Gut dysbiosis and age-related neurological diseases in females

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Abstract

Historically, females have been underrepresented in biological research. With increased interest in the gut microbiome and the gut-brain axis, it is important for researchers to pursue studies that consider sex as a biological variable. The composition of the gut microbiome is influenced by environmental factors, disease, diet, and varies with age and by sex. Detrimental changes in the gut microbiome, referred to as dysbiosis, is believed to influence the development and progression of age-related neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and stroke. Many are investigating the changes in microbial populations in order or to better understand the role of the gut immunity and the microbiome in neurodegenerative diseases, many of which the exact etiology remains elusive, and no cures exist. Others are working to find diagnostic markers for earlier detection, or to therapeutically modulate microbial populations using probiotics. However, while all these diseases present in reproductively senescent females, most studies only use male animals for their experimental design. Reproductively senescent females have been shown to have differences in disease progression, inflammatory responses, and microbiota composition, therefore, for research to be translational to affected populations it is necessary for appropriate models to be used. This review discusses factors that influence the gut microbiome and the gut brain axis in females, and highlights studies that have investigated the role of dysbiosis in age-related neurodegenerative disorders that have included females in their study design.

Keywords

Gut-brain axis; Dysbiosis; Microbiome; Sex differences; Neurodegenerative; Age; Alzheimer's disease; Parkinson's disease; Huntington's disease; Stroke

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1.   Introduction

The gut microbiome consists of a diverse and dynamic ecosystem of bacteria, fungi, archaea, viruses, and helminths. Recently, a large number of studies investigating the role of the gut microbiome in pathologies ranging from cancer (Sepich-Poore et al., 2021), inflammatory bowel disease (Ni et al., 2017), mood disorders (Huang et al., 2019), and neurodegenerative diseases (Cryan et al., 2020) have been published. Most research has focused on the bacterial populations, largely due to insights provided by 16S rRNA sequencing. The bacteria found within the gut have been broadly categorized into 11 phyla. The majority of the bacteria (>90%) consist of *Firmicutes, Bacteroidetes*, *Proteobacteria,* and *Actinobacteria* while *Fusobacteria* and *Vermcomicrobia* phyla are present in low abundance (Eckburg et al., 2005; Hugon et al., 2015; Li et al., 2014). Though most of the bacteria have been sequenced and identified, researchers are still in the process of identifying and characterizing new bacterial strains that colonize the gut. The gut microbiota contains a wealth of organisms, some of which generate metabolites that humans cannot produce (Brial et al., 2018; Lavelle and Sokol, 2020). Importantly, characteristic shifts in population ratios at the phyla, genus, and species level between healthy subjects and diseased patients have inspired the pursuit of causative, rather than correlative, research to understand the role of microbes in causing or preventing various diseases. The gut microbiome is especially unique in that it is relatively accessible for modulation, making it an exciting potential therapeutic option for many different diseases. However, the diversity and complexity of the gut microbiome still exceeds our understanding. More studies investigating the impact of various bacterial phyla and species on health outcomes is needed, especially as these relate to factors such as age and sex.

2.   The role of the gut microbiome

The role of microbes is multifaceted, and much of what we know has come from the study of "germ-free" animals. Germ-free animals are model organisms that are born and maintained in sterile environments. In the absence of microbial colonization, they can be compared to specific pathogen free (SPF) animals to determine how the microbiota and its secreted metabolites contribute to homeostatic function and development. Germ-free animals have abnormal immune development with alterations in immune cell populations and behavior (Erny et al., 2015; Erny and Prinz, 2020; Luck et al., 2020), also reviewed in (Kennedy et al., 2018). The gut is the largest immune organ in the body, and its epithelial cells, tight junctions, and mucosa serve as the main point of interaction between the host and the gut microbiota (Chassaing et al., 2016). The gut microbiota can stimulate T cells that aid in host defense against enteric pathogens involving local and systemic inflammation (Haghikia et al., 2015; Ivanov et al., 2008; Maeda et al., 2016; Tan et al., 2016). Diet derived long chain fatty acids interact with gut immune cells and decrease *Prevotellaceae* and *Bacteroidetes* populations, enhancing Th1 and Th17 cell responses and exacerbating inflammatory responses in murine experimental autoimmune encephalitis (EAE) (Haghikia et al., 2015).

Microbes produce unique metabolites that the host cannot. These metabolites have beneficial and detrimental effects in regulating the immune system and can influence development. A

