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Patient Experience, Gender, Age, Race, and Social Determinants of Health

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Women are disproportionately affected by disorders of gut–brain interaction (DGBI), including esophageal, gastroduodenal, bowel, and anorectal conditions, and frequently experience overlapping pain syndromes. This review synthesizes clinical and preclinical evidence on sex- and gender-related differences in DGBI, highlighting alterations in central pain processing, autonomic regulation, stress, microbiota composition, epithelial permeability, motility, genetic and epigenetic factors, and immune responses that may underlie observed disparities. Emerging data indicate that gonadal hormones, interacting with environmental stressors across the lifespan, modulate symptom severity and disease course. Social determinants of health, inadequate patient-provider communication, and disorder-associated stigma further exacerbate inequities in diagnosis and care. Research remains limited by lack of standardized definitions of sex and gender, under-representation of men and gender minorities, and insufficient consideration of hormonal changes and exogenous hormone exposure. Addressing these gaps is essential to advance our understanding of DGBI and guide gender-informed diagnostic and therapeutic strategies for DGBI management.

Keywords: Stigma; Gonadal Hormones; Lifespan; Sex.

Gender norms, race, age, social inequality, and discrimination profoundly influence health, shaping patients' experiences and clinical outcomes. Sex refers to the biological characteristics based on reproductive organs and chromosomal differences. Gender encompasses socially constructed roles, behaviors, and attributes deemed appropriate for men and women. Gender identity reflects personal perception, independent of biological makeup or sexual orientation, with many evolving terms. Differentiating between sex and gender is a simplification since biology, psychology, and environmental factors are intertwined. The term "sex/gender" is emerging to highlight the difficulty separating these influences.

Gender, Epidemiology, and Health Care Use

The Rome Foundation Global Epidemiology Study (RFGES) offers the most comprehensive data on global disorders of gut–brain interaction (DGBI) prevalence.[1] It included internet surveys in 33 countries and household interviews in 9 countries, and yielded data from 73,000 adults. Among the 54,000+ internet survey participants, gender representation was balanced (49.5% women), although gender was reported with only "male" or "female" as response options. Population-based pooled prevalence was higher in women across all DGBI categories, including esophageal, gastroduodenal, bowel, biliary, and anorectal DGBI. This difference was mainly driven by higher rates of dyspepsia, irritable bowel syndrome (IBS), and constipation in women. Other DGBI more common in women included functional dysphagia, chronic nausea vomiting syndrome, rumination syndrome, bloating/distention, functional biliary pain, levator ani syndrome, and proctalgia fugax. Cyclic vomiting syndrome and fecal incontinence affected both sexes equally, whereas men more often

Abbreviations used in this paper: **5-HT, 5-hydroxytryptamine or serotonin; ACTH, adrenocorticotropic hormone; ANS, autonomic nervous system; AP, abdominal pain; AP-DGBI, abdominal pain–related disorders of gut–brain interaction; BAs, bile acids; CC, chronic constipation; CPP, chronic pelvic pain; CRF, corticotropin-releasing factor; DGBI, disorders of gut–brain interaction; EC, enterochromaffin cell; ELA, early life adversity; ELS, early life stress; FD, functional dyspepsia; FDr, functional diarrhea; FM, fibromyalgia; FMT, fecal microbiota transplantation; GI, gastrointestinal; GR, glucocorticoid receptor; HCP, health care provider; HPA, hypothalamo-pituitary-adrenal; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome–constipation; IBS-D, irritable bowel syndrome–diarrhea; IL, interleukin; mRNA, messenger RNA; NE, norepinephrine; PI-IBS, postinfection–irritable bowel syndrome; POTS, postural orthostatic tachycardia syndrome; PTSD, post-traumatic stress disorder; QoL, quality of life; RFGES, Rome Foundation Global Epidemiology Study; SERT, serotonin reuptake transporter gene; SGM, sex and gender minority; TJ, tight junction; ZO, zonulin.**

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reported cannabinoid hyperemesis syndrome and functional diarrhea (FDr). A systematic review of 348 studies found that female sex is a risk factor for development of abdominal pain–DGBI (AP-DGBI) for both children and adults.[2]

The RFGES study of 5931 US, United Kingdom, and Canadian participants evaluated health care use by self-report.[3] A multivariate analysis identified risk factors for healthcare seeking among IBS patients, which included increasing age, insurance or free public healthcare, and bloating. Gender was not a predictor for being an IBS consulter. However, in comparing IBS patients with and without a doctor diagnosis of IBS, being a woman and reporting greater severity of pain were predictors of healthcare seeking.[4] Notably, the decision to access medical and mental health care is complex and influenced by a variety of lifestyle factors (eg, dietary patterns, education, smoking) and economic considerations (eg, insurance coverage).[5]

Life Stages, Transitions, and Aging

Children and adolescents with DGBI. Limited cross-sectional data suggest that gender differences in DGBI exist during childhood and adolescence. Most studies show a higher prevalence of DGBI in girls. In a study on recurrent AP, girls were more likely than boys to report persistent symptoms between early childhood and 12 years but not between 12 and 16 years.[6] Although the data are mixed, constipation is more common in girls. Girls, irrespective of pubertal status, have a higher percentage of hard stools than boys.

Notably, the transition from pediatric to adult care may be challenging. Adolescents often face disruptions in care coordination, communication, and access to specialized services. Both genders benefit from support in developing age-appropriate self-management skills, education, and mental health resources. Girls may also need additional attention related to menstrual health.

Menarche and menstrual cycle. Menstruation is a developmental landmark for girls. For many women, cyclical changes in symptoms occur throughout the menstrual cycle (ie, bloating and hard stools during midluteal phase and looser stool form and increased abdominal pain at premenses and/or menses; Figure 1). Although menstrual cycle–related gastrointestinal (GI) symptoms are common among women without GI disease, women with DGBI frequently experience amplified menstrual-related GI symptoms.

Whether the development of DGBI is linked with the start of menses-related AP symptoms is not known. The prevalence of IBS is higher in those with premenstrual syndrome, primary dysmenorrhea and those with both premenstrual syndrome and primary dysmenorrhea as compared with a healthy control group. A recent study using RFGES data found that menses-related symptoms are more pronounced in adult women with IBS and functional dyspepsia (FD) as compared with those with other DGBI. Women with IBS and FD also reported that their GI symptoms worsened at menses and many reported dyspareunia.[7]

Pregnancy. Overall, approximately 70%–95% of women report heartburn, nausea, or vomiting and constipation during pregnancy. High levels of estrogen and progesterone are linked to decreased GI motility and subsequent delayed gastric emptying and prolonged colonic transit time.[8] There is no evidence that women with a DGBI experience greater GI symptom distress with pregnancy than women without DGBI.

Perimenopause and menopause. During the perimenopause and menopause transition there are wide fluctuations in follicle-stimulating hormone and estrogen levels. How these fluctuations relate to the presentation of DGBI is unknown. The severity of DGBI symptoms may increase during the perimenopause transition for some women.[9] Whether this is due to the decrease in estrogen and/or use of menopause hormone therapy is not known.

Aging. Aging is associated with low-grade inflammation, as well as structural changes including loss of neurons from the enteric nervous system and tunica muscularis, and a decrease in the interstitial cells of Cajal, leading to a decrease in GI motility.[10,11] Only a minority of DGBI studies include individuals older than 65 years of age. Findings are often difficult to compare due to inconsistent definitions of older adults across studies.

Importantly, symptoms in older adults can be atypical or masked by comorbidities and polypharmacy, prompting the need for more diagnostic testing. Age older than 50 is a strong predictor of significant endoscopic findings in dyspepsia patients and malignancy is more frequent in patients older than 65 years of age. Treatment is complicated by side effects, cognitive decline, and limited access to virtual therapies. The inclusion of older adults in DGBI research is essential for development of accurate diagnostic criteria, effective treatments, and age-appropriate care strategies.

Both the incidence and prevalence of IBS decrease with age such that it is rarely diagnosed for the first time after age 65. Although IBS symptoms are comparable across age groups, diagnosis in older adults is more complex due to comorbidities, organic GI disorders, and polypharmacy.[12] Younger IBS-constipation (IBS-C) patients report more AP and distention than older adults, although bloating is the most bothersome symptom across all ages, postprandial bloating is more common in older adults. Presence of comorbidities in patients with IBS is associated with increased anxiety, interestingly, more so in younger than older adults.[13]

Chronic constipation (CC) increases with age due to decreased mobility, polypharmacy, cognitive decline, and reduced colon transit time. Preventing complications of CC is a major health and quality of life (QoL) issue and a metric of the quality of nursing home care. FDr prevalence decreases with age whereas fecal incontinence increases due to decrease in the anal sphincter tone and other factors.

