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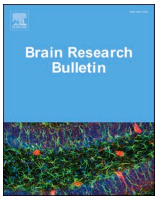

# Sex and gender as critical and distinct contributors to the human brain-gut-microbiome axis

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ABSTRACT

The brain-gut-microbiome axis (BGMA) is a pivotal contributor to human health. A large body of research, especially from animal models, has revealed bidirectional, causal relationships between the BGMA and sex. In particular, sex steroids appear to be affected by the BGMA, to influence the BGMA, and to moderate environmental effects on the BGMA. However, animal research on the relationship between sex and the BGMA has not translated well to human models. We contend that this is due in part to an oversimplified approach to sex: although BGMA researchers have traditionally approached sex as a unidimensional, dichotomous variable, it is in fact multidimensional and is comprised of both multi-categorical and continuous dimensions. We also contend that research on the BGMA in humans should approach gender as a variable that is distinct from sex and that gender may influence the BGMA through pathways that are independent from the effects of sex alone. Research practices that consider the complexity and distinctiveness of sex and gender in relation to the human BGMA will not only yield improved understanding of this consequential system, but will also enhance the development of treatments for adverse health outcomes with BGMA-related etiologies. We conclude with recommendations for the implementation of such practices.

## 1. Introduction

Advances in the accuracy, accessibility, and affordability of high-throughput sequencing have enabled a proliferation of high-quality research on the brain-gut-microbiome axis (BGMA) – the system by which the brain, gut, and microbiome interface – as a major component of human health and well-being. A rapidly growing body of work has revealed that the BGMA is sensitive to environmental inputs, which can lead to changes in the gut microbiome and contribute to or protect from adverse health and behavioral outcomes (Dinan and Cryan, 2017). Critically, this research has also revealed that the function of the BGMA and its sensitivity to these environmental inputs seem to covary with certain host characteristics. Considering that most of this work has been done in rodent models, researchers must critically consider how these host variables translate across species.

Sex is a highly consequential host trait to consider, as it has been linked to differences in BGMA function in rodent and human studies. Although, on the surface, sex appears to be a seemingly straightforward variable with high potential to be easily translated across species, closer consideration reveals that such translation is in fact quite complicated. Another major issue, the focus of this review, is an oversimplified approach to sex and, relatedly, gender in humans. In both humans and animals, sex typically refers to chromosomal sex, that is, having XX or XY chromosomes. However, sex can also refer to levels of sex hormones or to the presence of primary and secondary sex characteristics, both external and internal. Additionally, in human research, participants are often asked to self-report their sex. The variation of sex hormone levels, sex characteristics, and self-reported sex among individuals is only partially explained by chromosomal sex, with other factors such as puberty, menopause, and medical history playing a non-negligible role.

A factor unique to human models is gender: sex is related to, but distinct from, gender, which is defined as attitudes, feelings, and behaviors related to a person's sex (American Psychological Association, 2019). Gender can refer to an individual's chosen gender identity, the way an individual's gender is socially and culturally perceived by those around them, or the gender recorded on their legal documents, such as passports and driver's license (Lindqvist et al., 2020). Because gender is linked to factors, such as behaviors, social roles, and healthcare access, that may influence the functioning of the BGMA, gender may be an important variable to consider in BGMA research which has thus far

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largely neglected this variable, or worse, conflated it with sex. The BGMA research field is hardly unique in this respect; gender is rarely considered separately from sex in human research studies in any field. However, given that sex and gender stand to contribute unique variance to the functioning of the BGMA, we contend that studying both will contribute to improved understanding of the role of the BGMA in a range of health and behavior outcomes, particularly those that covary with these important biological and psychosocial variables.

While this manuscript specifically concerns human research, it should be noted that major issues in cross-species translation also stem from our treatment of sex differences in preclinical (e.g., rodent) models. Specifically, the inclusion of female rodents in basic preclinical research has only recently become a widespread practice, with higher hormonal variability and complexity of females often being cited as justification for systematically excluding them from subject populations (Miller et al., 2017; Shansky, 2019).

The aim of this manuscript is to consider how sex and gender, as discrete and measurable concepts, are linked or could be theorized to link to the BGMA, and to encourage the measurement of both sex and gender in human BGMA studies. To this end, this review will provide an overview of the relationship between the BGMA and sex hormones (for additional syntheses, we also refer readers to Holingue et al., 2020; Jaggar et al., 2020; Jašarević et al., 2016; So and Savidge, 2021; Yoon and Kim, 2021). Then, we will discuss the pathways by which gender, unique from sex, may relate to the BGMA in human models, using disordered eating as an example. Finally, we will conclude with future recommendations.

