Original article

Sex and Gender differences in Nutrition

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Abstract. Proper nutritional intake is essential for human wellbeing. To ensure effective nutrition, it is necessary to follow a healthy diet; in order to provide all nutritional elements adequate to lifespan, it is important to take into account sex, gender and age. Particularly, sex refers to the sum of biological characteristics that determine whether an individual is female, male and/or intersex, gender includes the roles, behaviours, activities, and attributes that a given society, at a given time, considers appropriate for men and women. Climate changes, pollution and global socio-economic disparities can compromise food production, making healthy diet more expensive and less available. There are still large areas of food insecurity, mainly in low and middle-income countries, where women are disadvantaged in term of access to healthy food. The eating habits of women and men are influenced by differences in body composition and energy expenditure, but also by stereotypes and psychological factors. Malnutrition, either for "defect" or for "excess", has different effects in both sexes with important consequences on individual health, but can also damage the offspring with epigenetic mechanism.

Key words: nutrition, food insecurity, oncology, malnutrition, obesity, microbiota, pollution

Socio-economic status and gender gap in nutrition

The second objective of 2030 Agenda for Sustainable Development includes ending hunger, achieving food security, improving nutrition and promoting sustainable agriculture (Sustainable Development Goals, SDG). Socio-economic status has a strong impact on maintaining food security for populations but nowadays there is still a gender gap also in countries with the highest incomes. Food insecurity is more prevalent among adult women more than men all around the world; and the gender gap expanded considerably in 2020 and 2021 due to the COVID-19 pandemic as women were more affected by job and income losses. In 2021 the gender gap affecting women reached 3,8%; falling to 2,3% in 2022 as work and economic activities resumed and falling to 1,3% in 2024 (1). According to ISTAT (Italian National Institute of Statistics), the prevalence of moderate or severe food insecurity in Italy was 1,5% in 2023 (down 0.8% compared to the previous year), with a wide difference between South (2,7%) and the rest of the country (0.8% in the North,

1% in the Centre). No significative difference was found between women and men (2). Healthy diet is based on a wide range of fresh or minimally processed foods, balanced across food groups, while limiting the consumption of highly processed foods and beverages is limited. The most socio-economically disadvantaged population groups, and, women in general, are at greater risk of not following a healthy diet, which is more expensive than a "globalised" diet. Due to the economic crisis enhanced by ongoing war and climate events, FAO (Food and Agricultural Organization), with the support of World Bank Data Group, systematically monitors the Cost and the Accessibility of a Healthy Diet (CoAHD). In 2022, at power parity per person per day, the cost was 3,96 dollars, increased towards 2021 (3,66$) (3). Food protein sources of high biological value, precious micronutrients and fresh vegetables are more expensive than carbohydrates and cereal based products. Mediterranean diet, one of most healthy for people and sustainable for the environment on our planet, is constantly threatened by the exponential increase of the costs of its ingredients.

Eating behaviour, psychological factors and gender stereotypes

Nutritional adequacy consists of the stable achievement of energy and nutrients levels appropriate to gender, age, physiological and pathological conditions through a healthy diet. In addition to biological factors (sex) several other conditions such as environmental, socio economic, cultural and psychological factors also play a role in gender differences (4). Stereotypes about female body image lead women to adopt different eating habits. Although women are aware of the need to manage their own nutrition and that of their families, they tend to take care of their families' nutrition and often, mainly in low-income countries, they eat last, in smaller quantities, and eat poorer quality food (5). Eating behaviour is acquired through a learning process that begins in childhood. This process is the result of complex biological and cultural mechanisms that have developed over centuries and influence people's eating habits in different ways. Woman has always been the main protagonist in conservation, preparation and cooking of food. The "PASSI" surveillance project of Italian Istituto Superiore di Sanità highlights how Italian women pay more attention to diet than man (6). In our country, women eat more fruits, vegetables, legumes and food rich in fibres, but have a clear preference for sweets than men. Men prefer foods rich of fat and proteins and drink more alcohol. This study also show that women are more prone to changing their diet, but less consistent in doing so. On the other hand, men find more difficult to change their diet, but are more constant to follow a new dietary style. Gender differences are also shown in physical activities, sports, works as well as alcohol and tobacco use. The response to both acute and chronic stress, can significantly impact eating behaviour. This impact is highly variable between individuals and it is also influenced by gender. According to epidemiological studies, eating disorders occur worldwide in individuals of all racial and ethnic backgrounds and they are more prevalent in females (7). The pathogenesis of these disorders is extremely complex, but the excessively thin aesthetic model imposed on women by the media is certainly a contributing factor to their onset. Restrictive diets applied to reduce weight, especially in adolescence, lead to food disinhibition, thus increasing the risk of triggering an eating disorder (ED). According to data from the Italian Society for the Study of Eating Disorders (SISDCA) the male-to-female ratio for both anorexia nervosa (AN) and bulimia nervosa (BN) is around 1:10, although some studies show a net increase among males, on the contrary binge eating disorder (BED) presents a more balanced male-to-female ratio (1:2). The prevalence of AN is about 0.4% among adolescents and young women. BN is more widespread, affecting about 1–1.5% of the same population. The prevalence of BED in the general adult population is approximately 1.6% in females (8).