Pathophysiology

Altered Central Processing and Modulation

The relationship between brain structure and function with gender is complex and dynamic throughout life. Systematic sex differences in brain structure exist already

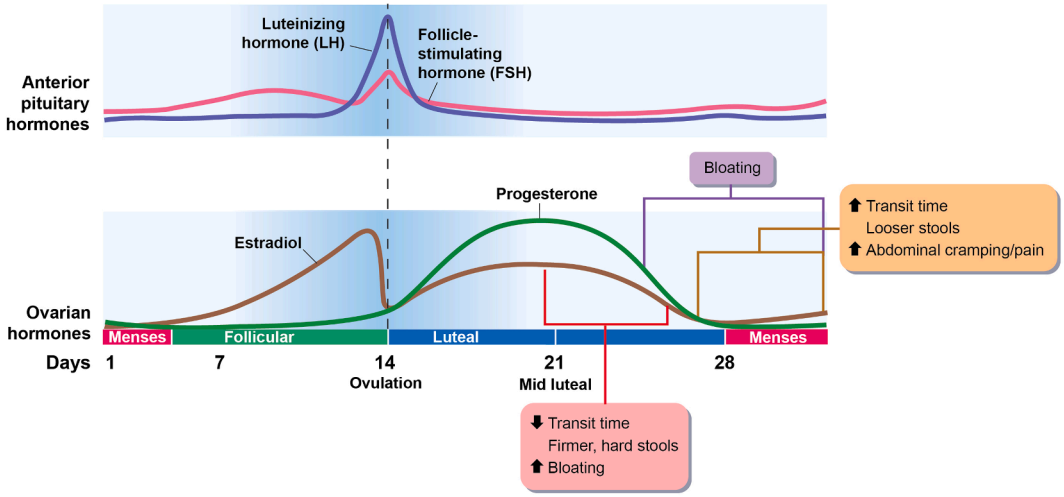

Figure 1. Normal variation in GI symptoms corresponding to hormonal shifts during the menstrual cycle. Cyclical changes in GI symptoms occur throughout the menstrual cycle in healthy women and correspond to hormonal shifts delineating the different cycle phases. While menstrual cycle–related GI symptoms are common among women without GI disease, women with DGBI frequently experience amplified menstrual-related GI symptoms.

during childhood, with a subsequent increase in these differences during adolescence.[14] However, data suggest no strict gender dichotomy in neurologic processing. Instead, there appears to be a continuum with the relative proportion of men, women, and unisex attributes varying substantially across individuals.[15] Brain structure and function are shaped by a complex interplay of chromosomes, hormones, gene expression, and environmental factors. These influences contribute to some gender-related differences in brain function, including clinically relevant variations in pain processing. For instance, women appear more susceptible than men to developing central sensitization (an increased responsiveness of nociceptors in central nervous system to either normal or subthreshold afferent input).[16]

Most literature related to DGBI and gender is derived from studies of patients with IBS. Gender-specific differences in IBS have mostly been reported in sensory-motor regions and in the salience network, which is responsible for the detection of behaviorally relevant stimuli as well as the response to experience or expectation of any interoceptive, ie, from within, and exteroceptive, ie, from outside, stimulus threatening bodily homeostasis. The salience network also coordinates the appropriate attentional, behavioral, affective, and autonomic nervous system responses to such stimuli.[17]

Men with IBS compared with women with IBS have increased positive connectivity of the dorsal anterior insula with the medial prefrontal cortex, whereas women have greater negative connectivity of the anterior insula to medial prefrontal cortex.[18] A study reported increased white matter density in women with IBS as compared with men with IBS, including tracts projecting to the thalamus, insular, and frontal cortical regions. Women also showed more microstructural alterations in sensorimotor, corticothalamic, and basal ganglia circuits involved in pain processing and integration of sensorimotor information. These findings support the hypothesis that symptoms in women with IBS may be driven by greater central sensitivity for multiple sensory stimuli.[19,20] Binary brain comparisons of men and women with DGBI should, however, be approached with caution. Notably, sample sizes in older neuroimaging studies are not only small but often lack equal gender representation. A recent study involving 182 participants examined the effects of neighborhood disadvantage (poverty, crime, unemployment, etc) on brain morphology and found gender-specific brain alterations in patients with IBS: prominent somatosensory alterations in women and cognitive control alterations in men, compared with healthy controls.[21] A visual summary of sex steroid hormones' influence in the central and peripheral pathways involved in the pathophysiology of DGBI is shown in Figure 2. The main sex and gender differences in the central and peripheral pathways involved in the pathophysiology of DGBI (both clinical and preclinical evidence) are shown in Figure 3.

Altered Visceral and Somatic Pain Perception

Clinical. In laboratory settings both visceral and somatic stimuli are used to test for pain outcomes. In healthy controls, there are no gender differences in visceral sensitivity to rectal or colonic distention, but men had larger volumes of rectal distention and compliance compared with women. Somatic pain perception does vary between men and women, indicating that gender differences in pain perception exist beyond the GI system. Gonadal hormones, gender socialization, and psychological factors such as anxiety may contribute to these differences.

Among DGBI patients, gender differences in visceral and somatic pain have been predominantly studied in FD and IBS patients. Women with FD report more discomfort at lower gastric volumes of nutrient drink and have slower gastric accommodation.[22] Men with FD have lower levels of

