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Sexual dimorphism in the context of nutrition and health

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Diets and dietary constituents that we consume have a considerable impact on disease risk. Intriguingly these effects may be modulated to some extent by sex. Lack of female representation in nutritional studies as well as a lack of stratification by sex has and continues to limit our understanding of these sex × diet interactions. Here we provide an overview of the current and available literature describing how exposure to certain dietary patterns (Western-style diet, Mediterranean diet, vegetarian/vegan, ketogenic diet) and dietary constituents (dietary fibre, PUFA and plant bioactive) influences disease risk in a sex-specific manner. Interestingly, these sex differences appear to be highly disease-specific. The identification of such sex differences in response to diet stresses the importance of sex stratification in nutritional research.

Sex difference: Cardiometabolic disease: Western diet: Mediterranean diet

A poor diet substantially increases the risk of developing numerous chronic health conditions including CVD, cancer and diabetes. In 2019, dietary risks were responsible for 7·94 million (6·47–9·76) deaths among adults globally[1]. As such, diet remains a considerably important factor in the mitigation of disease burden, particularly metabolic diseases which are notoriously difficult to treat. Females have been largely underrepresented in scientific research to date. This is certainly true from a nutritional research perspective, in which our current understanding remains heavily male skewed. Despite this there is reason to believe that food components and dietary patterns modulate disease risk in a sex-specific manner[2,3]. Indeed, sexual dimorphism exists in many organs and body systems, such as the heart, kidney, adipose tissue, immune system and the central nervous system[4,5,6,7]. From a metabolic perspective it is increasingly apparent that sex differences similarly exist[8,9]. The reasons for such differences have not been entirely elucidated; however, sex hormones, X chromosome dosage and the microbiome have been posited as contributing factors[10,11]. Involvement of sex hormones (to some degree) is highly probable and signifies a potential dynamic element to these sex effects, evolving throughout the ageing process (particularly for women across the menopause transition). Such metabolic differences will have implications from a nutritional perspective and may in part explain discrepancies in effectiveness of some nutritional interventions to date. It is therefore important for nutritional guidance to account for and adapt to these changes in order to enhance implementation. Fortunately, nutritional research is now being increasingly conducted across both sexes (although with still significant work to do) with various research councils and funding bodies making the inclusion of both sexes a mandatory component of experimental design. This will no doubt aid our understanding of these complex interactions, enabling us to make more informed decisions in relation to these issues.

Abbreviations: HFD, high-fat diet; MedDiet, Mediterranean diet.

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In the present review we explore how sex differences modulate physiological responses to various dietary patterns/constituents in the context of health, with a particular emphasis on cardiometabolic diseases. Comprehensively (but not exhaustively) reviewing the current evidence we highlight gaps in knowledge and comment on potential opportunities to further develop this important area of research.

Sex differences in cardiometabolic disorders

Cardiometabolic diseases are a group of common but often preventable conditions which span from obesity and type 2 diabetes right through to CVD. Reviewed extensively by Gerdts and Regitz-Zagrosek[12], cardiometabolic disease appears to be modulated by sex with sex-specific molecular mechanisms beginning to be uncovered. Type 2 diabetes for instance is an interesting example of this, with women exhibiting a stronger obesity-related diabetes risk than men of whom have greater susceptibility at a lower BMI[13]. Interestingly, such sex differences appear to differ from country to country, with cultural, lifestyle and socioeconomic factors presumably responsible[13]. Indeed, diet plays a prominent role in the development of cardiometabolic diseases. Given the emerging evidence implicating sex as a modulator of metabolism, it is probable that physiological responses to diet similarly differ across sex, perhaps contributing in part to the sex differences in cardiometabolic disorders.

Sex differences across dietary patterns

Western-style diet

Although not particularly well-defined, a Western-style dietary pattern generally consists of high intake of refined, energy-dense, nutrient-poor food sources[14].