The relationship between sex and the BGMA is highly complex. Although we cite some of the exemplary work on this topic, a thorough discussion of the underlying mechanisms would be outside the scope of this review. Moreover, many of these mechanisms have already been reviewed in recent publications. Throughout this manuscript, we refer the reader to such publications, where appropriate.

### 1.1. Sex Hormones

A brief primer on human sex hormones, also referred to as sex steroids, may be helpful for contextualizing subsequent sections. Humans produce three main types of sex hormones: estrogen, androgen, and progesterone (Hiller-Sturmhöfel & Bartke, 1998). Work on the BGMA has largely focused on estrogen and androgen, rather than progesterone. Although adult males typically produce more endogenous androgen than do adult females, and females tend to have higher levels of estrogen than most males, all healthy people endogenously produce both androgen and estrogen. Critically, sex hormone levels vary (sometimes a lot) between individuals; this variation is important for interpretation of BGMA research, and will be elaborated upon in greater detail later in the manuscript.

## 2. Sex and the brain-gut microbiome axis

Existing evidence suggests a bidirectional relationship between the BGMA and sex that may help to explain differential risk for certain sex-linked health outcomes. For example, several disorders that have been associated with BGMA function, e.g., irritable bowel syndrome (IBS), anxiety and mood disorders, and autism spectrum disorders, also vary significantly across sexes in terms of their incidence and presentation (El-Ansary et al., 2020; Kessler et al., 2005; Oka et al., 2020; Werling and Geschwind, 2013). The relationship between these disorders and sex has primarily been attributed to the actions of sex hormones (Valeri and Endres, 2021), suggesting that sex hormones may differentially affect the functioning of the BGMA or vice versa – with BGMA functions impacting sex hormones that may then influence health outcomes. The following section will review the evidence for each direction of influence separately.

### 2.1. The brain-gut-microbiome axis regulates sex hormone levels

Each node of the BGMA – the brain, gut, and microbiome – engages in sophisticated bidirectional communication via a range of interacting pathways including the vagus nerve (Forsythe et al., 2014), endocrine communication, especially via the hypothalamic pituitary adrenal (HPA) axis (Sudo, 2014), gut-derived metabolites (O'Mahony et al., 2015; Silva et al., 2020), and the immune system (Dinan and Cryan, 2017; Sudo, 2014). Emerging evidence suggests that the BGMA is a regulator of sex steroids. While this topic has been reviewed thoroughly elsewhere (e.g., Wang and Xie, 2022; Parida and Sharma, 2019), here we will provide a brief overview of the most compelling findings in the area. BGMA regulation of sex steroids may begin early in the life of the parent, with parental microbiome affecting offspring sex chromosome selection; for example, one study found that mouse dams fed a strain of *Lactobacillus reuteri* produced a greater ratio of female to male offspring than dams not fed this strain (Ibrahim et al., 2014). Postnatally, in male rats, the colon tissue of the host has been demonstrated to locally synthesize molecules involved in the genesis of steroids, including testosterone, progesterone, and estradiol (Diviccaro et al., 2020). The gut microbiome directly affects sex hormone levels by regulating the androgen levels of mice and adult men via intestinal metabolism and deglucuronidation, attributed to bacterial β-glucuronidase (Colldén et al., 2019), which, in humans, is positively correlated with *Clostridia* and negatively with *Streptococcus* and *Alistipes* (Flores et al., 2012) and may be regulated by 60 genera (Kwa et al., 2016). The gut microbiome also modulates the deconjugation of estrogens, also attributed to β-glucuronidase, leading to reabsorption (Kwa et al., 2016). Perhaps some of the strongest evidence that the gut microbiome is causally involved in expression and function of sex steroids comes from rodent models, in which experimental modulation of sex hormone levels has been achieved through manipulation of the gut microbiome. In one such study, transplant of caecal contents from adult male mice to prepubertal females led to an increase in testosterone levels in the prepubertal females (Markle et al., 2013), whereas the same was not true when cecal contents from adult females were transplanted. This study strongly suggests that the microbiome is an important regulator of sex hormone levels, at least in mice. In another study, inoculation of female rats with lactic acid bacteria resulted in effects, which varied by the strain of the lactic acid bacterium, on gut metabolites, gut microbiome diversity, and serum testosterone and estrogen (He et al., 2020). Again, these studies demonstrate a causal association between the gut microbiome and levels of sex hormones in non-human animals, potentially operating through the function of various gut derived metabolites which interact with sex steroids as well as production of the sex hormones themselves.