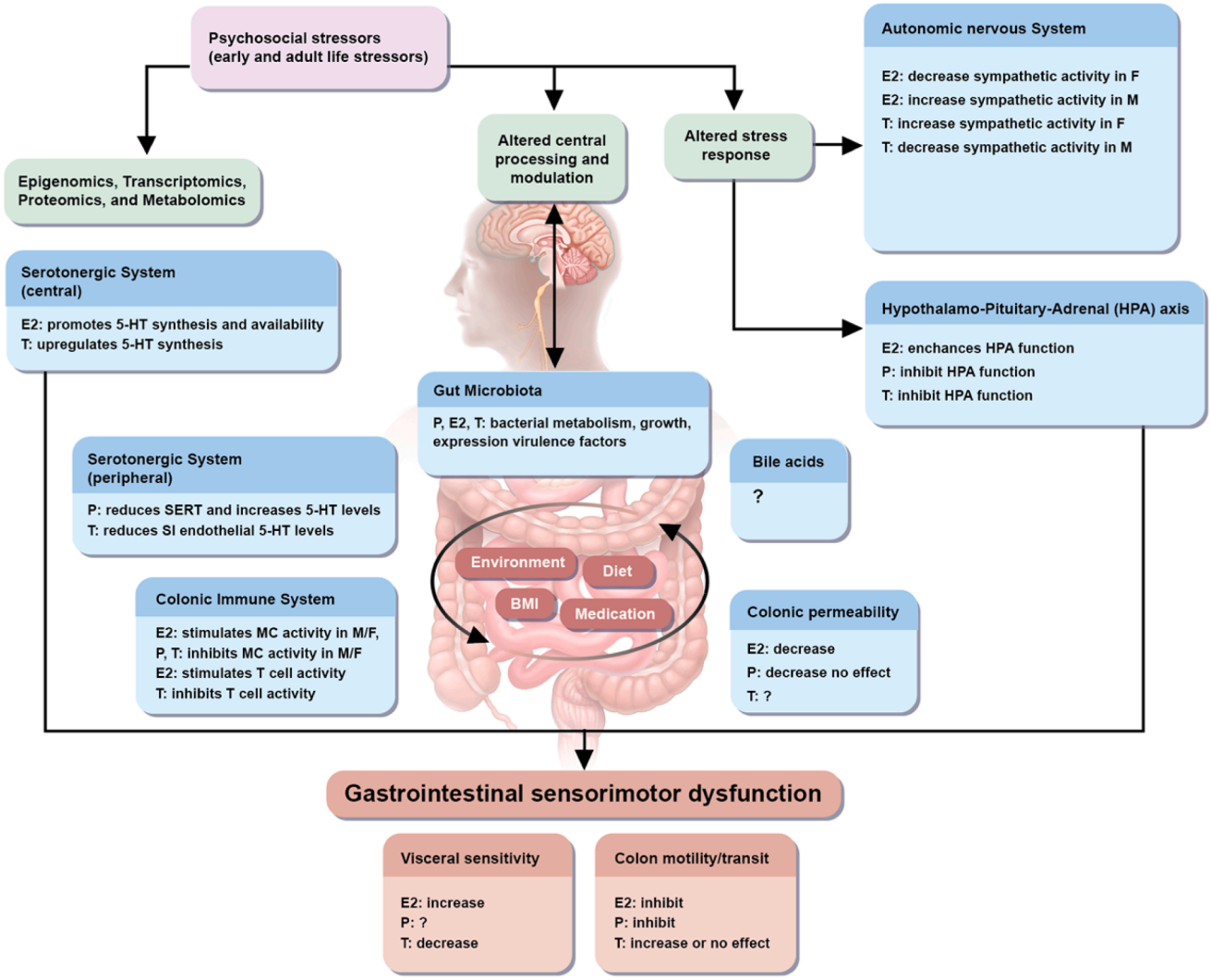

Figure 2. Influence of sex hormones in the central and peripheral pathways involved in the pathophysiology of DGBI. The ovarian (E2 and P) and testicular (T) sex hormones have a differential influence on the diverse central and peripheral pathways of the gut–brain axis, which contribute to the pathophysiology of DGBI. BMI, body mass index; E2, estradiol; F, female; M, male; MC, mast cell; P, progesterone; SI, small intestine; T, testosterone. Modified from So et al.[31]

neuropeptide ghrelin compared with healthy control men,[23] and decreased ghrelin levels delay gastric emptying and increase postprandial fullness. When compared with men, women—especially those meeting criteria for FD—are more likely to report meal-related discomfort or pain.[24]

The sensory response to rectal barostat distention in patients with IBS is mixed. In a meta-analysis of rectal barostat-related perception studies, no overall statistically significant gender differences were found.[25] However, 1 study found that in response to the rectosigmoid double-balloon stimulation, women (both healthy controls and women with IBS) had greater visceral sensitivity of the rectum compared with men with highest sensitivity seen in women with IBS.[26] In an older study, visceral sensitivity and symptoms were greater at menses as compared with other cycle phases.[27] Knowledge about visceral hypersensitivity in various hormonal states, eg, oophorectomy, pregnancy, and menopause, is limited.

Preclinical. Most IBS preclinical models align with clinical data in showing that colorectal distention increases the visceral pain response to greater degree in normal cycling females compared with males,[28] with some studies indicating no variation in sex response or males being more sensitive. Factors such as the stimulus testing protocol could contribute to these discrepancies.

Experimental stress models have been developed to determine how stress affects visceral sensitivity. The few studies performed in female rodents indicate that sex hormones significantly affect visceral sensitivity.[29] Stress, especially early life stress (ELS), which mimics early life adversity (ELA) in humans, produces stress-induced visceral hyperalgesia days or even months after the stress period, with female rodents being more susceptible[30] but not consistently. Both the stress paradigm used and the strain of animal determine which sex is more affected by the ELS. The reasons underlying sex-dependent differences in responses to ELS are currently unknown. Estradiol mediates the stress-induced exacerbation of the visceral pain responses to an adulthood stress in rodent ELS models.[30]

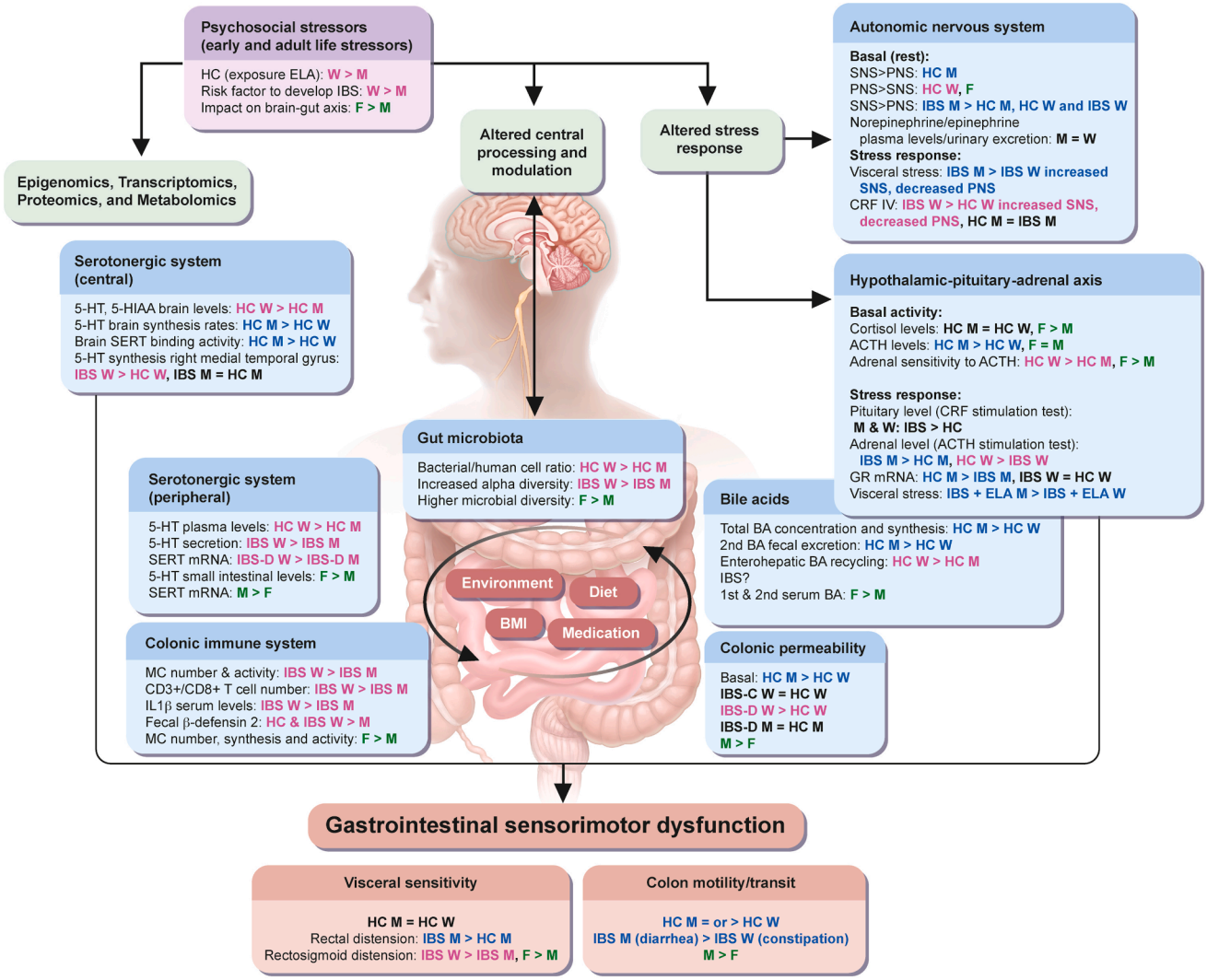

Figure 3. Clinical and preclinical evidence of sex/gender differences in the central and peripheral pathways involved in the pathophysiology of DGBI. Gender/sex differences are present in central and peripheral pathways leading to the GI sensorimotor dysfunction. Sex-related differences in mechanisms are written in color. Differences within HC and IBS men and in between men and women (HCs or IBS) where men predominate are in blue. Differences within HC and IBS women and in between men and women (HC or IBS), where women predominate are in pink, and sex differences in preclinical studies are in green. Lack of differences is noted as bold black text. 5-HIAA, 5-hydroxyindoleacetic acid; BMI, body mass index; EALs, early life adversities; HC, healthy control; IV, intravenous; PNS, parasympathetic nervous system; SNS, sympathetic nervous system; W, women. Modified from So et al.[31]

Cyclical hormonal variations related to the estrous cycle stage influence visceral pain, but the results are inconsistent. Hormonal status does affect the response to colorectal distension, basal conditions, or after stress. These effects may be mediated by central and peripheral estrogen receptors, or there may be an antinociceptive influence of estradiol via vagus nerve activation.[31]

Gastrointestinal Transit and Motility Disturbances

Clinical. In healthy individuals, esophageal anatomy and innervation do not appear to differ by gender. However, some studies have suggested that women have higher lower esophageal sphincter pressures compared with men.[32] Data regarding gender differences in gastric emptying appears to be more consistent. Women have slower gastric emptying rates than men as well as diminished proximal fundic accommodation relative to men. In contrast, small bowel transit appears to be similar among healthy men and women. Colonic transit times are similar between healthy males and females in some studies, and faster in males in others.[33–37] Anorectal function in healthy individuals varies significantly by gender. Anorectal motility studies show higher resting anal and squeeze pressures and higher rectoanal pressure differentials in

men relative to women.[38] Therefore, anorectal manometry normative values are gender specific.