Evaluation of Western-style diet across sex is relatively extensive in preclinical models compared to other dietary patterns/constituents (Table 1). Overall, this evidence appears to suggest that young male rodents have more negative changes in the body composition profile, as well as a higher susceptibility to diet-induced obesity when exposed to a high-fat diet (HFD)[15,16,17,18,19]. It must however be mentioned that some discrepancies exist and may relate to species and/or diet differences[16,20]. Young female mice appear to have a greater ability to utilise fat in the diet as a source of fuel[17], increase energy expenditure[16] and increase AQP7/Aqp7 glycerol channel abundance (regulation influences glycerol release by adipocytes and reduced function is associated with obesity)[21]. Additionally, a more favourable immune response is observed in young female rodents exposed to an HFD[22,23].

Although a consensus appears to be emerging in young animals, for aged animals the picture is less clear. It appears that the protection from HFD observed in young female mice diminishes with age, with females having greater weight gain and impairment in glucose tolerance compared to males[19,24]. This may in part relate to changes in sex hormones. Indeed, ovariectomy of HFD-fed female mice enhanced adipose tissue inflammation leading to moderate changes in metabolism. However, gonadectomised HFD-fed males had improved metabolic outcomes that were associated with increased CD11c+ adipose tissue macrophages and increased proinflammatory cytokines[25]. It should be noted that many diets utilised to model high-fat/Western-style diets in rodents (as outlined earlier) are refined (i.e. made from individual purified component rather than whole food). As such they lack many components of a complete control 'chow' diet. Indeed, dietary fibre source (e.g. soluble *v.* insoluble) and even amount are often overlooked in these studies, compromising the validity of these experiments. Morrison *et al.* utilised a refined diet with matched fibre source/content in their experimentation of low-fat diet *v.* HFD across both sexes, reporting that the lack of soluble fibre and not fat content primarily drives gut microbiota alterations previously associated with a refined HFD. In contrast to the aforementioned results, they report that male body weight increase is independent of dietary fat. However, when the amount of dietary fibre is comparable in all dietary groups, aged females do still appear to display increased weight gain in response to HFD[26]. This is in line with recent reports that the prebiotic effects of dietary fibres are sex-specific[27], although the mechanisms responsible for such differences remain to be elucidated.

Sex differences in response to other components of the Western-style dietary pattern (e.g. high fructose, high sugar, low fibre) have been less extensively covered, and the results are generally mixed. Greater metabolic abnormalities have been reported in female animals receiving 10 % fructose supplementation[28]. Similarly, a sweet-fat diet (standard laboratory control diet supplemented with sweet cookies, sunflower seeds and lard) resulted in more intense fat accumulation and weight gain in females as a result of suppressed carbohydrate and fat metabolism[29]. Furthermore, female mice maintained on a cafeteria diet had more extensive liver steatosis, higher non-alcoholic fatty liver disease scores and elevated triglyceride (TAG) content compared to males, with no difference in body weight gain or adiposity index observed[30]. High-sucrose consumption in mice led to more extensive dysregulation of the oxylipin profile (oxidation products of PUFA) in the brains of female mice[31]. The mechanistic basis for which remains unclear. Intriguingly, others have reported the complete opposite with males displaying greater weight gain, glucose intolerance and hepatic inflammation on either high-fat, high-sugar or high-fat, high-fructose diets in agreement with the HFD studies outlined earlier[32,33].

Ethical consideration and lack of stratification by sex mean that clinical evaluation of Western-style diets across sex is scarce. However, in one such study conducted in young healthy adults 7-d exposure to a high-fat, high-energy diet did not result in any metabolic outcomes in either males or females[34], indicating that young healthy individuals can tolerate acute exposure

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Table 1. Preclinical evidence for Western-style diet-related sex differences