### 2.2. Sex affects the brain-gut-microbiome axis

In addition to the effects of the BGMA on sex hormones, sex has itself been demonstrated to influence each node in the BGMA. There is evidence for a relationship between genes located on the sex chromosomes and the BGMA (reviewed by Bubier et al., 2021; Shobeiri et al., 2022), but chromosomal sex alone is insufficient to explain sex-related variation in the BGMA. Importantly, beyond genetic effects alone, sex hormones are a major and necessary mechanism for sex effects on the BGMA. In several rodent studies, for example, experimental gonadectomy (resulting in dramatic decreases in circulating sex hormones) and prenatal sex steroid exposure and have both been shown to alter the composition of the gut microbiome (Jaggar et al., 2020). The effects of sex steroids on the BGMA may even play a part in functional gut disorders, such as IBS and could help to explain the higher incidence of this disorder in females; for example, androgens seem to ameliorate sensitivity to pain in the gut, which is a symptom of IBS, while estrogens may increase pain sensitivity and promote gut dysmotility, another IBS symptom (So and Savidge, 2021).

Sex steroid changes attributed to normative factors such as puberty

or menopause have also been associated with changes in the BGMA. Though little work has been done in human adolescents, an observational study in humans found that post-pubertal subjects, compared to prepubertal, had elevated prevalence of *Betaproteobacteria* and *Burkholderiales* and reduced prevalence of *Clostridiales*, *Pasteurellales*, *Clostridiaceae*, *Coprobacillus* and *Haemophilus,* while *Adlercreutzia*, *Dorea, Clostridium* and *Parabacteroides* were associated with androgen levels in postpubertal subjects (Yuan et al., 2020). Sex differences in the murine gut microbiome, such as elevated alpha diversity in females and elevated abundance of *Porphyromonadaceae*, *Veillonellaceae*, *Peptococcaceae*, *Lactobacillaceae*, and *Enterobacteriacea* in males, emerge at the onset of puberty and may be eliminated via castration in males (reviewed in Valeri and Endres, 2021). In human females, both normative menopause and premature ovarian insufficiency are associated with gut microbiome disruption compared to premenopausal controls, but this is ameliorated in patients receiving hormone replacement therapy, which restores premenopausal sex hormone levels (Jiang et al., 2021; Leite et al., 2022). For example, the duodenal microbiome of postmenopausal females not receiving hormone therapy has been found to exhibit greater prevalence of cardiovascular disease-associated taxa and to be less diverse than that of postmenopausal women receiving hormone therapy and of reproductive age women, attributed in part to lower testosterone levels (Leite et al., 2022). In premature ovarian insufficiency, an increase in the presence of *Eggerthella* is linked to alterations in serum metabolites, but the changes in microbiome composition and metabolites are both reversed by hormone replacement therapy (Jiang et al., 2021). Thus, both earlier and later in life, normative, within-sex variation in sex steroids are associated with BGMA function, and manipulations in sex steroid levels (e.g., hormone replacement therapy) can change the composition of the microbiome in humans.

### 2.3. The sensitivity of the BGMA to environmental inputs covaries with sex

Given the data on bidirectional influences between sex hormones and the microbiome, it follows that the sex of the host covaries not only with characteristics of the BGMA, but also with the response of the BGMA to environmental inputs, such as early stress and experimental treatments. That is, certain environmental inputs seem to have a sex-specific effect on the BGMA. In rodent models, prenatal and early-life maternal stress alters the gut microbiome differently in male and female offspring, with these sex-specific alterations in the microbiome possibly exerting differential effects on neurodevelopment (Cusick et al., 2022; Jašarević et al., 2015, 2016). In mice, stress exposure and diet manipulation affect both microbiome composition and gut serotonergic activity in a sex-dependent manner (Lyte et al., 2022). Germ-free rearing, a severe environmental insult, induces sex-dependent differences in behavior (though results are heterogeneous among studies (Jaggar et al., 2020; Luk et al., 2018)), as well as in neurogenesis (Scott et al., 2020), hippocampal plasticity (Darch et al., 2021), and cerebral opioid receptor density (Effah et al., 2022) compared to control mice. Also in mice, antibiotic treatment seems to differentially affect the composition of the microbiome, the levels of health-related gut-derived metabolites, immune regulation, and anxiety-like behavior in males compared to females (Champagne-Jorgensen et al., 2020; Gao et al., 2019). These sex differences in BGMA sensitivity to environmental influence may help to explain why some health outcomes, especially those linked to early environmental insults, are sex-linked.