Overall, data on gender differences in motility in DGBI are limited. Studies in FD patients show inconsistent differences in gastric emptying by gender. In CC, resting anal and squeeze pressures tend to be higher, rectoanal pressure differential is mostly lower, and balloon expulsion time more likely to be prolonged in women as compared with men.[39]

Preclinical. Mice data suggest faster gastric emptying and small intestinal transit in females vs males.[40] Whether this is due to the direct action of gonadal hormones is suggested by the fact that both estrogen and progesterone receptors are expressed by colonic smooth muscle.[41] Additionally, exogenous progesterone decreases the contractility of circular muscle strips and reduces fecal output in murine diarrheal models.[42]

Sex differences exist in rats' central regulation of colorectal motility in response to pain, with males but not females showing enhanced motility.[43] Stress significantly decreases upper GI motility and increases lower GI motility in females vs male rodents. This is likely mediated by the corticotropin-releasing factor (CRF) 1 receptor, potentiated by estrogen and expressed by colonic myenteric neurons. Sex differences are also present in baseline colonic secretion and responses to stress-related peptides, with a peripheral injection of CRF-related peptides in mice inducing sex-different responses in secretion with males being more responsive via CRF2 receptor.[44]

One of the most comprehensive studies of sex hormones in GI transit in DGBI found that both men and women with IBS had lower levels of free testosterone compared with healthy controls, with free testosterone levels inversely correlated with IBS symptom severity.[45] Performing an orchiectomy on male mice led to 40% slower GI transit that was restored with exogenous androgen supplementation. A large subset of enteric neurons became androgen-responsive upon puberty and that androgen signaling was required for normal colonic motility in adult male mice.

Gastrointestinal Permeability

Clinical. Both lower[46] and higher[47] small intestinal and colonic permeability were found in adult healthy control women vs men. Most studies, however, have small sample sizes, which affects the ability to detect sex differences. In a large cohort of healthy control children younger than 2 years of age, boys presented with increased small intestinal permeability compared with girls.[48] There is a trend for women to have lower epithelial permeability than men throughout the gut. In eumenorrheic healthy women, intestinal permeability is unaffected by the menstrual cycle phase.[49] Oral contraceptive pill use and the menopause transition, which are characterized by lower endogenous estradiol levels, lead to a higher intestinal permeability, suggesting that estradiol levels are inversely related to permeability. Progesterone is reported to decrease gut permeability by tightening the epithelial barrier function, although there is no data regarding testosterone. Acute stress increases macromolecular jejunal epithelial permeability and is accompanied by a significant decrease in jejunal tight junction (TJ) protein expression in healthy women but not men.[8]

There is more convincing evidence of gender differences in permeability in patients with DGBI. Overall, patients with IBS have higher gut epithelial permeability than healthy controls, which can be correlated with symptoms, more so in IBS-diarrhea (IBS-D) than IBS-C. In a cohort of postinfection-IBS (PI-IBS) patients, men had higher small intestinal permeability than women.[50] In 1 study, IBS women exhibited a trend for higher expression of the TJ protein zonulin-1 (ZO-1) messenger RNA (mRNA) in colonic biopsies vs IBS men, providing 1 mechanism for the lower colonic permeability in women with IBS.[51] When women with IBS-D were compared with healthy controls, ZO-1 mRNA expression was decreased in colonic biopsies of IBS-D women vs healthy controls women suggesting that IBS subtype in women is important. Also, there were no differences in ZO-1 mRNA expression between IBS-D and healthy men.[46] A recent report confirms an increased permeability in IBS patients compared with healthy controls, independent of sex, with women having increased permeability compared with men independently of the disease state.[49] Men with FD exhibit higher levels of claudin-2 mRNA expression in gastric biopsies compared with healthy controls men, suggesting higher gastric epithelial permeability, whereas women are unaffected.[52]

In children (7–12 years old, premenarche girls), gastroduodenal permeability as measured by sucrose absorption was higher in IBS vs healthy control girls. In contrast, small intestinal and colonic permeability were higher in IBS vs healthy control boys.[53] These data suggest an interaction between gender and gut region in the alterations of epithelial permeability in children with IBS.

Preclinical. The influence of sex on rodent GI permeability is unclear perhaps due to varying assessment approaches. Cyclic fluctuations in ovarian sex hormones appear to affect colonic and ileal permeability and in vitro studies show that estradiol protects the epithelial barrier by modulating TJ proteins, whereas progesterone has no effect.[54] There is no data on testosterone's effects. Stress affects colonic permeability in a sex-dependent manner, with the impact varying based on the life stage in which it occurs.[55]

Immune Dysfunction

Clinical. Sex/gender differences in the innate and adaptive immune systems are well known.[56] Most immune cells express receptors for sex hormones, hinting that sex hormones may contribute to establishing sex differences in the immune response.[57]

Gender differences may exist in the activation and infiltration of gut immune cells of healthy individuals.[58] In contrast to men in the healthy control group, mucosal biopsy samples of the small intestine from women in the healthy control group exhibited greater immune activation and inflammation-associated gene expression.[58] These changes occurred together, with higher activation and

proliferation of peripheral blood T cells and up-regulated CD4+ T cells, interleukin (IL) 1β, and Th17 pathway genes. Yet in 1 study, no significant differences were observed between men and women in the healthy control groups overall or when any immune cell subtype (CD3+, CD4+, CD8+ T cells, CD79+ B cells, and mast cells) infiltrated the lamina propria of the proximal descending colon.[59]

Altered immune function is present in a subset of DGBI patients with upper and lower GI dysfunction,[60] and there is evidence of gender differences in PI-IBS.[61] In a subset of FD patients with PI-IBS, increased infiltration of intraepithelial CD8+ lymphocytes, CCR2+ macrophages, and CD68+ cells are present. Women with FD IBS overlap generally show more pronounced immune activation, although the precise direction of specific cellular infiltration varies.[60]

Multiple factors are thought to contribute to this immune dysfunction: genetics, environment, sex hormones, and gut microbiota.[62] To date, most of the studies on sex differences in DGBI-related immune dysfunction have focused on the colon of IBS patients. A meta-analysis concluded that IBS patients have an increased number of colonic mast cells, CD3+ T cells, and CD4+ T cells and that these changes are segmental- and IBS-subtype–dependent and likely not gender-dependent.[63] Importantly though, there is a clear association between sex hormone levels, increased mast cell number and activation, and higher disease severity in women and animals of female sex.[64] It is not known yet whether the abundance, activation, or even proximity of mast cells to nerves in the gut fluctuate with the hormonal status of IBS women. In this meta-analysis, no in-between-sex comparison was done, and women's hormonal status was also not considered.[63] A careful look at the studies reporting sex differences in cellular immune infiltration[63,65] suggests that more work is needed before making any firm conclusions regarding sex influence on colonic immune cell counts or lack thereof.

Studies of mucosal levels of cytokines show lower expression of the anti-inflammatory cytokine IL10 mRNA in rectosigmoid biopsies of IBS vs healthy control women. In addition, IBS women as compared with IBS men have higher serum levels of the proinflammatory cytokine IL1β,[46] suggesting that IBS women may present with higher levels of inflammation. In another study, the antimicrobial peptide β-defensin-2, an important protein of innate immune response, was higher in IBS girls vs healthy control girls and IBS boys, suggesting a higher immune activation in IBS girls.[66] Data are even more scarce regarding the role of mucosal inflammation in other DGBI.