Eating behaviour and the influence of endocrine factors

The taste consists of a complex sensory framework, which includes sensations caused by the excitation of specific taste receptors and also those evoked by the receptors of touch, heat and cold, olfactory (smell), and visual sensations. This complex sensory framework is processed by the brain and integrated with

knowledge, emotion, memory, and is modulated by the endocrine system, sex hormones, and a series of neuromediators that detect the metabolic state of nutrients, thereby determining significant interpersonal and gender differences in food choice and eating behaviour (9). During specific life stages in women complex mechanisms, triggered by the predominant action of progesterone, create interactions with glucose metabolism, reducing insulin sensitivity. This makes women crave sweet foods during their premenstrual period, along with a reduction in endogenous opioid neuromediators and serotonin, leading to decreased mood tone, depression, and increased appetite. During pregnancy, so-called "cravings" are compulsive eating behaviours induced by sensations likely related to specific needs and modulated by hormonal changes and dopamine secretion through neurons expressing D2 dopamine receptors in the nucleus accumbens, which act directly on food cravings. In postmenopausal, the change in the estrogens to androgens ratio and the increase in adrenal hormones affect negatively glucose metabolism and induce a state of insulin resistance, leading to a change in food intake and fat storage. Scientific studies also show a decrease in taste perception with increasing age, regardless of sex (10).

Impact of sex and gender on the physiology of nutrition

Women and men have different energy requirements, due to different body compositions. During physical exercise, women "burn" a mixture in which the fat/glucose ratio is higher. Women tend to lose less fat mass for the same energy deficit, a protective difference, related to the evolution process during which food insecurity was a constant factor. As they are involved in the reproductive process, women benefit from the ability to store energy more efficiently in adipose tissue. The 2024 Reference Intake Levels for Nutrients and Energy (LARN) (11) estimate that women have a 10-15% lower basal energy requirement than men at the same weight, age class, and height. Maximum energy and essential nutrient requirements are reached in males at 18 years. The basal energy requirement and daily energy consumption for a moderate physical activity level (PAL) of 1.6 reach their maximum values of 1670 kcal/day and 2670 kcal/day respectively in an 18-year-old male of 1.70 m height, while in a girl of the same height and PAL level, both the basal requirement (1450 kcal/day) and the energy consumption (2320 kcal/day) are lower. Over the years, these values gradually decrease, and the difference tends to disappear. Energy consumption and body composition are the result of lifestyle and physical activity, which are subject to strong gender stereotypes. It is assumed that women perform less heavy work, engage in less intense physical activity, and participate in competitive sports less frequently than men. The "gender" factor intersects with biological factors, and a gap exists not only between men and women but also between active and sedentary individuals.

Nutritional requirements and recommended intake

LARN (rev. 2024) document (11) reports average requirement, adequate intake, recommended intake and maximum intake. In women, protein consumption is lower than in men because the average weight is lower. The highest protein consumption is found in young males and in women during the third trimester of pregnancy. In the elderly, a higher protein intake of 1.1 g/kg/day is recommended compared to adults (0.9 g/kg of body weight), for the prevention of sarcopenia. In athletes, the requirement can increase up to 1.5-2.0 g/kg/day in cases of extremely intense activity (PAL greater than 2). Gender differences in protein requirements are closely linked to the level of physical activity and muscle mass of the individual, factors that in turn depend on different lifestyles and favour males. Per capita protein intake is an indicator of well-being of the population; proteins are sources of high biological value but they are more expensive than carbohydrates. Omega-3 polyunsaturated fats and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are essential for fetal growth and neurological and visual development of the child. During pregnancy and breastfeeding, an intake of 100-200 mg/day of DHA is recommended, in addition to the essential baseline intake of 200/250 mg of DHA and EPA, in order to ensure the proper development of

the offspring's nervous system. The recommendation for polyunsaturated fat (PUFA) intake refers total energy relative to body weight (25-30% for total lipids, 10% for saturated lipids, 5-10% for PUFA). For dietary fiber, at least 25 g/day is recommended for adults, equivalent to 12.6-16.7 g/1000 kcal, while in children and adolescents, the value is lower, at 8.4 g/1000 kcal. Excess fiber intake, more frequent in female, reduces the absorption of other elements. Higher levels of micronutrients (vitamin C, B6, A, E) and minerals (zinc, manganese, chromium, and fluoride) are recommended for males than for females, while the recommendation for iron intake reaches 18 mg/day in young women. In adults, the calcium requirement is 1000 mg/day for both sexes; in young people aged 11 to 14 years, it rises to 1300 mg/day, remaining at this level only in males up to the age of 18 years, and rising to 1200 mg/day in the elderly. During pregnancy and breastfeeding, the requirements for DHA, iron, iodine, and almost all micronutrients are higher than in adult women. In old age, the absorption and metabolism of many nutrients decrease, so periodic monitoring and supplementation in the diet are necessary.

Sex and gender differences in body composition

Substantial differences in body composition are related to sex, but the "gender" factor also influence the maintenance and modulation of body composition and adipose tissue. Levels of physical activity, work, and sports are important factors for muscle, bone, and fat composition; these factors have socioeconomic implications that significantly disadvantage women. On average, women are smaller and slimmer and therefore have lower energy and protein requirements than men. Women have a greater amount of adipose tissue, present more essential fat, and have a predominantly gluteo-femoral fat distribution. Men, despite having less adipose tissue, tend to accumulate it in the abdominal area, which is particularly active in producing inflammatory and atherogenic factors and is associated with a higher cardiovascular and metabolic risk (12). Postmenopausal women tend to take on an "androgenic" or "apple" shape with an increase in waist circumference and visceral adipose tissue. The amount of brown adipose tissue is physiologically greater in women (neck, shoulders, mediastinum), but interpersonal variables are dictated by genetics, exposure to cold, and the level of physical activity (13). A higher amount of brown fat is correlated with better health status, regardless of overall adiposity. Total body water mass, maximum in childhood, decreases with age and is lower in women than in men. Knowledge the chemical composition of the human body allows the evaluation of changes that occur in the organism in relation to sex, age, and various physiological and pathological conditions, and to accurately determine energy needs and nutritional requirements.