Western-style diet type	Species	Outcome (sex difference)	Reference
60 % energy from fat for 56 d	3-month-old C57BL/6 mice	*Males:* ↑body fat, ↓energy expenditure, *Females:* ↓diet-induced weight gain	(15)
60 % energy from fat for 10 weeks	Ten-week-old Sprague–Dawley rats and C57BL/6N mice	*Males:* ↑hyperphagia, *Females:* ↑HFD preference, ↑energy expenditure, *Male rats:* ↑brown adipose tissue thermogenesis, *Female rats:* ↓diet-induced weight gain, ↓metabolic complications, *Female mice*: ↑visceral fat	(16)
23 % energy from fat for 5 weeks	13-week-old C57BL/6J mice	*Males:* ↑fat mass, *Females:* ↓diet-induced weight gain, ↑ability to use fat as fuel source	(17)
60 % energy from fat for 11 weeks	4–17-week-old C57BL/6J mice	*Males:* ↑diet-induced weight gain, ↑glucose intolerance, *Females:* ↑anti-inflammatory cytokine profile, ↓diet-induced weight gain	(18)
62 % kJ from fat for 8/11 weeks	6-week-old C57BL/6J mice	*Males:* ↑glucose intolerance, ↑leptin, *Females:* ↑delay in diet-induced weight gain, ↑IGF2	(19)
60 % energy from fat for 4 months	3-months-old 3xTg-AD mice	*Females:* ↑metabolic consequences, ↓spatial learning, glucose intolerance (prediabetes) was correlated with increased hippocampal microgliosis	(20)
50 % energy from fat for 4 weeks	5-week-old Wistar rats	*Females:* ↑production of cytokines (IL-2 and IL-6), ↑T-helper cells	(23)
60 % energy from fat for 12 weeks	5, 8 or 31-week-old C57BL/6J mice	*Juvenile males:* ↑diet-induced weight gain, ↑glucose intolerance, *Young males:* no difference, *Middle-aged females:* ↑diet-induced weight gain, ↑glucose intolerance	(24)
45 % energy from fat for 4 weeks	Young (17 week) and aged (60 week) C57BL/6J mice	No HFD-related change to gut microbiota community, *Aged females:* ↑diet-induced weight gain	(26)
Fructose-water solution at 10 % (w/v) for 11 months	Sprague–Dawley rats (age not reported, 11 months+)	*Females:* ↑diet-induced weight gain, ↑adiposity, ↑hepatic TAG, ↑hyperglycaemia, ↑hyperuricaemia, ↑hyperleptinaemia, ↓INSULIN sensitivity	(28)
Sweet-fat diet for 10 weeks	Ten-week-old C57BL mice	*Males:* ↑lean mass gain, ↑insulin, ↑FGF21, ↑lipid and glucose oxidation, *Females:* ↑adiposity, ↓expression of lipogenesis and glucose metabolism genes	(29)
Cafeteria diet for 14 weeks	21-d-old Swiss mice	*Females:* ↑steatosis, ↑non-alcoholic fatty liver disease score	(30)
High-fat, high-sugar diet for 14 weeks	8-week-old C57BL/6	*Males:* ↑diet-induced weight gain, ↑microgliosis	(32)
Fructose-water solution at 15 or 30 % (w/v) for 9 weeks	3-month-old Swiss mice	*Males:* ↑glucose intolerance, *Females*: ↑passive stress-coping behaviour	(33)

FGF21, fibroblast growth factor 21; HFD, high-fat diet; IGF2, insulin-like growth factor 2.

to a Western-style diet. Consumption of a high-fructose meal however led to increased postprandial hepatic de novo lipogenesis in females only[35], suggesting that women may be more responsive to higher levels of fructose in the diet. It should however be noted that the opposite has also been reported[36] and in line with this, Couchepin *et al.* observed that healthy young female mice were more resistant to fructose overfeeding compared to their male counterparts[37].