Preclinical. Despite extensive evidence on the effects of sex hormones on immune cells, knowledge is limited regarding the effects of sex and gender on the function of the gut mucosal immune system.[67] Rodent data suggest that the sex bias in autoimmunity may be influenced by microbiota and sex hormones.[68] Gut immune cells, particularly mast cells, are highly susceptible to the hormonal environment[58] and present a very high sex-differential anatomic plasticity.[69]

Gut Microbiome

Clinical. Gender differences exist in gut microbiota composition and functionality between healthy men and women. Women have a higher ratio of gut bacterial cells to human cells number;[70] however, few studies have addressed the effects of gender on the gut microbiota composition in humans. Sex-dependent alterations in bacterial phyla, genus, and species have been reported with no consistent findings.

There is growing evidence that the gut microbiota plays a significant role in the pathophysiology of DGBI. Women with IBS have increased fecal α-diversity and abundance of specific bacteria order, families, and species and also more often present with small intestine bacterial overgrowth than men with IBS.[71] Healthy donor fecal microbiota transplantation (FMT) is gaining increased consideration as a potential treatment for IBS and studies suggest women respond better to FMT than men. Sex-discordant FMT for *Clostridioides difficile* treatment may increase the risk of developing PI-IBS in patients, an outcome potentially linked to the innate differences in the composition and structure of the gut microbiota between men and women.[72] The data on gender differences in microbiome composition in DGBI is emerging, eg, *Prevotella* species is higher in men with IBS when compared with women with IBS and a lower *Prevotella* count in women with IBS is associated with higher IBS disease severity.[73]

Gut bacteria composition is modulated by sex steroid hormones. Gut microbiome diversity is correlated with the levels of testosterone in healthy control men and estradiol in healthy control women, with higher levels of sex hormones in each sex being associated with higher diversity. The gut microbiota can influence the metabolism and levels of sex hormones by affecting their excretion and reuptake. The gut bacteria with β-glucuronidase enzymes have the ability to deconjugate the conjugated estrogens excreted in the bile, thus enabling estrogen reabsorption. Once reabsorbed, these deconjugated estrogens can affect multiple organs via estrogen receptors. The gut microbiota is also an important regulator of androgens.

Preclinical. Female rodents have higher microbial diversity than males. Many bacterial species are found to have a higher abundance in either 1 of the sexes, most likely due to differences in strain, diet, and sex hormones. Cecal α-diversity differs between males and females postpubertal but not prepubertal mice[74] similar to reports in human monozygotic and dizygotic twins. The microbiome of females is closer to that of castrated males than that of uncastrated males.[74] Interestingly, the correlation between mucosal-associated microbiota and sex hormones is more prominent than the fecal microbiota. Gut microbiota metabolism of sex hormones differs by sex in mice with male mice having higher fecal β-glucuronidase activity than females. Of translational relevance, estrous cycle and ovariectomy-induced changes in visceral pain are microbiota-dependent in mice, indicating a role for female sex hormones, estradiol most specifically, and the gut microbiota in visceral sensitivity in females.[75]

Genetics and Omics

Clinical. Sex differences in physiology and disease in mammals result from the effects of 3 classes of innately unequal factors between gender or sex. These include: (1) the reversible (activational) effects of gonadal hormones; (2) the permanent (organizational) effects of gonadal hormones; and (3) the cell-autonomous effects of sex chromosomes, as well as genes driven by the 3 classes of factors. Behaviors impacted by gender roles including eating choices, smoking, excessive drinking, professional choices, caregiving, and service duties, which can influence exposure to chemicals, pollutants, and stress, can have a significant impact via epigenetic changes. Throughout the lifespan, hormonal changes due to pregnancy, lactation, menopause, and andropause may affect transcription and possibly methylation patterns. As such, studies aimed at deciphering DGBI pathways should take into consideration how sex hormones and chromosomes can contribute to gender differences.[76]

Earlier studies on familial aggregation and twins suggested a genetic component to both IBS and FD, which appeared not to be influenced by sex.[77] Studies exploring whether specific genetic variants are associated with these disorders, although often controlling for sex and age, have not reported on the effect of sex. Those that have are too low in subject numbers, making findings inconsistent and any association with sex uncertain. In a sufficiently powered genome-wide association studies identified variants at the locus 9q31.2 [SNP rs10512344] in a region previously linked to age of first menstruation are associated with risk of IBS in women, IBS-C in women, and harder stools in women.[78] Furthermore, another genome-wide association stool frequency study identified a sex-specific locus on chromosome 19 [SNP rs10407548] linked to the gene FFAR3, activation of which leads to the suppression of serotonin-mediated gut motility. Genetic polymorphism studies also indicate sex differences in the serotonergic system.[79]

Preclinical. Experiments with the native 4 core genotypes mouse model, in which the gonads (ovary or testis) are independent of the sex chromosome complement (XX or XY),[80] suggest that activational hormone levels have the strongest influence on gene expression, followed by the organizational gonadal sex effect, and, last, sex chromosomal effect, along with interactions among the 3 factors. Sex hormone (estradiol or testosterone)–related tissue specificity is also prominent.[81]

Stress Response: Hypothalamo-Pituitary-Adrenal Axis and Autonomic Nervous System

Clinical. Stress, whether interoceptive or exteroceptive, is a well-established factor in the onset, exacerbation, and chronicity of symptoms in DGBI patients. Although resting levels of norepinephrine (NE) and epinephrine are generally similar between men and women,[82] women show a higher vagal tone at rest and increased NE and epinephrine release during stress.[83] The influence of gender on basal and stress-induced autonomic nervous system (ANS) alterations in DGBI is also complex and may depend on the stress paradigm used.[84] Using CRF injection to mimic acute stress, women with IBS exhibited altered sympathovagal balance responses compared with healthy control women, whereas men with IBS did not differ from healthy control men.[83]

Under basal conditions, most studies report that healthy control men, compared with healthy control women, exhibit a higher secretion of adrenocorticotropic hormone (ACTH) together with comparable total cortisol levels, suggesting an increased sensitivity of women's adrenal cortex compared with men.[85] The hypothalamo-pituitary-adrenal (HPA) axis response to a challenge differs by gender depending on the type of stressor applied, with women having an overall increased cortisol response compared with men.

In IBS, there are divergent gender effects in the cortisol response to CRF and ACTH. The cortisol response to ACTH is increased in men with IBS but blunted in women with IBS. In peripheral blood monocytes, men with IBS exhibit reduced glucocorticoid receptor (GR) mRNA compared with healthy control men.[86] Administration of CRF produces a greater ACTH response in men with IBS than in healthy control men, but no differences in women.

A history of trauma or abuse and female gender is a risk factor for the development of AP-DGBI.[2] Women and men with IBS report significantly higher rates of adverse childhood experiences, with emotional abuse linked to IBS in women and sexual abuse in men. Anxiety mediates the adverse childhood experience–IBS link in both, whereas resilience is protective especially in women.[83,87]

A history of ELA may be associated with differences in cortisol levels between men and women with IBS.[88] In 1 study, IBS patients with ELA had significantly higher cortisol levels after flexible sigmoidoscopy than those without ELA, and the effect of ELA was more pronounced in IBS men compared with IBS women.[89] Whether this more robust response of the HPA in men explains the lower incidence of IBS when compared with women is unknown.

Testosterone and progesterone inhibit the HPA function, whereas estrogen enhances it. Endogenous levels of progesterone in the follicular phase, when levels are most similar to men, negatively correlate with stress-induced ACTH and cortisol release.[90,91]

In women, the use of oral contraceptives decreases the free cortisol response to a social stressor, whereas young men receiving a 48-hour treatment with estradiol exhibit an enhanced ACTH stress response.[92] Whether sex differences are linked to the opposing effects of ovarian and testicular hormones on the expression of CRF and GR is unknown.[93]

Estradiol inhibits GR activation and decreases GR expression, reducing cortisol HPA axis negative feedback. Estradiol may also directly enhance CRF gene transcription in the hypothalamus through binding to estrogen-responsive elements on the CRF gene. Even under induced hypogonadal conditions, sex differences in stimulated HPA axis activity are found to exist, suggesting that sex chromosomes have an important part in the HPA axis sex-based stress response.[94]

Preclinical. Female rodents show higher basal levels of corticosterone while having similar levels of ACTH, indicating a higher sensitivity of adrenal glands compared with males. Females also exhibit greater and faster responses to acute stressors as shown by increased ACTH and cortisol levels and failure to adapt to chronic and repeated stress.[95,96]

Sex hormones modulate the HPA axis, with effects emerging at puberty. ACTH and corticosterone levels, vary as a function of the estrous cycle under both basal and stimulated conditions. While estradiol increases HPA responses, testosterone and progesterone have an inhibitory effect.[97,98]

The sex differences in the ANS activity are already present prenatally at the central level, in terms of neuronal connections, neuropeptide distribution, and activity. Female rats as compared with male rats exhibit greater vagally mediated heart rate variability and higher heart rate. In females, diestrus, a period of low estrogen levels, is associated with increased basal heart rate and arterial pressure, as well as decreased baroreflex sensitivity.[99,100] During the proestrus/estrus stage characterized by high estrogen levels there is increased cardiovascular autonomic modulation.[101] Intravenous or intracerebral administration of estrogen in male rats increases vagal tone and suppresses sympathetic efferent activity. In addition, there is evidence that testosterone enhances NE synthesis and clearance.