Impact of sex and gender on malnutrition

Malnutrition is the result of an inadequate nutritional state, leading to altered body composition with a negative impact on health, potentially resulting in disease (14).

Global deficit of energy and nutrients or protein-energy malnutrition

Protein-energy malnutrition is a global deficit of energy relative to consumption, due to a lack of all macronutrients, primarily proteins. Worldwide, and notably in low-income countries, the gender gap is evident and works against women and girls (15). Women are more vulnerable to malnutrition than men due to their smaller size, greater need for essential nutrients during pregnancy, breastfeeding, and menstrual cycles. Protein-energy malnutrition also exists in middle-high income countries, among vulnerable populations, such as elderly patients, those with chronic or debilitating diseases, and hospitalized patients, where the risk of malnutrition increases with the length of hospital stay. Elderly women are more affected by protein-energy malnutrition and are more susceptible to the acid load of the diet, compromising lean mass and increasing the risk of sarcopenia. The sex-specific predictors of malnutrition have been explored in "The Irish Longitudinal Study of Ageing dataset" and are for women, cognitive deficits and lack of social support while for

men, previous hospitalization, falls in the last two years, and difficulty climbing stairs (16).

Deficiency malnutrition in oncology

Global energy and nutrients malnutrition in cancer patients has a negative impact on survival and quality of life, moreover it is associated with longer hospital stays, and higher hospital costs. Identifying malnutrition status and planning early interventions to correct it, has a positive impact on quality of life, treatment tolerance, psychological stress and risk of death. A 2021 review reports that 20-70% of cancer patients suffer from malnutrition and identifies malnutrition as a cause of death in 10-20% of cancer patients (17). Unfortunately, many cancer patients are currently not even assessed for malnutrition status using the screening tools recommended by the ESPEN (European Society of Parenteral and Enteral Nutrition) guidelines (18). The Italian PreMiO study - Prevalence of Malnutrition in Oncology, involving about 2000 cancer patients evaluated at diagnosis with the MNA test (Mini Nutritional Assessment), shows that 51% had altered nutritional status, with 9% being frankly malnourished and 42% at risk for malnutrition (19). Clinical studies assessing nutritional status in cancer patients show no significant differences between men and women, while the prevalence of malnutrition seems more associated with the tumour site and disease stage. A major limitation is that many studies do not report the gender of the evaluated subjects, and other studies report conflicting data. Attention to nutritional aspects in oncology is a relatively recent topic, and the assessment of nutritional status is not always an integral part of the diagnostic-therapeutic pathways for all cancers.

Selective micronutrient deficiencies

Selective micronutrient malnutrition constitutes a historical chapter in medicine: pellagra, scurvy, beriberi, rickets were endemic diseases in the last centuries and caused millions of deaths. With improvements in economic and social conditions and food security, the prevalence of these diseases has significantly reduced; however, selective deficiencies of many nutrients continue to exist in our society, especially among women, children, and vulnerable population groups (20). There is a gender difference in the main selective micronutrient deficiencies worldwide, linked to biological differences and higher needs at certain ages and physiological states. The absorption and utilization of micronutrients depend on dietary patterns, and are subject to significant gender disparities. Substances introduced through food or air, such as cigarette smoke, drugs, and environmental pollution, can negatively affect the absorption and metabolism of micronutrients. Both smoking and excessive alcohol consumption (more common in men) are antifolic agents, many pollutants are thyroid-static and harmful to gut flora, and photochemical smog reduces the cutaneous synthesis of vitamin D. We are therefore faced with "new paradoxical deficiencies of today's world," where gender differences are mainly dictated by environmental, socio-economic, and cultural factors.

Mineral and vitamin selective micronutrient deficiencies

According to WHO, the most widespread mineral micronutrient deficiencies are related to iodine, iron, calcium, and zinc. The most common vitamin micronutrient deficiencies include vitamin A, followed by vitamin D, folic acid, and the B complex (21). Increased needs due to menstrual losses, pregnancy, and breastfeeding make adolescents and pregnant women physiologically more vulnerable to global and selective micronutrient malnutrition. According to estimates from the Global Dietary Database on nutrient intake from food, over 5 billion people do not consume enough iodine (68% of the world's population), vitamin E (67%), and calcium (66%). Over 4 billion people do not consume enough iron (65%), riboflavin (55%), folate (54%), and vitamin C (53%) (22). Within the same country and age groups, inadequate intake of iodine, vitamin B12, iron, and selenium is estimated to be higher in women than in men, and higher in men than in women for magnesium, vitamin B6, zinc, vitamin C, vitamin A, thiamine, and niacin. A recent review of the population in the Eastern Mediterranean from a gender perspective indicates that the prevalence of malnutrition in these regions is 19% and concerns

caloric-protein deficiency but also micronutrients, especially iron and vitamin D deficiency in women (15).