### 2.4. The relationship between the brain-gut-microbiome axis and sex may explain differential risk for health outcomes

The reciprocal, multifaceted relationship between the BGMA and sex hormones may explain sex differences in risk for and presentation of adverse health outcomes and, ultimately, inform treatment and prevention. For instance, Markle et al. (2013) found that in a mouse model of type 1 diabetes, the sex difference in risk was reduced when mice were raised in germ-free conditions (disease risk is typically elevated in females). Moreover, the transplant of gut microbes from adult male rats to young females raised the females' testosterone levels and conferred protection against type 1 diabetes. In this mouse model of diabetes, disease risk seemed to be dependent on an interaction between the BGMA and sex hormones. Another prominent example of the interaction between the BGMA and sex hormones is seen in IBS, which is more prevalent in females: components of IBS, such as visceral sensitivity and dysmotility, likely depend on interactions between sex hormones, gut tissue, pain receptors in the gut, and the microbiome, though there are many inconsistencies in the literature (reviewed by So and Savidge, 2021). In one study, for example, ovariectomy induced visceral hypersensitivity in conventional mice, but not those raised in a germ-free environment (Tramullas et al., 2021). A similar study showed that ovariectomy was associated with improvement in anxiety- and depression-like behaviors in rodents, but, again, in a microbiome-dependent manner (Sovijit et al., 2021).

Links between BGMA and health outcomes are not limited to females. Autism spectrum disorders, which have a higher prevalence and unique presentation in males, may depend on sex differences in the BGMA, leading to differential effects of environmental factors on neuroinflammation, though specific mechanisms are still under study (reviewed by Kopec et al., 2018). As elucidation of BGMA-related disease etiology may ultimately lead to uniquely noninvasive interventions and treatments, such as fecal transplants, dietary changes, and pro- or pre-biotic administration, evidence for the role that sex differences might play in the effectiveness of those treatments is a critical research topic.

BGMA regulation of the immune system is a particularly compelling mechanism for sex-related differences in health risks. As reviewed by Rizzetto et al. (2018), the gut microbiota and sex steroids co-regulate immune function, and further research into specific bacterial metabolites that regulate immunity could inform dietary interventions to prevent or treat autoimmune disease. Sex differences in the properties of microglia (reviewed by Kodama and Gan, 2019) could also differentially affect susceptibility to pro- and anti-inflammatory products of the microbiota.

For further reading on the relationship between the BGMA and sex-related health outcomes, we refer readers to Holingue et al. (2020) for a discussion of mental health outcomes and to So and Savidge (2021) for a discussion of IBS.

## 3. Translation from animal to human research: rethinking the measurement of sex and gender

Although there is increasing evidence for a bidirectional relationship between sex, the BGMA, and health outcomes, the majority of studies contributing to this evidence base use animal models. As translation from animal to human models is underway, researchers must be wary of challenges unique to human research. Indeed, in humans, relative to rodent models, sex explains little variance in microbiome characteristics (Jaggar et al., 2020). Approaching sex as a complex variable distinct from gender may be one way to improve the human research in this field, increasing the predictive power of these variables, and lessening the potential for mistranslation.

### 3.1. Sex

Oversimplified approaches to the definition of sex pose a major barrier to cross-species translation of sex differences in the BGMA. In human studies, sex is most commonly defined as chromosomal sex, that is, having XX (female) or XY (male) chromosomes (Miller et al., 2017). However, sex also encompasses levels of sex steroids, which can influence health and behavior beyond the effects of chromosomal sex alone.

Moreover, the development of human primary sex characteristics, namely, reproductive organs, is dependent not only on chromosomes, but also on sex hormones. Further, secondary sex characteristics, such as fat distribution, muscle mass, facial hair, and body hair are dependent on chromosomes, sex hormones, and age. Importantly, sex hormones, primary sex characteristics, and secondary sex characteristics can also be altered by hormone therapies and surgical procedures.

