that would decrease responses to therapies independent of the menopausal status. Most premenopausal women undergoing breast cancer report adjuvant chemotherapy weight gain (60%–90%, depending on the study). Obesity increases inflammation, insulin resistance, local estrogen production, and a decrease of adiponectin (134). Women with high BMIs had higher levels of markers that indicate an increased risk for breast cancer and an increased risk for more aggressive forms of breast cancer (135). Synthetic estrogens, known as preferential estrogens, and their pathway are thought to block the effect of

these obese-associated factors, which in turn could reduce the risk of breast cancer (135).

Estrogens also have major effects on the vasculature arteries that bring blood to the heart and the microvasculature. Estrogens initiate pathways that change nitric oxide production, which is essential for vasodilation; thus, dietary botanical estrogens may improve cardiovascular disease risks (136). Women tend to have more prevalent microvascular damage related to estrogen action in the endothelial cells. Botanical estrogens seem to have favorable actions with regard to vascular functions, with no risks to the reproductive tissue (137). Thus, botanical estrogens have the potential to improve cardiometabolic health during the menopause transition, but further work is needed in this area.

## The Influence of Dietary Behavior on Women's Eye and Brain Health

As previously stated, women have a clear survival advantage over men. Even so, women are faced with more morbidities that, while not fatal, lead to disability and diminished quality of life, including connective tissue disorders, diabetes, cataracts, age-related macular degeneration, glaucoma, and cognitive impairment and dementias (138–142). Many of these degenerative diseases are known to be mitigated through dietary interventions, such as increased intake of carotenoids (143–145).

A particularly cogent example is the highly comorbid conditions of age-related macular degeneration and the Alzheimer's form of dementia (138, 139). Both of these conditions are more prevalent in women (about two-thirds of all cases are female) and both are known to be influenced by dietary intake. The pigmented carotenoids lutein (L) and zeaxanthin (Z) concentrate in the macula (and may be reduced in women) and key locations within the brain, and are thought to retard many of the processes that lead to the degradation of these central nervous system tissues.

L and Z are xanthophylls (oxygenated carotenoids) that cross the blood-retina barrier to preferentially accumulate in the central region of the retina, called the macula (hence the term macular pigment). In that location, L and Z are thought to protect the retina through antioxidant and anti-inflammatory mechanisms. L and Z likely serve these functions in the brain as well (113). Because they are blue-absorbing pigments, in the retina they also serve to screen the cones from highly actinic and deleterious visible light (the so-called blue-light hazard). This screening serves to reduce glare disability, discomfort, and photostress, while simultaneously improving the chromatic contrast and visual range (e.g., the ability to see through blue atmospheric haze) (113). These effects on input reflect changes in neural output, such as improved visual processing speeds, problem solving, memory, and executive functions (presumably due to local effects in areas such as the hippocampi and frontal cortex) (146).

Despite similarities in serum and dietary L and Z, adipose levels of L and Z in females are significantly higher than those in males (147, 148), and this may confer a metabolic advantage in terms of storage for reproductive needs. This may also, however, signal concern that less L and Z are available for use in the brain and retina. L and Z levels are significantly lower in the retina [measured as macular pigment optical density (MPOD)] for obese adults, even at the same levels of dietary intake (149).

Higher MPOD has also been associated with overall academic achievement, as well as achievement in mathematics



and language composition, among preadolescent children (ages 8–9 years; using models that controlled for IQ and other related potential confounders) (150). MPOD in adolescence has also been related to efficiency in performing cognitive tasks (151), enhanced executive functioning, and intellectual ability (152). Increasing intakes of L and Z in children would appear warranted, but more research is needed to know how to do this most efficiently. For example, some data suggest that genetic variation (specifically CD36-rs3173798 genotypes) may be important moderators independent of dietary intakes of L and Z (153). In younger adults, supplementation with L and Z clearly increases serum concentrations and MPOD. These increases in turn lead to better outcomes, such as improved neural processing speed and efficiency (154), as well as chromatic contrast and recovery from photostress (155).

There is increasing empirical evidence that L and Z are good for the aging brain. For example, 1 year of a daily supplement with both carotenoids improved memory and resulted in fewer errors in new learning among middle-aged adults (i.e., 45 years) (156). Similarly, when compared with placebo, older adults (i.e., ~74 years) who received supplements containing 12 mg/day of L and Z had higher MPOD, as well as better attention and cognitive flexibility; in men only, supplementation produced overall improvements in composite memory (145). In a cross-sectional analysis of older adults, both plasma concentrations of L and Z and MPOD were associated with better Isaacs Set Test scores, which measure the ability to recall information; Benton Visual Retention Test scores, which measure memory and visual perception; and Free and Cued Selective Reminding Test scores, which predict dementia (157).

Using longitudinal data from the Rush Memory and Aging Project, both overall dietary carotenoids and specifically L and Z were related to lower HRs for incident Alzheimer's dementia. Only higher L and Z levels were related to less plaques and tangles after 7 years of follow-up (158). After 28 years of follow-up, participants with the highest carotenoid intakes in the NHS also had lower odds of cognitive decline (159).

In sum, a confluence of evidence from a variety of sources supports the conclusion that L and Z are particularly good candidates for dietary interventions aimed at issues that disproportionately affect women. This is especially true for individuals with a low baseline carotenoid status or MPOD, as these groups are more likely to be “deficient” (160). Given the higher risk of cognitive decline and dementia among women, the totality of evidence strongly supports the vital role of L and Z for potential preventative strategies (161).