Iron is necessary for haematopoiesis in synergy with vitamin C and the B complex. As is well known, the iron present in plants is less bioavailable than that found in animal foods bound to haemoglobin (heme iron). Iron-deficiency anaemia is a prevalent condition among women and girls, linked to menstrual losses after menarche and increased needs during pregnancy and breastfeeding. A large study conducted in four European countries analysed gender differences in iron deficiency anemia, has confirmed that the condition is more prevalent in women of childbearing age and during pregnancy, while in men it is more present after the age of 60 (23).

Iodine is a micronutrient necessary for the synthesis of thyroid hormones. It is introduced through animal foods, mainly of marine origin, and water. Distance from the sea and diets low in animal products, vegan or vegetarian diets rich in vegetables with antithyroid properties (cruciferous vegetables) promote the onset of thyroid diseases, notoriously more prevalent in women: an adult woman has a 20% higher chance of developing thyroid disease. During pregnancy, there is an increased need for iodine. The prophylaxis campaign with iodize salt has been effective in the adult Italian population, eliminating the endemic goitre, but to date pregnancy and breastfeeding are still at risk of iodine deficiency (24).

Selenium is a component of the enzyme glutathione peroxidase, which deiodinates thyroid hormones, and is therefore involved in regulating thyroid activity. It also acts as an antioxidant and works together with vitamin E. Selective selenium deficiency is rare but generally associated with malnutrition, and a diet low in animal products promotes its deficiency. Its deficiency is implicated in the pathogenesis of thyroid disorders prevalent in women (25).

Calcium is essential for bone growth and formation but also for other biological processes, acting synergistically with vitamin D. It is found in water and many foods, particularly concentrated in dairy products. Most adults have an inadequate intake of calcium: according to the American Dietary Guidelines 2020-2025, 30% of men and 60% of women over the age of 19 do not consume the appropriate amount of calcium, due to a reduced intake of dairy products and fortified foods. Calcium has been particularly studied in women concerning the osteoporotic disease more common in females, related to the lower peak of bone mass in young age and especially to the significant reduction of estrogen levels after menopause. In low-income countries, insufficient calcium intake during pregnancy can impact maternal-fetal health, leading to the onset of preeclampsia, preterm birth, and increased maternal mortality (26).

Zinc is a component of several hundred enzymes, found in many foods, mainly of animal origin. A diet high in fiber and phytates reduces zinc absorption. Selective zinc deficiency is rare and difficult to diagnose, occurring in cases of global protein-caloric malnutrition, to which females are more susceptible. Zinc deficiency in mothers can cause fetal malformations and very low birth weight, while in children, it can lead to growth and sexual maturation arrest, and recurrent infections. In adolescent males, zinc deficiency can compromise sexual maturation and development (27).

Magnesium requirements do not vary between the sexes. Magnesium intake is inadequate in 56% of the adult population in the United States, with a higher prevalence among adolescents, women, and the elderly. Studies on a large female population aged between 18 and 79 years show that muscle mass and strength are lower in women with a reduced dietary intake of magnesium (28).

Vitamin A is a fat-soluble micronutrient that, along with its natural derivatives and synthetic analogs, constitutes the group of retinoids. It is found in meats, fish, eggs, liver, and red-orange vegetables. Vitamin A is the most multifunctional vitamin in the human body, involved in various essential physiological processes, from embryogenesis to adulthood, such as vision, immunity, cellular proliferation and differentiation, embryological development, antioxidant functions, intermediate metabolism, and insulin sensitivity. According to the World Health Organization, vitamin A deficiency, along with protein malnutrition, is the most common nutritional disorder worldwide (20). Vitamin A deficiency affects maternal and fetal health and increases the risk of maternal mortality during pregnancy.

Vitamin D, which is fat-soluble, is found in whole dairy products and fish, particularly in the liver

of North Sea fish and in the fatty-tissue of fish like salmon and bluefish, but it is also synthesized in the skin through sunlight exposure. Vitamin D deficiency is currently a global public health issue; over 50% of the elderly population of both sexes in Europe and in USA has a deficiency or insufficiency. Vitamin D levels differ between women and men, with females being more vulnerable to deficiency. Vitamin D plays an important role in growth and bone metabolism, and is able to improve the intestinal absorption of calcium consumed in our diet, approximately of 80% (29,30). In perimenopausal women, vitamin D requirements increase compared to men: visceral adipose tissue sequesters this fat-soluble vitamin, reducing its circulating levels. Some studies show that low levels of vitamin D are found even in postmenopausal women without osteoporosis and/or musculoskeletal disorders (31). Low vitamin D levels contribute to increase parathyroid hormone levels, with excessive bone remodeling leading to bone weakening. The resulting osteopenia/osteoporosis, combined with decreased muscle strength and sarcopenia, increases the risk of falls and fractures. Sex significantly influences vitamin D status, with lower levels observed in women compared to men, play a more important role in determining the severity of cardiovascular risk (32). The main proposed mechanism to explain the relationship between vitamin D deficiency and predisposition to metabolic syndrome and type 2 diabetes consists of increased insulin resistance and pancreatic β-cell dysfunction. Vitamin D supplementation may help to prevent abnormalities in glucose metabolism, but its effect is less pronounced in women. In addition, many studies highlight the effects of vitamin D on the immune system, as a regulator of macrophages and certain T-cell types, as well as its potential role in cancer prevention (33). Moreover, a recent review analyzed the role of sex hormones on vitamin D levels and on intestinal microbiome, suggesting gender differences in the presentation of allergic and immune-mediated diseases (34).