microbially derived metabolite that has garnered considerable interest is Trimethylamine N-oxide (TMAO). TMAO increases in patients with atherosclerotic disease, recently reviewed in (Yang et al., 2019), and is elevated in male and female patients with Alzheimer's disease (Vogt et al., 2018). Alternatively, selective microbial communities are known to produce beneficial products by fermentation. On that note, insoluble fiber, such as inulin, can be digested by gut bacteria to produce short-chain fatty acids (SCFA) such as acetate, butyrate, and valerate. SCFA promote regulatory T cell responses and ameliorate inflammation (Haghikia et al., 2015; Lee et al., 2020). Levels of SCFA butyrate in serum is greater in males than females, which may contribute to variations in Treg abundance (Vemuri et al., 2019). SCFA also influence healthy development in infants (Erny et al., 2015; Yang et al., 2020), and even rescue detrimental neurological effects found in offspring of obese mothers (L et al., 2021). The absence of the SCFA butyrate, due to disruption of bacterial populations or lack of insoluble fiber in diet, can have a causal role in diseases such as hypertension (Ganesh et al., 2018). The composition of species within a single population is the alpha diversity, and it describes the richness (number) and distribution (evenness). Beta diversity compares environmental variables and microbial composition differences between populations. Metrics for beta diversity include Bray-Curtis dissimilarity (compares differences in microbial abundances between two samples at the species level), Jaccard distance (compares the presence or absense of a species between two populations), and UniFrac (unweighted only compares sequence differences, and weighted applies the relative abundance of species with the sequence differences). Alterations and loss of biological diversity in the gut microbiome that are associated with detrimental outcomes are considered "dysbiotic changes." The makeup and diversity of the biome changes in response to pathology, medications, the environment and most importantly diet (Jaggar et al., 2020).

3. Factors that influence the gut microbiome

The gut microbiome is first colonized at the time of birth and reflects the composition of the maternal biome (Nash et al., 2017). Over the first five years of life, the gut microbiome increases in number and diversity, then stabilizes with age (Cheng et al., 2015). Diet is a major modifiable factor that can result in the selection of various microbes that then flourish within the gut. In particular, the western diet, consisting of high fat, high sugar, low fiber foods have been shown to increase the lipopolysaccharide (LPS) producing Gram-negative bacteria (Bailey and Holscher, 2018; Cani et al., 2007). Women who are obese are more likely to have atherosclerotic disease, which is associated with proinflammatory states and gut dysbiosis (Zhai et al., 2019). Increased adipose tissue from obesity can result in an increase in systemic estrogen, which reduces LPS-induced inflammation (Blasco-Baque et al., 2012) and bacteria containing β-glucuronidase, an enzyme that deconjugates estrogens into their active forms, can contribute to an increase in systemic estrogen (Baker et al., 2017). Estrogen has a widespread influence on human physiology, effecting vascular function, inflammatory responses, development of multiple cancers, and also has demonstrated neuroprotective effects in stroke, Alzheimer's, and Parkinson's disease (Deroo and Korach, 2006; Murphy, 2011). Gut microbiome richness and diversity in males and post-menopausal women is directly correlated with the amount of excreted estrogen in urine, and fecal β-glucuronidase levels are inversely related to excreted fecal estrogen levels (Fuhrman

et al., 2014). In fact, some researchers refer to the gut microbiome as an "endocrine organ", due to the productive and tightly integrated role it has with the endocrine system, which may variously influence the development, manifestation and progression of diseases in males and females (Clarke et al., 2014).

The gut microbiome diverges in males and females starting at puberty in humans (Yatsunenko et al., 2012) and in experimental mouse models (Steegenga et al., 2014). These differences are partially attributed to increased estrogens in females and increased androgens in males (Klein and Flanagan, 2016). Many diseases are sexually dimorphic, and a better understanding of alterations in the gut microbiome may reveal potential mechanisms for these differences (Mauvais-Jarvis et al., 2020). However, while most studies have observed sex differences in the gut microbiome, specific microbial population tend to vary widely in clinical populations and their attributed beneficial or detrimental consequences remain undefined (Kim et al., 2020). Two separate studies observed that men have higher levels of *Bacteroidetes* and *Prevotella* than women (Dominianni et al., 2015; Mueller et al., 2006). In contrast, a different study observed a significant decrease in the Bacteroides genus (a member of the Bacteroidetes phylum) in males compared to females (Haro et al., 2016). Differences in geographic distribution, diet, genetics, environment, and health disparities make characterizing universal differences in the gut microbiome based on sex extremely difficult in clinical populations (Kim et al., 2020).

In preclinical studies, where variables such as diet and environment can be controlled, a comparison of males and females from 89 inbred mouse strains demonstrated significant sex differences in the gut microbiome across all strains (Org et al., 2016). Notably, the specific changes in microbial composition differences depended on strain, with no consistent sex dependent trends, suggesting that factors beyond gonadal hormones or sex chromosomes, such as host genetics, influence microbiome composition. To directly assess the role of sex hormones, males and females from three different mouse strains underwent gonadectomy. All strains demonstrated sex differences compared to shams, with sham females presenting with a greater abundance of *Akkermansia*. Interestingly, administration of testosterone in males prevented the gonadectomy associated increase in the family *Ruminococcacea* in all strains. Together, these results reveal that both host genotype and the presence of sex hormones contribute to sex differences in the gut microbiome (Org et al., 2016). Work from our lab has also shown significant changes in acyclic females compared to young females (unpublished). To further investigate the interaction between estrogens and the gut microbiome, researchers modulated the gut microbiome in rats using letrozole induced polycystic ovarian syndrome (Guo et al., 2016). Rats treated with fecal matter transplants FMT from healthy females or with *Lactobacillus* probiotics improved their estrus regularity, decreased androgen biosynthesis, and normalized ovarian morphologies. Additionally, increased *Lactobacilli* correlated with increased estradiol and estrone levels (Guo et al., 2016).