Numerous preclinical reports indicate that ELS exposure affects the HPA axis and ANS function in adulthood, impacting both its basal and stress-induced activity. Females' HPA axis is more susceptible to ELS but the mechanisms behind this are poorly understood. The sex-differential effects of ELS exposure on corticosterone levels are age-dependent.

Serotonin

Clinical. Serotonin (5-HT), a neurotransmitter and paracrine signaling molecule involved in central nervous system and enteric nervous system functions, plays a role in visceral sensitivity, secretion, and motility. In healthy control women, levels of 5-HT in the cerebrospinal fluid are higher compared with men. At the peripheral level, women have higher levels of circulating 5-HT than men.

Studies of both central and peripheral serotoninergic pathways linked to IBS differ by gender and sex steroids.[102,103] Centrally, 5-HT synthesis is greater in the right medial temporal gyrus (multimodal sensory association cortex) of IBS vs healthy control women, a difference not observed in men.[104] At the peripheral level, women with IBS-D have increased serotonin reuptake transporter gene (SERT) mRNA expression in mucosal rectal biopsies compared with IBS-D men.[105] Along this line, IBS-D men show a reduced frequency of the SERT gene polymorphism 5-HTTLPR (ss) genotype. SERT gene SLC6A4 rs2020938 is also identified as a functional SNP associated with IBS-C risk in women.[79] The HTR3E c.*76G > A (rs56109847 = rs62625044) is associated with IBS-D in women.[106] These sex-specific alterations in serotonergic signaling may help explain why IBS-C is more common in women, potentially reflecting enhanced SERT activity and reduced serotonin availability in the gut.

Preclinical. Sex differences are present in both peripheral and central serotonergic pathways. Female mice exhibit greater colonic mucosa levels of 5-HT than males, which could be linked to their reduced expression of SERT gene.[107] The higher levels of colonic 5-HT and the increased 5-HT signaling at the dorsal spine leads to visceral hypersensitivity in female but not male SERT-knockout rats.[108] The enterochromaffin cell (EC)–mucosal afferent circuit is tonically engaged in female rodents and contributes to visceral pain.[109]

The effects of sex hormones appear to be organ and compartment dependent. Centrally, estradiol and androgens induce an overall net increase in 5-HT synthesis and availability. Peripherally, progesterone decreases SERT and increases 5-HT levels in the colon of naive male mice in vivo.[110] In male rats, the plasma level of androgens negatively correlates with 5-HT level in the endothelium of the small intestine. In the small and large intestine of male Wistar rats, orchiectomy did not alter plasma 5-HT levels but reduced 5-hydroxyindoleacetic acid levels, indicating suppression of 5-HT metabolism in the absence of androgens.[111] Sex hormones, including estradiol, androgens, and progesterone, have organ- and compartment-dependent effects on 5-HT (serotonin) synthesis, metabolism, and availability, influencing it differently in central vs peripheral locations.

Bile Acids

Clinical. In healthy controls, there is evidence for gender differences in bile acids (BAs) synthesis, secretion, recycling, and excretion. Total BAs concentrations, BAs synthesis, fecal concentrations, and excretion of secondary BAs are higher in healthy control men than healthy control women. The enterohepatic recycling of BAs is more efficient in healthy control women than men.[112] Estrogens and androgens regulate BAs production and serum cholesterol levels via hepatic feedback mechanisms and act by transcriptionally regulating liver enzymes.

BAs secretion and excretion are associated with changes in GI transit in IBS patients that correlate with bowel habits: IBS-D patients (without overt BAs malabsorption) have greater BAs secretion whereas IBS-C patients have lower BAs.[112,113] Despite these reports, no study has yet explored the influence of gender in BAs pathways in DGBI.

Preclinical. Both mice and swine exhibit sexually dimorphic rates of BAs synthesis and BAs pool composition. However, in mice the sex difference is opposite to the one reported in humans, a consideration when using mice as a model for BAs. In mice, the primary conjugated BAs species are more abundant in females than males, independent of gut microbiota. Females also show higher levels of secondary BAs than males indicating a role for gut bacteria capable of BA biotransformation.[114]

Gender and Overlapping Conditions

Patients with DGBI may experience the simultaneous presence of comorbid conditions including additional DGBI, other GI disorders, and "extraintestinal" conditions. Patients with IBS report an average of 4 overlapping conditions with fibromyalgia, chronic fatigue syndrome, and chronic pelvic pain (CPP) being the most common.[115] Having an overlapping condition is linked to increased DGBI symptom severity and poorer QoL. Overlapping conditions are more frequently reported by women and men are under-represented in research, which may represent a bias in the available evidence.[57]

Several pathophysiological mechanisms, including shared genetic risk factors, somatization, visceral hypersensitivity, central pain sensitization, chronic inflammation, mast cell activation, dysbiosis, and organ cross-sensitization, are proposed. Notably, these disorders have distinct pathophysiology, and the overlap is not due to "somatization" alone.[116]

Psychological

Common psychological comorbidities in DGBI patients include anxiety, depression, somatic disorder, post-traumatic stress disorder (PTSD), and eating disorders.[59,117] Patients with either IBS or FD are 2–3 times more likely to experience anxiety and depression when compared with healthy controls.[118] A prior history of trauma is a risk factor for the development of DGBI. A meta-analysis of 8 studies (n = 4 cross-sectional, n = 4 cohort studies; 648,375 subjects) found PTSD to be a significant risk factor for IBS.[119] This same analysis found no gender-related difference in the relationship between PTSD and IBS severity. Compared with men, women with IBS are more likely to restrict their diet in response to their symptoms, suggesting a higher risk for eating disorder.[120]

Gastrointestinal

In general, the overlap of DGBI is more common in women as compared with men and more common in tertiary health care systems.[121,122] The most common overlapping DGBI conditions is IBS with FD. Other GI disorders associated with DGBI are celiac disease, inflammatory bowel disease, and metabolic-associated fatty liver disease. Patients with more than 1 DGBI have higher disease severity, lower QoL, and increased healthcare use. Men with more than 1 DGBI report statistically significantly better QoL than women with multiple DGBI but the differences are small.

A worldwide epidemiology study reported DGBI overlap data by 4 anatomic regions (esophageal, gastroduodenal, bowel, and anorectal). Among participants meeting Rome IV criteria, the overlap of having 1, 2, 3, or 4 DGBI was 68%, 22%, 7%, and 2%, respectively, and all higher in women.[122] Emerging data suggest metabolic dysfunction, including metabolic-associated fatty liver disease, overlaps with DGBI via shared gut-liver mechanisms, supporting reciprocal screening.