Vitamin B group are water-soluble micronutrients found in many foods of both animal and plant origin (such as legumes, cereals, and leafy greens), and they are affected by cooking and preservation processes. Deficiency occurs due to an imbalance between dietary intake and requirements, especially when the latter are increased. Vitamin B9 (folate) plays a crucial role in pregnancy: requirements increase to prevent neural tube defects like spina bifida. Since these defects occur in the first month after conception, it is important for women to start taking folate before becoming pregnant (35). Vitamin B12 deficiency is also common in women due to drug interactions with gender-specific medications such estrogen-progestin and anti-inflammatories drugs. Restrictive diets, especially vegan diets, are associated with B12 deficiency, more pronounced in women during pregnancy and breastfeeding. Changes in nutritional status can alter nutrient levels in the blood and brain tissue, potentially affecting cognitive functions throughout life.

Vitamin C, water-soluble and highly sensitive to heat, is mainly obtained from fresh vegetables and fruits. Epidemiological studies have shown different distribution patterns of vitamin C levels between women and men, linked to different pharmacokinetics. Therefore, brain distribution and utilization of ascorbic acid may vary by gender; several mechanisms have been proposed to explain these differences, including specific brain hormones, oxidative stress, permeability of the choroid plexus, and the distribution of transport protein. A retrospective study analysed the relationship between plasma vitamin C levels and cognitive functions in a healthy adult group, both men and women, after adjusting for variables like age, prescribed medications, and vitamin C supplementation. The results show a significant difference between plasma vitamin C levels and gender cognitive functions. Older women appear more vulnerable to decreases in plasma vitamin C concentrations, which are associated with impaired brain regulation of this vitamin (36).

Overnutrition or global energy excess malnutrition: overweight and obesity

Common polygenic obesity is a multifactorial disease whose prevalence is increasing exponentially worldwide (37). The prevalence of obesity is higher in women than in men in many countries, and it is also rising in childhood. The gender gap has its roots in numerous and complex etiological factors. Biological factors, genetic risk, and psycho-social-economic factors

interact with each other and differently influence eating behaviour, caloric intake, and nutritional adequacy. Although excess calories consumption remains the primary cause of obesity, there is also the involvement of "obesogenic" foods and molecules—foods that stimulate food intake and increase triglyceride storage in adipocytes and adipogenesis through various mechanisms. These substances can also alter the gut microbiota and intestinal wall permeability. Some authors studied the relationship between women's participation in the labour market and overnutrition, highlighting an inverse relationship between female employment and obesity prevalence in some countries (38). In just over 30 years, the percentage of obese children and adolescents worldwide has more than quadrupled, predominantly among males. Conversely, among adults, women now have the highest prevalence (39). The European Office of the WHO ranked Italy fourth among European countries for the number of obese adults. According to the Italian Obesity Barometer Report 2024 (40), there are almost 6 million obese in Italy, representing 10,3% of the adult population, with slight differences between men (10,8%) and women (9,0%). The "PASSI" surveillance site of the ISS confirms this data and highlights other aspects: higher obesity rates among people with economic difficulties and those with lower education levels (6). Therefore, we can state that adult obesity is a gender-related disease with a significant gap between men and women. Obese women experience reduced fertility due to abnormal secretion of gonadotropins, higher androgen levels, decreased sex hormone-binding globulin, increased peripheral aromatization of androgens into estrogens, and abnormal insulin secretion and response. Women with polycystic ovary syndrome tend to have central obesity, and during menopause, there is a "androgenization" of the female figure with a tendency to accumulate abdominal fat. Gender differences also influence the treatment of obesity. The 2020 International Congress on Obesity highlighted the existence of significant differences in approach and management of obesity care. Women are more likely to follow weight loss programs (average 4.6 vs. 3.1) and to undergo pharmacological or surgical treatments, although 75% tend to regain weight after 6 months, compared to just over half of men.

Malnutrition, epigenetics and fetal-placental unit health

It is well known that a woman's nutrition during pregnancy affects the future health of the newborn. In light of advances in scientific research in epigenetics and molecular biology, the nutritional status before conception has a profound impact on maternal health, fertility, and pregnancy outcomes but also on the health of the newborn. It affects the development and function of the fetal-placental unit and the so-called "fetal programming" (41). Nutrients, bioactive substances of dietary or metabolic origin, exogenous toxic substances, and pollutants are able to modulate gene expression by activating or repressing genes responsible for the regulation of organs and systems, metabolism, adipogenesis, the immune system, and mechanisms of protection against toxins and stress resistance. Gene expression modulation occurs in both male and female gametes, but current literature mainly studies manifestations in the female. Micronutrient deficiency before and during pregnancy can alter the development and function of the fetal-placental unit and organogenesis. Crucial nutrients for the proper completion of these processes and for genetic methylation are methyl donors: vitamin B12, folic acid, vitamin B6, sulphur amino acids, bioactive compounds (choline, phosphatidylcholine, betaine), and metabolic intermediates such as homocysteine.

The impact of gender on factors modulating nutritional effectiveness

"Exposome" is an innovative concept for the study of gender differences in nutrition. It can be defined as the set of environmental factors and pathogenic agents to which each individual is exposed throughout life, starting from conception (42). Different susceptibility and responses to these exposures create gender differences in nutritional status and human health. Therefore, we will analyse two key elements in this innovative chapter: the environmental pollution and the microbiota.