Observational studies evaluating sex differences are similarly lacking and can be difficult to discern whether differences relate to biological/metabolic effects or merely food preference/portion size. Indeed, in a cross-sectional multi-ethnic study of middle-aged individuals (45–57 years) it was reported that women have a higher diet quality (as assessed by the HEI-2010)[38]. Diet quality reduced adiposity across both sexes but intriguingly females displayed a stronger association than men[38]. In line with this, Ruiz-Canela *et al.* reported (in a study population of 55–80-year-olds with CVD risk) that significant differences in BMI relating to consumption of a pro-inflammatory diet were restricted to females, although other indices of general and abdominal obesity were consistent across both sexes[39]. Furthermore, in a Japanese cohort, increased SFA intake was associated with increased all-cause mortality in females only[40]. Similarly, UK Biobank analysis (of 40–69 years) suggested that higher sugar, SFA and dietary fibre intake may subtly modulate all-cause mortality and/or dementia risk to a greater extent in females[41]. In contrast to the aforementioned studies, a cross-sectional study of a Taiwanese population with dyslipidaemia described that greater consumption of a Western-dietary pattern (highest quartile) increased general obesity, central obesity and high body fat regardless of sex[42].

It has been posited that these sex difference may relate to changes in the microbiota. Indeed, in human subjects, a Western-style diet (high-fat/low-fibre) reportedly leads

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to an altered microbial profile across males and females, with higher levels *of Campylobacter*, *Blautia*, *Flavonifractor* and *Erysipelatoclostridium* in females[43]. However, a functional understanding of these changes requires further elucidation. HFD feeding in rats induces sex-related alterations in gut microbiome composition and metabolome[43,44,45] which correlate to metabolic measures such as insulin resistance[45]. Kim *et al.* suggest that the microbial impact may be mediated via the pregnane X receptor (a xenobiotic-sensing nuclear receptor) which reportedly primes the gut microbiome towards an obesity-prone microbial configuration in a sex (male) specific manner[46] (Table 2).

Mediterranean diet

A Mediterranean diet (MedDiet) pattern appears to be highly beneficial, with adherence associated with a reduction in all-cause mortality. The MedDiet consists of a proportionally higher intake of unprocessed cereals, legumes, olive oil, fruits, nuts and vegetables, along with moderate consumption of fish, dairy and meat products[47].

In contrast to Western diet, preclinical studies investigating MedDiet across sexes are limited. This predominantly relates to the fact that preclinical studies tend to focus on aspects/constituents of the MedDiet rather than MedDiet in its entirety. Some of these constituents such as dietary fibres, lipids (e.g. MUFA and PUFA) and plant bioactives will be discussed in later sections.

Human evidence evaluating MedDiet across sexes is surprisingly limited with many studies failing to provide stratification of results/analysis by sex, despite inclusion of both sexes in the experiment. This is quite a significant issue, presumably relating to a lack of power that needs to be resolved imminently. From the available evidence, studies in younger (24–53 years, premenopausal) adults suggest that the MedDiet confers more favourable changes in glucose/insulin homoeostasis in men than in women[48,49]. In line with this, improvements in TAG levels, HDL-cholesterol ratios and waist circumference are more pronounced in men than in women[50]. Furthermore, MedDiet adherence leads to a significant decrease in adiponectin concentration in men only[51], as well as a more favourable redistribution of LDL subclasses from smaller to larger LDL[52]. This appears to be independent of circulating NEFA concentrations (believed to be an important factor in insulin resistance). Similar results were reported after 3-year MedDiet adherence in older (~66 years) overweight/obese individuals with metabolic syndrome, in which a reduction in weight, waist circumference, fasting glucose, insulin and TAG were more pronounced in men than in women[53]. This appears to be consistent with CVD, in which an association between MedDiet adherence appears to be stronger[54,55], although no difference has also been reported[56]. In contrast to this, 1-year Mediterranean-like diet intervention in elderly healthy subjects led to female-specific (but also country-specific) reduction in epigenetic ageing score[57]. Also, from a neurological disease perspective, women appear to have more favourable outcomes in response to MedDiet adherence. Indeed, an inverse association between MedDiet and dementia risk was established among women, but not among men[58]. Similarly, in a cross-sectional analysis adherence to both MedDiet and Mediterranean-dietary approaches to stop hypertension intervention for neurodegenerative delay diet was significantly associated with a higher age of Parkinson's disease onset[59], especially in women. However, for colorectal cancer no disease-modifying effect was observed as a result of MedDiet[60]. This was also true for all cancer risk, which despite displaying an inverse association in females only, failed to reach significance after full adjustment of confounding factors[60,61] (Table 3).