Another issue with the approach to sex in human studies is that it has historically been treated as a binary variable, a practice that remains common today and that can lead to loss of critical information. In fact, it has been estimated that as many as 2% of live births are not captured by this binary comparison and can be considered non-binary or intersex–for example, having sex chromosomes other than XX or XY (e.g., XXY in Klinefelter syndrome), having XX or XY chromosomes but ambiguous genitalia (e.g., congenital adrenal hyperplasia) or having XY chromosomes and a vagina (e.g., some forms of adrenal insensitivity) (Blackless et al., 2000). For comparison, the prevalence of intersex individuals is similar to the prevalence of autism spectrum disorders among 8-year-old children in the United States (Maenner et al., 2020), a condition that routinely makes its way into screening forms for psychology and neuroscience studies that are not specifically aimed at investigating autism. Following this logic, and because 2% of the population is non-trivial, simply ignoring the existence of non-binary sexes, particularly when sex related factors contribute significant variance to the BGMA, is poor scientific practice.

Sex characteristics, especially hormones, also vary naturally among people of the same chromosomal sex due to pubertal status (Breehl and Caban, 2022), older age and menopausal status (Gray et al., 1991; Laughlin et al., 2000), medical procedures, such as hormone replacement therapy or gonadectomy (Hashemi et al., 2018; Laughlin et al., 2000), current pregnancy (O'Leary et al., 1991), past pregnancy (Musey et al., 1987; Schock et al., 2016), or other genetic and environmental factors. Therefore, sex can and should be approached as a variable consisting of multiple dimensions that are not dichotomous, but multicategorical or continuous. Such an approach should, at a minimum, include the significant portion of the population that does not fall into the standard XX and XY categories. This may even help to explain additional variance and lead to more interpretable findings that generalize to a broader population, compared to a traditional approach.

Contributing to the problems caused by a binary approach to sex is the ease and, consequentially, the overwhelming historical frequency of measuring sex via assignment at birth. Assigned sex at birth is determined using external genitalia, recorded on birth certificates, and is most often self-reported by a participant or gleaned from their medical records. However, in BGMA research, there are more informative alternatives. It is true that sex assigned at birth, though imperfect, is usually an adequate proxy for chromosomal sex. But, as reviewed earlier, a large body of research on the relationship between sex and the BGMA has focused on sex hormones in addition to or instead of chromosomal sex. Due to intersex conditions, medical history, age, and other sources of variation, sex hormones and even sex chromosomes differ among individuals self-reporting the same sex assigned at birth. Thus, researchers of the human BGMA should consider directly measuring sex hormone levels when attempting to understand sex differences in the microbiome, or even when attempting to control for the influence of sex on the microbiome. While this may not be feasible for all studies, at least a thorough appreciation for the limited usefulness of the 'assigned sex at birth' variable in the context of the human microbiome is warranted.

### 3.2. Gender

Although sex and gender are distinct constructs, much scientific literature conflates them, with differentiation between sex and gender only recently increasing in popularity as a research practice. According to guidelines published by the American Psychological Association, while sex refers to biological assignment, "gender is a social construct and a social identity" (American Psychological Association, 2019). It is estimated that 0.39% of American adults report a gender identity different from their assigned sex at birth and that this proportion is increasing on a yearly basis, which is hypothesized to be due to decreasing stigma and increased awareness (Meerwijk and Sevelius, 2017). For youth ages 13–17, the proportion is even higher: about 1.4% (Herman et al., 2022). While the association between gender and the BGMA is yet to be researched, given that gender is associated with many features known to affect the microbiome, it is possible that gender may have a unique association, independent of sex, with the BGMA. As such, we argue that failure to measure participants' gender as distinct from their assigned sex at birth in human microbiome studies will lead to loss of relevant information and lessen research progress. Here, we use disordered eating as an example to illustrate the point.

Eating disorders are closely tied to gender. Women and girls consistently report more disordered eating behaviors (e.g., purging, fasting, diet pill use, etc) than boys and men (Beccia et al., 2019; Croll et al., 2002; Hautala et al., 2008; Hoerr et al., 2002; Simone et al., 2022; Striegel-Moore et al., 2009). Additionally, internalized societal body attitudes differ by gender, with women experiencing a drive for thinness and men experiencing a drive for muscularity (Douglas et al., 2019). For heterosexual men, adherence to masculine gender norms is associated with higher levels of muscle dissatisfaction as well as muscularity-based disordered eating behaviors, while adherence to feminine gender norms was associated with those same outcomes in addition to thinness-related disordered eating (Griffiths et al., 2014). Moreover, transgender individuals and individuals with conflicted gender identity report more body dissatisfaction than cisgender individuals and those without conflicted gender identity, respectively (Ålgars et al., 2010; Jones et al., 2016). Additionally, screening tools for eating disorders often include questions about symptoms that are more prevalent in women than in men, or vice versa, leading to under-diagnosis (Gallagher et al., 2021), and lack of knowledge about the presentation of eating disorders in men may lead to a delay in clinical identification of an eating disorder at all (Thapliyal et al., 2018). Furthermore, gendered norms may prompt men to delay seeking care for eating disorders (Räisänen & Hunt, 2014; Thapliyal et al., 2018). For transgender patients, stigma may lead to the delay or avoidance of treatment altogether (Thapliyal et al., 2018). In sum, variance in the presence and manifestation of disordered eating is associated with gender-related social norms, gender-related body dissatisfaction, and gender differences in access to treatment.