Environmental pollution, nutrition and gender

Endocrine disruptors are a broad, heterogeneous, not fully understood, and increasing group of persistent pollutants of various nature. According to the European Union, they are "substances or mixtures able to alter the endocrine system, causing adverse effects on the health of an organism or its progeny (43)."Endocrine disruptors introduced with food, interfere with the synthesis, secretion, transport, binding, and catabolism of natural hormones in both humans and animals, with significant effects on growth, development, sexual maturation, and reproductive health. Some types of endocrine disruptors, such as Bisphenol A, have an estrogenic effect, but recently, various compounds have shown anti-estrogenic, androgenic, and anti-androgenic actions in various compounds, both in vivo and in vitro. Their toxic action primarily impacts reproductive health, reducing fertility in both women and men, and altering the timing of puberty and menopause (44). Endocrine disruptors can also induce insulin resistance, promote obesity and increase the risk of type 2 diabetes, cardiovascular diseases, and osteoporosis. Many of these substances affect thyroid function by disrupting mechanisms involved in the synthesis, transport, and metabolism of thyroid hormones, interfering with thyroid hormone receptor binding and iodine uptake. The higher prevalence of thyroid diseases in women highlights the greater impact of these substances on the female gender. The dietary intake of various endocrine disruptors widely used in the chemical industry, such as pesticides, heavy metals, micro- and nano-particles poses a risk for developing fatty liver disease, especially in highly urbanized contexts and in combination with other risk factors. The liver also appears to be the primary target of nano- and microplastics, produced through degradation via multiple mechanisms: physical erosion, biodegradation, and photo-oxidation. Micro- and nano-particles can induce damage by activating inflammatory cytokines, oxidative stress, and altering lipid metabolism in the liver, leading to increased apoptosis of liver cells (45). Liver steatosis disease has a high prevalence (30% in the general population) and is caused by excessive accumulation of lipids in hepatocytes, which can present as simple fatty infiltration and metabolic dysfunction (metabolic dysfunction associated steatotic liver disease, MASLD) (46) or with inflammatory damage to hepatocytes, meaning metabolic dysfunction associated with steatohepatitis (metabolic-dysfunction–associated steatohepatitis, MASH). This is a new and more comprehensive definition of non-alcoholic fatty liver disease that includes the association with at least one cardiometabolic risk factor: overweight, obesity, type 2 diabetes, hypertension, and dyslipidemia. A gender difference in susceptibility to metabolic liver steatosis has been documented, with a lower prevalence in females until menopause, after which the gap narrows. In animal models, this condition is induced by high-fat diets; activation of the estrogen receptors α gives in females a limited capacity for metabolic adaptation by reducing lipid accumulation, a response not seen in males.

Microbiota, nutrition and gender

The microbiota is a universe inside our body that affects our health and shows some gender-specific differences linked to biological and gender factors: ethnicity, age, body mass index, and eating behaviour (47). The microbiota works in harmony with its host in a symbiotic relationship, subject to external factors that can modify itself throughout different life stages. Diet significantly influences the colonization of microbiota across all our mucous membranes and tissues. The most beneficial diet for a symbiotic microbiota is a healthy, varied diet rich in nutraceutical value, such as the Mediterranean diet (48). Bacterial Phyla develop and proliferate differently depending on the dietary composition, positively affected by prebiotic fibers and polyunsaturated fatty acids, and negatively affected by excess energy and macronutrients, including proteins. At birth, the female microbiota, develops in parallel with the increase of sex hormones in the newborn, diverging between sexes after puberty (49). In adult women, a group of microorganisms called the "estrobolome" transforms estrogen into its active form, playing an important role in the development of primary and secondary sexual characteristics and

in the onset of reproductive system disorders (50). During pregnancy, microbial diversity modulates inflammatory status and insulin resistance, providing a preventive activity against gestational diabetes. In the last trimester of pregnancy, bacterial strains change, with an increase in Bifidobacteria, Bacteroides, and E. coli, which are crucial for the health of the newborn if the delivery is vaginal. Women play a key and emerging role in the initial exchange of microorganisms with their children, both during intrauterine life via the placenta and during labor through the birth canal. The bacterial colonization of the foetus prepares their immune system to face the outside world. Later, breastfeeding, weaning, and environmental exploration in the first three years complete the development of the adult microbiota. Each individual acquires a personal gut microbiota, a genetic imprint, a digital fingerprint, whose strength lies in its high diversity. The microbiota can produce bioactive substances, vitamins, short-chain fatty acids, and neuromediators directly or indirectly. Its actions are involved in the pathogenesis of many diseases. The literature studying gender differences in this field is currently limited but rapidly developing. A recent study conducted on a cohort of 400 children of both sexes (CHILD Cohort Study) indicates that the different microbiota in boys and girls leads to a faster language development in females. In girls, a higher percentage of Bacteroides was found, one of the key species capable of producing sphingolipids, which are essential for nervous system development. The low diversity of the gut microbiota and the altered Firmicutes/Bacteroides ratio favouring the former, are significant factors in obesity across both genders. Some studies showed the presence of different microbiota profiles in hypertensive men and women, with a prevalence of Firmicutes in women and Bacteroides and Prevotella in men; the levels of neuroendocrine inflammatory mediators produced by the microbiota also differ between sexes. Gender influences the development and diversity of the microbiota through biological differences, dietary habits, lifestyle, and varying adaptation to environmental factors. Further scientific researches that consider gender are necessary to enhance prevention strategies and to develop new targeted therapeutic approaches.