Vegetarian/vegan diets

Food constituents derived from animal sources are limited/absent from vegetarian/vegan diets. Despite an abundance of studies investigating such diets in the context of metabolism and disease, sub-analysis by sex is consistently missing. As such, the existence of any sex differences in response to vegetarian diet is not entirely clear. Blood sampling of healthy age-matched vegetarians and non-vegetarians revealed a purportedly beneficial increase in adiponectin levels in female vegetarians, which was not present in males[63]. However, no diet-dependent or sex-dependent differences were found in insulin, Homeostatic model assessment for insulin resistance index (HOMA2-IRI), inflammatory and metabolic biomarkers[63]. Reviewed extensively by Adams and Sabaté, there is evidence to suggest that the cardio-protective effects of a vegetarian diet may be sex-specific[64]. The available evidence suggests that a vegetarian dietary pattern is associated with a reduction in CVD outcomes for vegetarian men relative to omnivorous men, whilst for women this association is less strong/non-existent[64]. In line with this a 4-year longitudinal study reported that low intake of vegetables was significantly associated with type 2 diabetes risk in men, but not in women. Although this may relate to the lack of study power (fewer women in the low-intake category), it could also relate to differences in vegetable preference[34]. Conversely, Kim *et al.* did not find any association between plant-based diet and CVD, nor any apparent sex differences within a US population[65]. They did however report that those with a high plant-based diet index (i.e. above median) had a 5 % lower risk in all-cause mortality in the overall study population which was not influenced by sex[65]. Together there is some evidence to support vegetarian diet-related sex differences, particularly in the context of CVD however further investigation is clearly warranted to gain a greater understanding metabolically and for other diseases.

Ketogenic diet

Ketogenic diets are low in carbohydrate content and high in fat, shifting energy reliance from glucose to ketone bodies. Twenty-five day ketogenic diet adherence in individuals with severe obesity resulted in significantly larger excess body weight loss and a greater reduction in γ-glutamyl transferase in males[66]. This greater benefit in males has been reported by others[67,68]. Interestingly,

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Table 2. Human evidence for Western-style diet-related sex differences

Intervention/measure	Population group	*N*	Study type	Outcome (sex difference)	Reference
7 d of a high-fat (65 % energy) high-energy (+50 % kJ) diet	Young healthy (mean age: male 24, female 25)	21 (11 male, 10 female)	Randomised-controlled trial	No difference	(34)
Acute fructose feeding	Healthy adults (mean age: male 42·8, female 46·6)	16 (8 male, 8 female)	Randomised-cross-over study	*Females:* ↑hepatic de novo lipogenesis	(35)
Acute fructose feeding	Healthy adults (mean age: male 25·1, female 23·8)	18 (9 male, 9 female)	Clinical study	*Males:* ↑VLDL TAG, ↑hepatic de novo lipogenesis, ↓lipid oxidation	(36)
Isoenergetic diet supplemented with 3·5 g fructose for 6 d	Healthy adults (mean age: male 22·5, female 22·9)	16 (8 male, 8 female)	Randomised-controlled trial	*Males:* ↑TAG, ↑endogenous glucose production, ↑alanine aminotransferase, ↑fasting insulin concentrations	(37)
Association of diet quality with body fat distribution	Good general health (60–72 years)	1861	Prospective cohort	*Females:* ↑HEI-2010 score, ↑association between diet quality and adiposity	(38)
Dietary inflammatory index and anthropometric measures of obesity	No previous CVD but at risk of CVD (men aged 55–80 years and women aged 60–80 years)	7236	Cross-sectional study	*Females:* ↑association between dietary inflammatory index and BMI	(38,39)
Association between fat intake and mortality	Individuals without cancer, stroke or CHD	12 953 men and 15 403 women	Prospective cohort	*Males:* ↓all-cause mortality with higher PUFA, ↓all-cause mortality with higher total fat, *Females:* ↑all-cause mortality with higher SFA	(40)
Association of energy and macronutrient intake with all-cause mortality, CVD and dementia	(55·5 years for women and 56·5 years for men)	120 963	Prospective cohort	*Males:* ↑risk of death with increased sugar intake, ↓CVD risk with both moderate energy intake and moderate/high protein intake, *Females:* ↑risk of death with increased carbohydrate intake, ↑risk of death with moderate total fat intake, ↓dementia risk with moderate sugar intake, ↓dementia risk with highest fibre intake, ↑dementia risk with increased SFA	(41)
Association of dietary patterns and metabolic parameters	20–50 years with dyslipidaemia	14 087	Cross-sectional study	No difference in Western diet	(42)