## Sex Differences in Clinical Trials: The Rise of Precision Nutrition

Given all of the differences in nutritional needs and health outcomes across the life course for women, it is imperative that the scientific community thinks more carefully about clinical trials and the role of sex, which has largely not been an *a priori* focus for most large- and small-scale clinical trials. Randomized clinical trials offer the strongest evidence regarding the effects of dietary exposures and dietary supplements, and health outcomes.

Many large-scale, long-term clinical trials testing dietary supplements, such as the Physicians' Health Study I (162) and II (163) and the Women's Health Study (164), have strong internal validity and have provided important scientific contributions. However, the generalizability of these and other trials has often

been limited to men or women individually. Comparing clinical trials done separately in men and women becomes problematic, since it introduces differences in the dietary supplements tested, temporal trends in event rates and prevention strategies, and other characteristics of study populations based on the eligibility criteria. We limit study populations to men or women in observational cohort studies to eliminate confounding by sex. However, in clinical trials, we often focus on sex-specific outcomes for more targeted hypotheses or convenience samples; the purpose is not to eliminate confounding. As a result, we lose the value of subgroup analyses by sex to examine whether the effects of dietary supplements are similar for the same intervention tested in all trial participants.

Published meta-analyses and systematic reviews of clinical trials for different dietary supplements have also insufficiently highlighted differences by sex. Multivitamin-multimineral (MVM) supplements, with their countless combinations and forms, offer a particularly complicated story when considering whether there are sex differences across different trial populations, formulations, and outcomes, making uniform MVM use recommendations almost impossible to formulate. MVMs have been tested in a diverse set of trials and populations. Overall, there may be potentially important sex differences for MVM use and cancer, cardiovascular disease, and cognitive functions across these trials that have not been fully addressed to date. Understanding the sex-specific differences becomes essential in terms of conceptualizing the results for dietary supplements for application to clinical and public health guidelines. It is especially crucial to consider sex-specific differences in nutritional status for the impacts of diet, body weight, and energy balance on dietary supplement use at different phases of life (165).

Hybrid clinical trials are optimally positioned to examine sex-based differences in baseline nutritional status, given the important differences in nutritional needs and patterns between women and men across the life span (166). Precision nutrition approaches use dietary habits and eating patterns, together with information on genetics, circadian rhythms, health status, socioeconomic and psychosocial characteristics, food environments, physical activity, and the microbiome, to identify modifiable factors to improve the nutritional status and health outcomes. In contrast, personalized nutrition or nutrigenomics relies solely upon genomics to identify nonmodifiable factors, building upon previous studies that have identified markers of nearly all essential vitamins and minerals. Genomics tests alone are used to tailor guidance on dietary patterns and dietary supplements (167).

Understanding differences between women and men is a critical component of precision nutrition predicated upon accurate and reliable dietary assessments, objective nutritional biomarkers, and multiomics, consisting of the gut microbiome, metabolomics, proteomics, epigenetics, and genomics, analyzed via machine learning and data science. The future of dietary supplement research is therefore predicated upon well-designed small- and large-scale hybrid clinical trials inclusive of women and men to directly address sex differences through precision nutrition, with comprehensive nutritional and other clinically relevant assessments.

## Discussion

Women differ biologically and physiologically from men, particularly with regard to their body hormonal milieu, adiposity, and energy requirements. The several physiological

life stages that women experience (i.e., adolescence, pregnancy, perimenopause, postmenopause) pose additional challenges in terms of weight regulation and the need for adequate nutrition. Women have unique nutritional needs that are influenced by the menstrual cycle, age and menopause, oral contraceptives, and pregnancy. Notably, women are more likely to take dietary supplements than men (168). In different types of dietary supplements, those same patterns persist; for multivitamins, multimineral, and individual supplement product types, there is a persistent pattern of women being more likely to use dietary supplements than men (169). With aging, people are more likely to use dietary supplements than those who are younger (169). Nevertheless, it is clear women can and do experience shortfalls in their nutrition and critical micronutrients during key periods of their lives, which may differentially impact their risks of not only chronic diseases like cardiovascular disease, stroke, impaired cognitive function, cancer, eye diseases, and poor bone health, but also influence other conditions like sleep, mental health, and overall quality of life. Better tools for assessing nutrient intakes and evaluating biochemical levels are urgently needed to accurately identify micronutrient insufficiencies using precision nutrition approaches. Hybrid clinical trials offer the potential to identify specific mechanisms of effect underlying clinical outcomes, which is critically important as we move into the era of precision nutrition. The landscape of addressing female-specific nutritional needs continues to grow; now more than ever, it is essential to increase our understanding of the physiological differences between men and women, and determine how these physiological considerations may aid in optimizing nutritional strategies to support certain personal goals related to health, quality of life, and exercise performance among women. Moreover, women face increased risks of heart disease and arthritis with aging and of overweight/obesity throughout adulthood, all of which can be directly targeted through dietary modifications.

### Acknowledgments

The authors' responsibilities were as follows – all speakers at the meeting; provided written sections for this document; AE, SHM, AW, HN: developed the content and scientific session, and provided critical feedback; RLB: had primary responsibility for the final content; and all authors: read and approved the final manuscript.

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