Conclusion

Nutrition is closely linked to sex and gender. Body composition, energy consumption and hormonal factors in addition to eating behaviours and exposure to environmental factors, modulated by socioeconomic status, are the main determinants of sex and gender differences in nutrition. Health policies should focus on research into sex and gender differences in nutrition and on disseminating scientific findings to promote actions that strengthen the culture of healthy eating and women's economic independence, with positive implications for nutritional status and the protection of both current and future health of general population.

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References

1. FAO, IFAD, UNICEF, WFP, WHO. The state of food security and nutrition in the world 2024: Financing to end hunger, food insecurity and malnutrition in all its forms. Rome: FAO; 2024. doi:10.4060/cd1254en
2. ISTAT. Rapporto SDGs 2024 per l'Agenda 2030. Informazioni statistiche Italia. [Internet]. Available from: https://www.istat.it/storage/rapporti-tematici/sdgs/2024/Rapporto-SDGs2024-Ebook.pdf
3. FAO. FAOSTAT: Cost and affordability of a healthy diet (CoAHD). [Internet]. FAO; 2023 May. Available from: www.fao.org/faostat/en/#data/CAHD
4. Cattaneo A, Adukia A, Brown DL, Christiaensen L, et al. Economic and social development along the urban–rural continuum: New opportunities to inform policy. World Dev. 2022;157:105941. doi:10.1016/j.worlddev.2022.105941

5. World Food Program USA. Women are hungrier. [Internet]. Available from: https://www.wfpusa.org/women-are-hungrier-infographic/
6. Sistema di sorveglianza PASSI. Istituto Superiore di Sanità. [Internet]. Available from: https://www.epicentro.iss.it/passi/
7. Attia E, Walsh BT. Eating disorders: A review. JAMA. 2025;333(14):1242–52. doi:10.1001/jama.2025.0132
8. Donini L, Nizzoli U, Bosello O, et al. Manuale per la cura e la prevenzione dei disturbi del comportamento dell'alimentazione e delle obesità (DA&O). Milano: SICS Editore; 2017.
9. Domini LM. Nutrizione e genere. L'Endocrinologo. 2018;19(5):128–31. doi:10.1007/s40619-018-0449-9
10. Barrag R, Coltell O, Portoles O, et al. Bitter, sweet, salty, sour and umami taste perception decreases with age: Sex-specific analysis, modulation by genetic variants and taste-preference associations in 18 to 80 year-old subjects. Nutrients. 2018;10(10):1539. doi:10.3390/nu10101539
11. Società Italiana di Nutrizione Umana (SINU). Livelli di assunzione di riferimento di nutrienti ed energia (LARN) per la popolazione italiana. 5a ed. Milano: Biomedia; 2024.
12. Gómez-García I, Trepiana J, Fernández-Quintela A, et al. Sexual dimorphism in brown adipose tissue activation and white adipose tissue browning. Int J Mol Sci. 2022; 23(15):8250. doi:10.3390/ijms23158250
13. Wibmer AG, Becher T, Eljalby M, et al. Brown adipose tissue is associated with healthier body fat distribution and metabolic benefits independent of regional adiposity. Cell Rep Med. 2021;2(7):100332. doi:10.1016/j.xcrm.2021.100332
14. Cederholm T, Bosaeus I. Malnutrition in adults. N Engl J Med. 2024;391:155–65.
15. Jabbour J, Khalil M, Ronzoni AR, et al. Malnutrition and gender disparities in the Eastern Mediterranean Region: The need for action. Front Nutr. 2023;10:1113662. doi:10.3389/fnut.2023.1113662
16. The University of Dublin. The Irish Longitudinal Study on Ageing (TILDA). [Internet]. Available from: https://tilda.tcd.ie/data/
17. Beirer A. Malnutrition and cancer: Diagnosis and treatment. Memo. 2021;14:168–73. doi:10.1007/s12254-020-00672-3
18. Muscaritoli M, Arends J, Bachmann P, et al. ESPEN practical guidelines: Clinical nutrition in cancer. Clin Nutr. 2021; 40:2898–913.
19. Muscaritoli M, Lucia S, Farcomeni A, et al. Prevalence of malnutrition in patients at first medical oncology visit: The PreMiO study. Oncotarget. 2017;8(45):79884–96. doi:10.18632/oncotarget.20168
20. Allen LH. Micronutrients: Assessment, requirements, deficiencies, and interventions. N Engl J Med. 2025;392: 1006–16.
21. World Health Organization. Micronutrients. [Internet]. Available from: https://www.who.int/health-topics/micronutrients#tab=tab_1
22. Passarelli S, Free CM, Shepon A, et al. Global estimation of dietary micronutrient inadequacies: A modelling analysis. Lancet Glob Health. 2024;12:e1590–9. doi:10.1016/S2214-109X(24)00276-6
23. Levi M, Simonetti M, Marconi E, et al. Gender differences in determinants of iron-deficiency anemia: A population-based study conducted in four European countries. Ann Hematol. 2019;98(7):1573–82.
24. De Angelis S, Medda E, Rotondi D, et al. Fifteen years of iodine prophylaxis in Italy: Results of a nationwide surveillance (period 2015–2019). J Clin Endocrinol Metab. 2024;109(2):e495–e507. doi:10.1210/clinem/dgad593
25. Mojadadi A, Au A, Salah W, et al. Role for selenium in metabolic homeostasis and human reproduction. Nutrients. 2021;13(9):3256.
26. Gomes F, Ashorn P, Askari S, et al. Calcium supplementation for the prevention of hypertensive disorders of pregnancy: Current evidence and programmatic considerations. Ann N Y Acad Sci. 2022;1510(1):52–67.
27. Fallah A, Mohammad-Hasani A, Colagar AH. Zinc is an essential element for male fertility: A review of Zn roles in men's health, germination, sperm quality, and fertilization. J Reprod Infertil. 2018;19(2):69–81.
28. Souza ACR, Vasconcelos AR, Dias DD, et al. Integral role of magnesium in muscle integrity and aging: A comprehensive review. Nutrients. 2023;15(24):5127. doi:10.3390/nu15245127
29. Christakos S, Dhawan P, Verstuyf A, et al. Vitamin D: Metabolism, molecular mechanism of action, and pleiotropic effects. Physiol Rev. 2016;96(1):365–408. doi:10.1152/physrev.00014.2015
30. Amling M. Calcium and vitamin D in bone metabolism: Clinical importance for fracture treatment. Unfallchirurg. 2015;118:995–9.
31. Wierzbicka A, Oczkowicz M. Sex differences in vitamin D metabolism, serum levels and action. Br J Nutr. 2022; 128:2115–30.
32. Renke G, Starling-Soares B, Baesso T, et al. Effects of vitamin D on cardiovascular risk and oxidative stress. Nutrients. 2023;15(3):769. doi:10.3390/nu15030769
33. McDonnell SL, Baggerly CA, French CB, et al. Breast cancer risk markedly lower with serum 25-hydroxyvitamin D concentrations ≥60 vs <20 ng/ml (150 vs 50 nmol/L): Pooled analysis of two randomized trials and a prospective cohort. PLoS One. 2018;13(6):e0199265. doi:10.1371/journal.pone.0199265
34. Murdaca G, Tagliafico L, Page E, et al. Gender differences in the interplay between vitamin D and microbiota in allergic and autoimmune diseases. Biomedicines. 2024;12:1023.
35. Mishra J, Tomar A, Puri M, et al. Trends of folate, vitamin B12, and homocysteine levels in different trimesters of pregnancy and pregnancy outcomes. Am J Hum Biol. 2020;32(5):e23388. doi:10.1002/ajhb.23388