Musculoskeletal/Neurologic

The disorders associated with DGBI are temporomandibular disorders, fibromyalgia (FM), hypermobility/hypermobile Ehlers-Danlos syndrome, postural orthostatic tachycardic syndrome (POTS), and chronic back pain. All have a female predominance. Patients with IBS, regardless of subtype, have a higher risk of temporomandibular disorders. IBS and FM often co-occur, with 10.7% of IBS patients also having FM.[123]

POTS, marked by excessive heart rate without a decrease in blood pressure, is more common in women (4.5:1 ratio).[124] It frequently co-occurs with hypermobility syndromes (hypermobility/hypermobile Ehlers-Danlos syndrome) and mast cell activation syndrome. The most established DGBI associated with POTS and joint hypermobility include IBS, gastroparesis, FD, constipation, and pelvic floor dysfunction.[124,125]

Gynecologic/Urologic

Gynecologic disorders associated with DGBI include endometriosis, dysmenorrhea, dyspareunia, polycystic ovary syndrome, and CPP. The odds of developing IBS in women with endometriosis is approximately 2–3 times that of women without endometriosis regardless of whether the endometriosis involves the bowel wall.[126] Dysmenorrhea overlaps with IBS with a prevalence of 6%–30% in adolescent and adult women.[127]

Sexual dysfunction is more commonly reported by both women and men with DGBI than healthy controls. In 1 study, 56% of women between 18 and 45 with dyspareunia had a DGBI diagnosis with CC being the most common followed by functional diarrhea, IBS, and FD.[122]

Over a third of patients with IBS have symptoms consistent with CPP, which can overlap with painful bladder syndrome.[128] This relationship may result from bladder–gut–brain axis dysregulation and cross-organ sensitization between the bladder and GI tract.[129] Women with IBS and FD are more likely to have painful bladder syndrome, whereas migraine and FD are more commonly associated with CPP. In 1 study, PTSD occurred early in the chronological sequence, suggesting its potential role in the development of CPP. In men, pre-existing IBS increases the risk of subsequent prostatitis.[130] Brain imaging studies have identified differences between IBS and chronic urologic pain.[131]

Gender and Treatment Response

Most studies on over the counter and prescription medications lack gender-specific data, with men often being under-represented. This limits firm conclusions about treatment differences. Although pharmacokinetics is generally similar across genders, some variations may exist, particularly with alosetron and ramosetron.

Serotonin Receptor Antagonists

Alosetron is a Food and Drug Administration–approved 5-HT_3 receptor antagonist for severe IBS-D in women who

have not responded to other treatments. In a dose-ranging study, a proportion of women reported adequate IBS symptom relief, but men did not.[132] Although both sexes saw similar improvements in stool consistency and frequency, only women had slower colon transit and some individuals in both groups did not respond. Clearance of alosetron is faster in men, leading to higher serum concentrations in women. Men with IBS-D show a reduced frequency of the 5-HTTLPR (ss) genotype.[133] Additionally, in response to rectosigmoid stimuli, alosetron decreases brain emotional motor system activity, which differs between men and women. A dose-ranging study in men showed that all alosetron doses improved stool consistency, but only the 1 mg twice-daily dose provided adequate relief of pain/discomfort compared with placebo. Importantly, no improvements in urgency, number of bowel movements, bloating, or incomplete evacuation were seen.[134]

Ramosetron is a $5HT_3$ receptor antagonist that is approved in Japan and southeast Asia for treatment of IBS-D as well as nausea and vomiting. An initial study reported higher responder rates in men than women with IBS-D. A phase III study of women with IBS-D demonstrated that ramosetron also was more efficacious than placebo in global response, improving stool consistency, reducing abdominal pain, and improving QoL.[135]

Neuromodulators

Most published studies did not evaluate gender effects in neuromodulator treatment trials.[136,137] A recent study found that US primary care providers showed greater confidence in prescribing neuromodulators as compared with European primary care providers.[138]

Nonpharmacologic

Approximately 30%–50% of IBS patients opt for nonpharmacologic treatments, often combining multiple therapies. Women are more inclined to use these therapies and more likely to participate in clinical trials. Common brain–gut behavioral therapies include cognitive behavioral therapy, gut-directed psychotherapy, gut-directed hypnotherapy, and mindfulness training. The 2021 Rome Foundation working team recommended that gut-directed psychotherapy be used for IBS symptoms in both men and women.[139]

Dietary advice is a common IBS treatment, but studies conflict on gender differences in adherence. In children with functional abdominal pain, being a girl was a predictor of response to change in diet.[140] A higher rate of restrictive dieting in women with IBS warrants caution from providers considering elimination diets like low-FODMAP, due to risks of nutritional deficiencies and triggering avoidant/restrictive food intake disorder—a fear-driven eating disorder increasingly recognized in DGBI populations.

Social Determinants of Health

Racial Disparities

Race, and the sociocultural milieu surrounding it, impacts every aspect of the patient and provider interaction. Data on the impact of disparities in DGBI is minimal. Regardless, increased awareness and general practical recommendations apply. These include the recruitment of a more racially and ethnically diverse gastroenterology workforce reflective of the communities they serve, increased awareness of the multiple cultural factors that can complicate or alter the patient-provider relationship, and recognition of the role of all forms of stigma faced by minority patients with DGBI.

In a US survey, Hispanics and non-Hispanic Blacks with IBS-D reported more severe AP compared with non-Hispanic Whites.[141] Additionally, non-Hispanic Blacks with IBS-D were more likely to have sought care for their symptoms ever or in the past year compared with non-Hispanic Whites. In a recent claims study, IBS healthcare spending was lower in Asian and Hispanic patients than in White patients. Compared with White patients, Black patients had higher total IBS-specific costs and emergency department care, whereas Asian and Hispanic patients incurred lower costs for emergency department care.[142] A retrospective study of IBS patients and controls seen at 2 US tertiary care centers found that the racial and ethnic minority IBS patients were less likely to be referred to a gastroenterologist and more likely to have undergone invasive diagnostic testing, eg, endoscopy.[141,142] Although the reasons for these findings could not be discerned from the study, the authors suggested that increased diagnostic procedure referrals in a disease (IBS) that generally does not require endoscopic diagnosis could result from communication difficulties between patients and providers.

Epidemiologic studies may not fully account for disparities arising from underlying inequities. Sasegbon and Vasant[143] present a comprehensive disparities framework that emphasizes the role of cultural factors. Specifically, they highlight the influence of patient-healthcare provider and organizational cultural factors on racial disparities in healthcare.

Disparities Among Sexual and Gender Minorities

Sexual and gender minority (SGM) populations include those who identify as lesbian, gay, bisexual, asexual, transgender, two-spirit, queer, and intersex and are likely at disproportionate risk for DGBI, regardless of race. Data on DGBI in this population is very limited. SGM individuals likely experience a higher prevalence of IBS and increased IBS severity,[144] attributed to elevated rates of mental health challenges compared with their cisgender and heterosexual counterparts. This highlights the need to recognize the distinct obstacles faced by SGM patients, who are more likely to encounter discrimination in medical settings.

Patient Experience With DGBI

For many patients, the emotional and social implications of the disease hold greater significance than the physical limitations.[145] Patients with DGBI often have reduced work productivity, feel isolated due to their symptoms, experience social stigma, and report dissatisfaction with their healthcare experiences. The symptoms

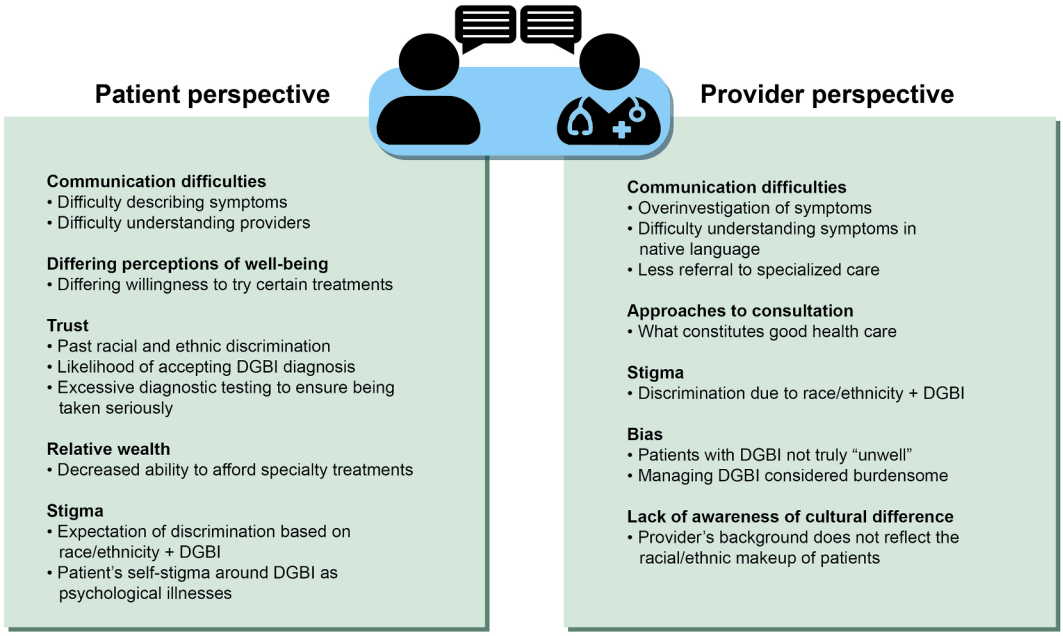

Figure 4. Patient and provider perspectives important to consider in DGBI care. Patient-provider and organizational cultural factors may influence disparities in health care. From the patient's perspective, the ability to communicate with their provider can be hampered by language barriers, impacting providers' ability to understand their patients—all exacerbated by organizational factors that limit support for other languages. Racial/cultural differences may impact patients' trust in their providers and their likelihood of accepting medical advice. Providers may exacerbate these factors with biases and a lack of awareness about racial/cultural differences. These patient-provider barriers, related to racial disparities, can add additional hurdles to forming a therapeutic patient-health care provider relationship already fraught with concerns about provider stigma against those with DGBI and the internal stigma felt by patients with DGBI.