this difference does not appear to be present when considering post-menopausal females[66], again emphasising the importance of the menopause (and likely sex hormones) in metabolism and response to diet. In rats maintained on a high-fat, high-sugar-diet, the beneficial effects of ketogenic diet intervention were largely similar across both sexes although these benefits correlated significantly with plasma β-hydroxybutyrate in females only[69]. In the context of pancreatic cancer, strict ketogenic diet in combination with gemcitabine (chemotherapy medication) prolonged survival. Intrudingly, when stratified by sex this result remained significant for males only[70].

Sex differences across other dietary constituents

Dietary fibre

Often overlooked as a key contributor in health and disease, dietary fibre is the undigestible part of the plant, typically obtained from wholegrain cereals, fruits and vegetables. European and US guidelines suggest an intake of 30–35 g daily for men and 25–32 g daily for women (discrepancy between males and females relates to fact that many countries calculate recommendation based upon for total energy intake) but actual dietary fibre intake is significantly lower[71]. In adolescents, increasing dietary fibre to recommendation levels decreased predicted fasting glucose, fasting insulin, Homeostatic model assessment for insulin resistance (HOMA-IR), Systolic blood pressure (Hg SBP), and diastolic blood pressure (Hg DBP) regardless of sex[72]. In line with this a cross-sectional analysis found that higher daily dietary fibre consumption was associated with beneficial effects on cholesterol in both males and females[73]. Analysis of the European prospective investigation into cancer and nutrition cohort revealed that total dietary fibre was inversely associated with colorectal cancer (Hazard Ratio per 10 g daily

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Table 3. Human evidence for Mediterranean style diet-related sex differences

Intervention/measure	Population group	*N*	Study type	Outcome (sex difference)	Reference
4-week MedDiet adherence	Adult (24–53 years) with slightly elevated LDL-C concentrations (3·4–4·9 mmol/l) or total cholesterol:HDL-C ratio ≥5·0	70 (38 men and 32 women)	Clinical trial	*Males*: ↑medium LDL, ↓sdLDL ↓sdLDL cholesterol ↓insulin sensitivity, ↓plasma insulin, ↓adiponectin, ↓ApoA-2, ↓insulin concentrations 2 h after the oral glucose administration, *Females:* ↓medium LDL, ↑sdLDL	(48,49,51,52)
12-week MedDiet nutritional programme	Adults (25–50 years)	123 (64 men and 59 women)	Clinical trial	*Males:* ↓waist circumference, ↓total-cholesterol, ↓HDL-C ratio, ↓TAG, ↓TAG to HDL-C ratio	(50)
3-year MedDiet intervention	Adult overweight or obese and/or metabolic syndrome (65·6(SEM 4·6) years)	105 (54·3 % women)	Prospective cohort	*Males:* ↓body weight, ↓glycaemic and cardiovascular parameters, sex differences in endocannabinoids	(49,53)
Adherence to the Mediterranean and early vascular ageing	Adults without CVD (35–75 years)	501 subjects 50 % female	Cross-sectional	*Males:* ↓early vascular ageing probability	(50,54)
MedDiet and CVD	Jewish adults, aged 35+	520 men and 639 women	Cross-sectional	*Males:* ↓Myocardial infarction, ↓coronary bypass, ↓angioplasty, ↓CVD for each Mediterranean diet (MD) score increase	(55)
1-year Mediterranean-like diet	Adults aged 65–79 years free of major overt chronic diseases	120 randomly selected subjects (60 from the Italian cohort and 60 from the Polish one)	Subset pilot analysis of randomised-controlled trial	*Polish females:* ↑epigenetic rejuvenation	(57)
MedDiet and risk of dementia and Alzheimer's disease	Adults (30–70 years)	25 015	Prospective cohort	*Females:* ↓AD risk	(58)
MIND and MedDiet associated with later onset of PD	Control and PD	225 participants with PD (age of onset within the last 12 years) and 156 controls	Cross sectional	*Females:* ↑age of onset correlated most strongly with MIND diet adherence	(59,62)
MedDiet and overall cancer incidence	55–69 years	120 852	Prospective cohort	No sex difference	(61)
MedDiet and colorectal cancer incidence	55–69 years	120 852	Prospective cohort	No sex Difference	(60)