While being robustly linked to gender, disordered eating is also bidirectionally related to the BGMA. Dietary changes, such as those associated with disordered eating and eating disorders, can change the microbiota (Seitz et al., 2019), while it is also hypothesized that existing dysfunction in the microbiome may contribute to the development of eating disorders (Inui et al., 2015). For example, Anorexia Nervosa (AN), a psychiatric disorder with both psychological and behavioral components, is associated with differences in the gut microbiome (Butler et al., 2021; Seitz et al., 2019). Studies have found reduced alpha diversity (Kleiman et al., 2015; Mörkl et al., 2019) and higher beta diversity (Kleiman et al., 2015; Mack et al., 2016) within groups of AN patients compared to non-patients; that is, AN patients had microbiomes that were less diverse within person and more dissimilar between person, while non-patients had microbiomes that were more diverse within person and homogenous between person. Moreover, there is evidence to suggest that changes in microbiome in those with AN may be long term and persist even past treatment. Indeed, changes in diet upon treatment, such as refeeding to promote weight restoration, can further affect the microbiome (Seitz et al., 2019). Additionally, it has been proposed that the BGMA exerts an effect on factors such as self-regulatory behaviors, weight regulation, and appetite that are precursors to the development of eating disorders (Himmerich et al., 2019; Inui et al., 2015).

Inflammation, which has been implicated in BGMA dysregulation, has also been implicated in the development of eating disorders, with inflammatory cytokines playing a role in appetite and in weight loss

(Butler et al., 2021). Furthermore, patients with eating disorders have increased risk of autoimmune disease (Raevuori et al., 2014) and inflammatory bowel disease (Ilzarbe et al., 2017). This substantiates an additional, albeit indirect, link between the BGMA and eating disorders.

The differential expressions, screening, diagnosis, and treatment of eating disorders by gender may lead to differences in the effect of disordered eating symptoms on the BGMA. For instance, men or transgender individuals who do not receive timely treatment may struggle with disordered eating symptoms for longer periods of time, thereby worsening effects on the microbiome. Thus, gender is an important covariate or even focal predictor for BGMA researchers, especially researchers who directly study the relationship between the BGMA and eating disorders, and even for those who study the BGMA in populations with high eating disorder prevalence; for example, the prevalence of disordered eating is 13%– 55% among adults with gastrointestinal disorders (Peters et al., 2022) and 2.1%– 20.4% in adolescents