and high prevalence of anxiety and depression can impact on daily life, particularly social situations that involve food or intimacy. Consequently, patients may develop maladaptive coping mechanisms such as avoidance, withdrawal, vigilance, concealment, and low self-esteem, worsening their feelings of isolation and stigmatization. Patients' experiences of illness are profoundly shaped by their socialization and the societal expectations imposed on them. These expectations frequently demand adherence to traditional gender roles, even as our understanding of gender evolves beyond the binary categories of "female" and "male." The binary gender concept fails to reflect societal complexities, shaping illness experiences and healthcare-seeking behaviors.

Stigma related to gender can also be experienced in the healthcare setting (Figure 4).[146] In 1 study, researchers recruited general population participants to evaluate 6 clinical vignettes describing either men or women patients with IBS, inflammatory bowel disease, and asthma.[147] Overall, IBS patients were stigmatized more than other groups. Women patients' symptoms were more often taken less seriously or dismissed as psychosomatic based on cultural gender biases.

Patients' Health Care Experience

Because the biomedical model in Western medicine relies on disease biomarkers, when tests are negative or inconclusive, symptoms may be dismissed as psychological, leaving patients feeling ignored, frustrated, and without adequate medical attention. Negative health care provider (HCP) attitudes contribute to delegitimizing and stigmatizing of DGBI. A therapeutic patient-HCP relationship is an important predictor of clinical outcomes in the field of DGBI.[138] This relationship encompasses active listening, empathy, cultural sensitivity, and adaptability to individual patient needs, empowering clinicians to deliver compassionate, patient-centered care. Furthermore, a therapeutic relationship fosters professional satisfaction among HCPs. The goals of clear communication are to establish a definitive diagnosis, align patient and HCP treatment goals, and empower the patient to self-manage the symptoms. For example, using vague or "qualified" language (eg, "may have IBS") when discussing DGBI diagnosis can leave patients uncertain, increasing fear of something being missed. This uncertainty often prompts additional visits and requests for more tests. Clarity in communication about the diagnosis should extend into a shared decision-making about treatment. Clearly explaining the purpose, mechanism, and expected benefits of a medication—while setting shared goals—helps patients feel informed and engaged, supporting adherence and better outcomes.

Artificial intelligence is quickly emerging as a tool in DGBI care. Early applications include detecting subtle endoscopic changes in IBS, using brain imaging to distinguish FD patients from healthy controls, correlating bowel sounds with IBS, and developing symptom-tracking smartphone apps.[148,149] Further development is needed to fully harness artificial intelligence's potential in DGBI.

Table 1. Clinical Pearls on Gender, Age, Race, and Social Determinants in DGBI

Topic	Clinical pearls	Practical implications
Epidemiology	DGBI are more common in women. Cyclic vomiting and fecal incontinence occur equally; functional diarrhea and cannabinoid hyperemesis are more common in men.	Consider DGBI in men despite lower prevalence. Ask about cannabis use in men with cyclic vomiting.
Life stages: children/adolescents	Similar rates of DGBI in boys and girls.	Support pediatric-to-adult care transition. Start early; ensure communication across care teams.
Life stages: puberty	Symptoms often worsen at menarche. Contraception and societal pressures may play a role.	Consider DGBI with new bowel symptoms postmenarche. Collaborate with gynecology to avoid delays and unnecessary testing.
Menstrual cycle	Symptoms may worsen premenses. Hormones (estradiol, progesterone) impact DGBI. Symptoms often change during menopause transition.	Ask about cycle-phase symptom changes. Inquire about hormone use.
Aging	DGBI is less common with age. Older adults report less severe symptoms but may develop restrictive eating.	Rule out organic causes in older adults. Involve a dietitian if recommending diet-based therapy.
Pregnancy	GERD and constipation are common.	Treat symptoms proactively throughout pregnancy.
Overlapping conditions	Multiple DGBI and comorbidities are common, especially in women.	Screen for multiple conditions and use multitargeted therapies. Refer early when appropriate.
Sexual dysfunction	Common in both genders but often under-reported.	Ask about pelvic, urinary, or sexual symptoms in all patients.
IBD/DGBI overlap	Patients with IBD in remission may also have DGBI.	Distinguish between active IBD and overlapping DGBI to avoid unnecessary workup.
Disordered eating	Common in DGBI and often overlooked.	Screen for ARFID. Refer to dietitian. Ask about food avoidance and strict dietary rules.
MAFLD and DGBI	Frequently coexist.	In MAFLD patients, screen for DGBI symptoms.
Gender and treatment	Drug trials focus on women. Most FDA-approved medications work for both genders; Alosetron only for women.	Use Alosetron only for women with severe IBS-D.
Nonpharmacologic therapies	Women use these more often and are more prone to restrictive diets and ARFID.	Screen both sexes for supplement use and dietary restrictions. Refer to dietitian when needed.
Social determinants	Often overlooked but impact outcomes.	Screen for SDH: access to care, tech use, cost, or food availability. Involve social work.
Patient experience	Positive patient-provider relationships improve outcomes.	Use I'M LATE mnemonic (Impression, Minute of silence, Listen, Acknowledge, Touch, Empathy).
Stigma	Gender and racial stigma affect diagnosis and care.	Recognize bias: men may be dismissed; women may be offered psychotherapy instead of other options.

ARFID, avoidant/restrictive food intake disorder; FDA, Food and Drug Administration; IBD, inflammatory bowel disease; MAFLD, metabolic-associated fatty liver disease; SDH, social determinants of health.

The landscape for DGBI is rapidly evolving, with advances in biomarkers enabling more tailored and personalized treatments, including nutritional strategies. Virtual healthcare platforms are improving access to multidisciplinary care, and the rise of Food and Drug Administration–cleared digital therapeutics offers further opportunities.

Research Recommendations

Interpretation of past research—from the standpoint of age, gender, sex, and other social determinants of health—has been hampered by the lack of intention in collecting and evaluating data regarding these factors. Through monitoring of sample collection to ensure underrepresented groups are recruited mindfully, there is much opportunity to explore the role of social determinants of DGBI. With the pooling of data with meta-analyses, studying the effects of social factors remains eminently possible. Prospective researchers are directed to the Sex and Gender Equity in Research guidelines and the National Institutes of Health Policy on Sex as Biological Variable.

Summary

Differentiating between sex and gender considers the complex interplay of biology, psychology, and the environment. DGBI disproportionately affect women, and gender differences become more pronounced postpuberty. Understanding age- and gender-specific differences in DGBI pathophysiology is rapidly evolving, particularly in the field of brain imaging, microbiome, and immunology. The impact of social determinants of health is often underappreciated, along with the therapeutic patient-HCP relationship and the need for multispecialty patient-centered care. Clinical pearls are in Table 1.

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Conflicts of interest
These authors disclose the following: Margaret M. Heitkemper served as a consultant to Abyle Health. Kyle Staller has served as a consultant for AbbVie, Ardelyx, Gemelli, Salix, and Takeda. Lucinda A. Harris has received research support from Takeda and Anyx; and served as a consultant for Sancuso, Ardelyx, and Gemelli. Johannah Ruddy is the Senior Director of Patient Advocacy at Ardelyx, Inc. The remaining authors disclose no conflicts.

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