ApoA-2, apolipoprotein A2; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; MedDiet, Mediterranean diet; MIND, Mediterranean-dietary approaches to stop hypertension intervention for neurodegenerative delay; PD, Parkinson's disease; sdLDL, small-dense LDL.

increase in fibre 0·87, 95 % CI: 0·79, 0·96) which did not differ by sex[74]. Similarly, an inverse relationship between dietary fibre and multiple sclerosis has been reported in a case control study with the trends similar across males and females[75]. In the context of depression, dietary fibre may be more favourable in females with an inverse association between depression and dietary fibre consumption established in females only[76]. Discrepancies in the impact of dietary fibres across sex may relate to changes in the gut microbiota, indeed oligofructose supplementation in mice led to broad changes in faecal community structure (increasing *Bacteroidetes* at the expense of *Lachnospiraceae*) in females but not males. How dietary fibre type (e.g. soluble or insoluble) influences metabolism and health outcomes across sex is yet to be explored and represents a major gap in our current knowledge.

PUFA

As alluded to in the Western-diet section of this review, lipid metabolism appears to be sexually dimorphic. Indeed, vast differences in lipid species have been identified across sex, particularly when considering age × sex

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interaction, with the most prevalent of these differences found across phosphatidylcholine, sphingomyelin and TAG species[77]. It is therefore not surprising that specific dietary lipid types e.g. PUFA exert different effects across the sexes. Females have significantly higher peripheral DHA than males[78]. In rats this higher DHA concentrations is found in the liver, plasma, erythrocytes and heart (53, 75, 36 and 25 % higher, respectively, compared with males) but not the brain[79]. This may be linked to higher Δ6-desaturase expression in females relative to males, which appears to be limited to the liver[79]. Women show a greater increase in circulating EPA in response to α-linolenic acid consumption[80]. Similarly, EPA and DHA supplementation increases plasma TAG EPA to a greater extent in females[81]. The source of PUFA (e.g. krill oil *v.* fish oil) may also alter these sex differences adding further complexity to the interaction[82].