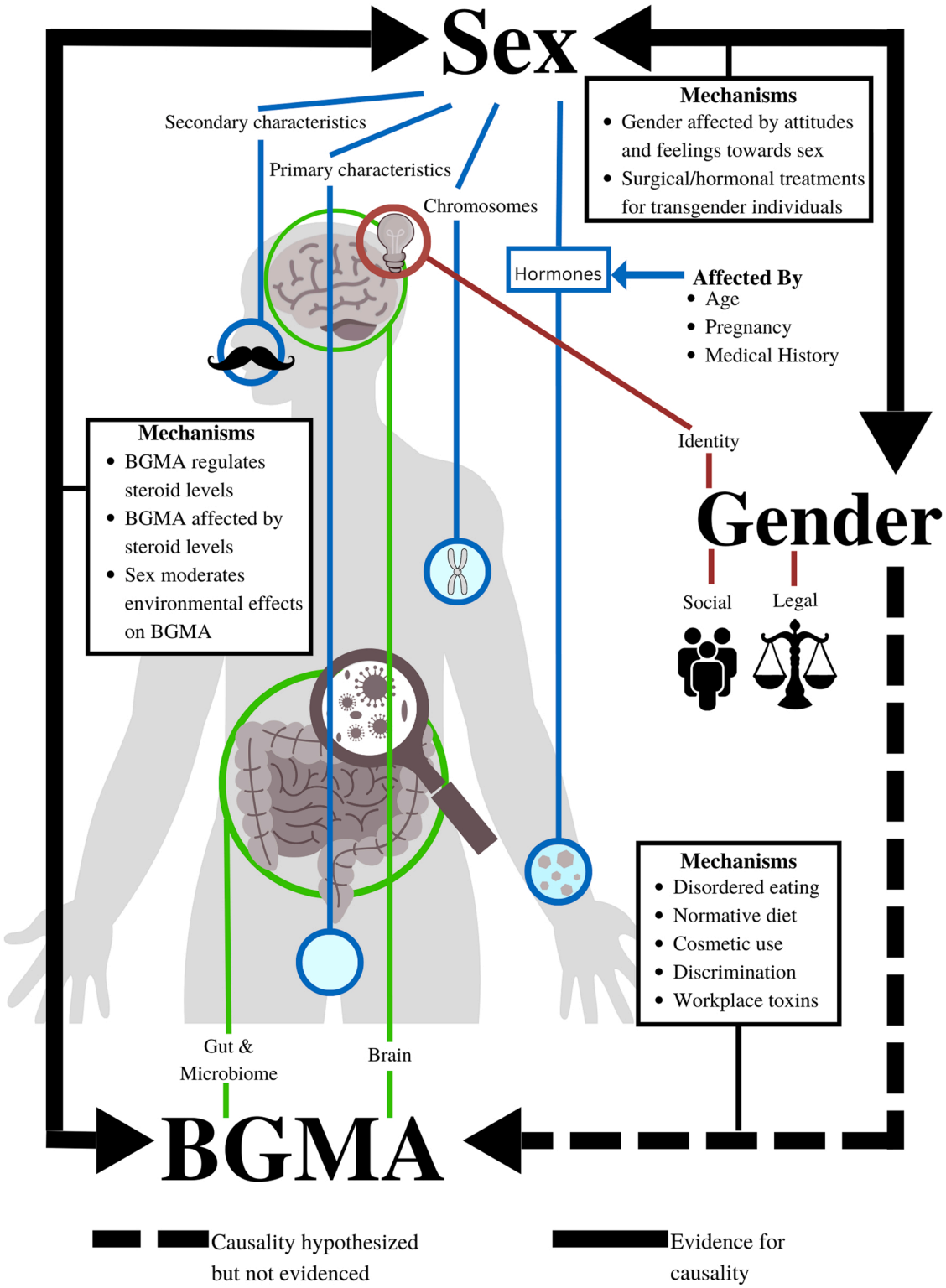


**Fig. 1.** (see attached PDF for image; color should be used in print).

(Neumark-Sztainer et al., 2011).

We have used disordered eating to illustrate a pertinent potential link between gender and the BGMA. However, other, more normative behaviors may also substantiate such a link. For example, non-disordered eating habits, such as the proportion of meat in a diet, are highly motivated by gender norms, such as the association of meat-eating with masculinity, and can affect the microbiome, increasing levels of *Bacteroides* and *Alistepes* (reviewed by Rosenfeld, 2020; Singh et al., 2017). Similarly, women tend to be more knowledgeable about probiotic products and more likely to try them (Al-Nabulsi et al., 2014). Beyond diet, gender norms for cosmetic use may introduce toxins, such as heavy metals, (Zota and Shamasunder, 2017) which could affect the microbiome and alter cellular characteristics such as metal resistance (Tsiaoussis et al., 2019). On the other hand, masculine gender norms may cause men to be exposed to more microbiome-relevant toxins, such as those found in pesticides (Tsiaoussis et al., 2019) in the workplace, where men are more likely to be employed in occupations with elevated exposure to chemical substances, herbicides, et cetera (Eng et al., 2011). Gender-diverse identities (Diamond et al., 2021) and interactions between gender and ethnicity (Cuevas et al., 2020) could affect the BGMA via stress response dysregulation caused by discrimination and social threat. Indeed, self-report of discrimination based on gender or ethnicity has been found to be associated with an increase in inflammation-associated taxa in the gut microbiome (Dong et al., 2022). Furthermore, the manner in which an individual's gender is perceived by healthcare professionals, in interaction with sociocultural norms, can even affect the medication they are prescribed (Samulowitz et al., 2018). For example, women are more likely than men to be prescribed antidepressants (Samulowitz et al., 2018), which have been postulated to have antimicrobial effects in the gut (McGovern et al., 2019). Additionally, there is a possibility for a bidirectional relationship between the BGMA and gender: emerging evidence has suggested that prenatal androgen exposure in humans may affect gender identity or gendered behaviors later in life (Endendijk et al., 2016; Leinung and Wu, 2017; Meyer-Bahlburg et al., 2004; Pasterski et al., 2015), though much of this work has examined androgen level variation specifically due to genetic conditions, and it is not yet evident how the BGMA of the parents or infant could regulate prenatal sex steroid levels. In sum, when researchers of the human BGMA focus on sex alone without measuring participant gender, they may lose such information. This especially applies to researchers interested in variables that are known to be gender-related, including diet, exercise, and workplace environment. (Fig. 1).