36. Travica N, Ried K, Hudson I, et al. Gender differences in plasma vitamin C concentrations and cognitive function: A pilot cross-sectional study on healthy adults. Curr Dev Nutr. 2020;6:867.
37. NCD Risk Factor Collaboration. Worldwide trends in underweight and obesity from 1990 to 2022: A pooled analysis of 3663 population representative studies with 222 million children, adolescents, and adults. Lancet. 2024;403:1027–50.
38. Costa-Font J, Györi M. The weight of patriarchy? Gender obesity gaps in the Middle East and North Africa (MENA). Soc Sci Med. 2020;266:113353. doi:10.1016/j.socscimed.2020.113353
39. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in underweight and obesity from 1990 to 2022: A pooled analysis of 3663 population representative studies with 222 million children, adolescents, and adults. Lancet. 2024;403:1027–50. [DUPLICATED]
40. Novelli G, Busetto L, Corsaro L, et al. Obesity monitor. Obesità la pandemia del futuro. Milano: IBDO Foundation; 2024. [Internet]. Available from: https://www.creasanita.it/obesity-italian-monitor-2024/
41. Cena H, Conino D, Coss A, et al. Nutrition in pregnancy: Three crucial periods for mothers and newborns. Ital J Gynaecol Obstet. 2018;30(2):27–37.
42. Vineis P, Robinson O, Chadeau-Hyam M, et al. What is new in the exposome? Environ Int. 2020;143:105887. doi:10.1016/j.envint.2020.105887
43. Rahman Kabir E, Rahman MS, Rahman I. A review on endocrine disruptors and their possible impact on human health. Environ Toxicol Pharmacol. 2015;40(1):241–53.
44. Dolce A, Della Torre S. Sex, nutrition, and NAFLD: Relevance of environmental pollution. Nutrients. 2023;15:2335.
45. Yin J, Ju Y, Qian H, et al. Nanoplastics and microplastics may be damaging our livers. Toxics. 2022;10:586.
46. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). Clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol. 2024;81(3):492–542.
47. Tarracchini C, Alessandri G, Fontana F, et al. Genetic strategies for sex-biased persistence of gut microbes across human life. Nat Commun. 2023;14:4220.
48. García-Montero CC, Fraile-Martínez O, Gómez-Lahoz AM, et al. Nutritional components in Western diet versus Mediterranean diet at the gut microbiota–immune system interplay: Implications for health and disease. Nutrients. 2021;13(2):699.
49. Kim YS, Unno T, Kim BY, Park MS. Sex differences in gut microbiota. World J Mens Health. 2020;38:48–60. doi:10.5534/wjmh.190009
50. Baker JM, Al-Nakkash L, Herbst-Kralovetz MM. Estrogen–gut microbiome axis: Physiological and clinical implications. Maturitas. 2017;103:45–53. doi:10.1016/j.maturitas.2017.06.025

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