Sex × diet interactions may influence brain PUFA concentrations[83]. Higher *n*-3 PUFA concentrations appear to benefit different cognitive domains in a sex-specific manner[84]. In mice receiving DHA supplementation, a reduction in anxiety and depressive-like behaviours was observed in male mice only and coincided with sex-specific gut microbiota interactions in response to DHA which correlated with behavioural finding[85]. This in contrasts with a report in human subjects which showed *n*-3 fatty acid intake to be negatively associated with depressive symptoms in only women[86]. From a diabetes perspective *n*-3 PUFA status was inversely associated with diabetes in overweight/obese females but not in males[87]. This is supported by a systematic review and meta-analysis of randomised controlled trials which found that *n*-3 PUFA intervention improved insulin resistance in women but not in men[88]. Furthermore, PUFA appear to be more protective against hypertriglyceridaemia in females, compared to males[89]. Interestingly, the ability of *n*-3 PUFA to reduce platelet aggregation (a factor in CVD) is sex-specific. In men, only EPA treatment reduces aggregation, whilst in women, only DHA treatment reduced platelet aggregation[90]. Both increased *n*-3 and *n*-6 PUFA intake were found to be inversely associated with non-alcoholic fatty liver disease risk, irrespective of sex[91]. There is growing evidence suggesting that oxylipin (bioactive oxidation products of PUFA) production and profile is differentially altered across sexes in response to the intake of various *n*-3 and *n*-6 PUFA[92,93,94,95], although this seems to be less extensive in the brain[96]. As mediators of PUFA, such differences in the oxylipin profile may provide in part some explanation for the varying disease-modifying influences observed across sexes.

Plant bioactives

Sex has been suggested to modulate both the metabolism[97] and physiological effects of plant bioactives such as (poly)phenols[98]. HPLC-MS/MS analysis of acute doses of grape seed (poly)phenols established clear sex differences in the metabolism and distribution of flavanols throughout the bodies of rats, with quantitative differences found in the plasma and brain[99]. In line with this supplementation with an oral formulation of resveratrol, JOTROL™ in 3xTg-AD mice resulted in Alzheimers disease (AD)-related gene expression changes (*Adam10*, *Bace1*, *Bdnf*, *Psen1*) some of which were brain region-dependent and sex-specific[100]. Analysis of the Primary prevention of cardiovascular disease with a mediterranean diet (PREDIMED) study revealed that catechins, proanthocyanidins, hydroxybenzoic acids and lignans were inversely associated with type 2 diabetes, with women displaying stronger inverse associations. Additionally, a cross-sectional analysis of a Korean population reported an inverse association between flavonoid intake and obesity in women, whilst for men a positive association was determined for some subclasses (namely, flavonols, flavanones and anthocyanidins)[101]. In a randomised double-blind parallel trial, a combination of 548 mg daily of polyphenols and 2 g daily of L-citrulline reduced ambulatory systolic blood pressure in women, but not in men[102]. Furthermore, a systematic review and meta-analysis described an inverse association between (poly)phenol consumption and gastric cancer. Interestingly, the risk reduction was greater for females, which the authors suggest may be partly explained by the fact that (poly)phenols can regulate female hormones which play a protective role against cancer[103]. These differences may relate to impact on the gut microbiota which may be modulated in a sex-specific manner, indeed microbial changes associated with 7,8-dihydroxyflavone predicted body weight changes in females but not in males[104]. In contrast to the female-specific improvements outlined earlier, the Reasons for geographic and racial differences in stroke (REGARDS) prospective cohort study reported that the inverse association between flavanone intake and ischaemic stroke risk did not differ by sex[105]. Additionally, in mouse models of CVD both blackberry and gallic acid supplementation reduced atherosclerosis in males only[106]. Consistent with this, nettle extract altered lipid metabolism differently across sexes, with the activation of transcription factors that control lipid metabolism, and subsequent increase in HDL-cholesterol, specific to male mice[107].

Conclusions

Despite considerable underreporting, it is apparent from emerging literature that sex differences exist in response to various dietary patterns and components. These differences are not trivial as they likely contribute to sexual dimorphism that similarly exists in the patterns of health and disease. Such discrepancies (and heterogeneity between males and females) may even explain why some promising nutritional interventions fail to show benefits at more advanced stages of experimentation. These interactions are complex and display both disease and region specificity. As such, future nutritional studies should aim to consistently provide comparison across both sexes, either in initial experiment set up or via extended subgroup analysis. This could potentially improve the effectiveness

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of dietary advice and treatments enabling us to adapt to specific needs of both men and women as we strive towards a more personal/precise nutritional approach.

Conflict of Interest

None.

Authorship

M. G. P., D. V. and M. M. jointly planned, wrote and edited the manuscript.

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