Overview of the relationship among sex, gender, and the brain-gut-microbiome axis (BGMA) Aspects of sex include secondary characteristics, primary characteristics, chromosomes, and hormones. Hormones are affected by age, pregnancy, and medical history. Aspects of gender include identity and social and legal factors. The BGMA is comprised of the brain, gut, and microbiome. Sex is bidirectionally related to the BGMA, with evidence for causality, through these mechanisms: the BGMA regulates steroid levels; the BGMA is affected by steroid levels; sex moderates environmental effects on the BGMA. Sex is bidirectionally related to gender, with evidence for causality, through these mechanisms: gender is affected by attitudes and feelings towards sex; surgical and hormonal treatments for transgender individuals affect aspects of sex. Gender may affect the BGMA through the following hypothesized mechanisms: disordered eating; normative diet variation; cosmetic use; discrimination; workplace toxins.

## 4. Recommendations and future directions

### 4.1. Sex

We recommend that researchers of the human BGMA approach sex as a non-dichotomous variable. This could entail measures as simple as adding an *other* option, in addition to *male* and *female*, when asking participants to self-report sex assigned at birth. It also entails careful consideration of which aspect or aspects of sex are relevant to the research question at hand. For example, even when sex steroid levels cannot be measured directly, researchers interested in sex steroid levels can ask participants to self-report history of medical procedures, such as hormone replacement therapy, that can affect hormone levels. Researchers should also attend to variables, such as age, associated with sex steroid hormones. For direct measurements, steroids can be assayed from serum or, less invasively, from urine (Singh et al., 2015) or saliva (Granger et al., 2004; Lewis, 2006).

Some of these measures may not be feasible for all studies. For instance, in studies with a small sample size, it may be necessary to exclude intersex people in order to achieve statistical power. Even in large studies, sex steroid assays may be cost-prohibitive, leading researchers to rely on sex assigned at birth as a proxy. However, these must be understood as limitations. Otherwise, measurement only of sex assigned at birth, limited to male or female, will lead to models that are less able to elucidate mechanisms and less generalizable to populations such as transgender, intersex, pregnant, adolescent, and aging people, whose sex steroid levels may differ from the 'norm'.

### 4.2. Gender

We recommend that researchers record participants' gender separately from and in addition to their sex. We refer readers to Lindqvist et al. (2020) for more detailed guidelines on this practice, including recommendations for continuous dimensional measurement of gender norm endorsement and for measurement of conflict between aspects of gender, such as norms and expression. More commonplace measurement of participant gender will enable increased understanding of ways in which gender, as well as the social norms and psychological identities entailed therein, could exert unique effects on the BGMA. Given the size of the intersex population and that the percentage of transgender individuals is increasing in much of the world, it is critical that more researchers explore this topic. While it is not yet known whether gender, specifically, is a correlate of BGMA characteristics, the cost of recording this variable is negligible, and therefore outweighed by the potential to glean valuable information. Measurement of gender, which can be accomplished by brief participant self-report, is feasible for virtually all studies and should be universally implemented. We further recommend that more research examine the little-explored relationship between gender and the human BGMA.

Additionally, in order to enable others to easily synthesize the relationship between either sex or gender and the BGMA from literature, it is essential that researchers not conflate sex and gender-related terminology in publications and other documents. We refer readers to the American Psychological Association guidelines on bias-free language (American Psychological Association, n.d.).

## 5. Conclusion

A large body of work, mostly on rodent models, has demonstrated that the BGMA is affected by and, in turn, influences sex. This is especially true of sex steroids. Sex steroids are continuously distributed factors that not only vary among individuals self-reporting the same sex, but also are only one of several aspects of sex. Gender refers to social presentation and perception and psychological identity. Though it is not yet known how gender may relate to the BGMA, gender does covary with behaviors that influence the BGMA, and research on the relationship between the BGMA and gender is critically needed. Although researchers have historically reduced sex and gender to a single, dichotomous variable, limited to *male* and *female*, such practice leads to a loss of much of the rich, relevant information that underlies these two complex variables.

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## Declaration of Competing Interest

None of the authors have declared a conflict of interest.

## Data Availability

No data was used for the research described in the article.

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