Estrogen levels in post-menopausal women are noted to have a different microbiome composition, specifically an increase in the class *Clostridia*, including the order *Clostridiales* and the family *Ruminococcaceae* and a decrease in the genus *Bacteroides* (Fuhrman et al., 2014). Notably, estrogen levels in males and postmenopausal females correlate with richness

and diversity of the microbiome (Vemuri et al., 2019), further indicating that estrogen, regardless of the host sex, influences the gut microbiome. Estrogen levels increase in the luteal phase and decrease in the follicular phase of the menstrual/estrus cycle, and is at its highest levels during pregnancy. Levels decrease at menopause when estrogen production by the ovaries cease (Fig. 1). Interestingly, there are no reported differences in the gut microbiome during the estrus cycle in female mice (Wallace et al., 2018), and information on alterations in the gut microbiome throughout the human menstrual cycle is sparse. One study found no significant changes in beta diversity between the luteal and follicular phase of the menstrual cycle for 9 women, but they did observe a relative increase in diversity when compared to women taking combined hormonal contraceptives (decreasing estradiol) (Mihajlovic et al., 2021). Premenopausal women have rapidly fluctuating estrogen levels, and no correlation between excreted estrogen levels and gut microbiome diversity or β-glucuronidase levels has been observed (Fuhrman et al., 2014). During pregnancy there is an overall increase in diversity and in *Proteobactena* and *Actinobactena,* (Koren et al., 2012). However, it is not clear if these changes are due to a direct effect of hormones, or secondary to indirect effects on the immune system (Tetel et al., 2018). Studies investigating changes in the gut microbiome through the female lifespan are presented in Table 1. Moreover, rather than defining specific populations of microbes present in females, it is advantageous to understand how the host's immune system interacts with the gut microbiome in females compared to males.

Hormonal effects and sex chromosomal differences (XX vs. XY) contribute to differences in immunity (Ahnstedt and McCullough, 2019). This is due to differential expression of two X chromosomes in females, in addition to influences of estrogen on immune cell behavior and activation of estrogen receptors and estrogen dependent transcription factors (Klein and Flanagan, 2016). Females have increased levels of peripheral T cell proliferation and activation, with more CD4 T cells and IL-1β and Th17 than males (Sankaran-Walters et al., 2013). To elucidate the role of sex chromosomes, the Four Core Genotype model was developed by deleting the *Sry* gene, the mammalian sex determining gene, from the Y chromosome. This model generates XX and XY mice that each have either testes (with Sry, XXM, or XYM) or ovaries (without Sry, XXF, or XYF). This model revealed that the sex chromosomes contribute to increase in infarct size and innate immune response in XXF and XXM aged mice after stroke (McCullough et al., 2016). In addition, the presence of two X chromosomes is linked to increased adiposity and dyslipidemia in mouse models and in XXY men (Zore et al., 2018). The influence of the microbiome on obesity and diabetes has been well documented (Napolitano and Covasa, 2020), but the contribution of sex chromosomes to biome composition and diversity has been less studied. As females age and estrogen levels decrease during reproductive senescence, there is a correlative functional decline in immune function, characterized by a persistent increase in proinflammatory factors (Castelo-Branco and Soveral, 2014). Collectively, accounting for chromosomal and hormonal effects in females is challenging, and often studies only use males in their studies. Furthermore, aging alters the composition of the microbiome accompanied by a decrease in the protective mucosal later of the gut, loss of enteric neurons, and increased gut permeability (Crapser et al., 2016; Jasarevic et al., 2016). Fundamental alterations in the gut

microbiome and sex differences in immune system regulation may contribute to difference in disease susceptibility, progression, response to therapy, and development.

4. The gut brain axis

A notable contribution of the gut microbiome is in the bi-directional communication between the gut and the central nervous system, often referred to as the gut-brain axis. The gut microbiota influences neurological health, and likewise, dysbiotic changes to the gut microbiome occur after neurological injury in what is referred to as the gut-brain axis (Lee et al., 2020; Spychala et al., 2018). Systemic inflammation which weakens gut integrity (Ahnstedt et al., 2020; Blasco et al., 2020), vagus nerve stimulation effecting the parasympathetic system, bacterial translocation, and metabolite production are mechanisms that contribute to dysbiotic changes that exacerbate brain pathology (Fried et al., 2021; Morais et al., 2020) depicted in Fig. 2.

Conversely, interventions at the level of the gut microbiome in pre-clinical models can improve mortality and morbidity after neurological injury (Lee et al., 2020; Spychala et al., 2018). One method of intervention is administration of a probiotic, or a specific bacterial strain demonstrated to have beneficial effects on the host. Most studies have implicated certain bacterial species, or even phyla as being pro-inflammatory or anti-inflammatory. This is an oversimplification, made apparent in studies testing the effects of specific probiotics in disease outcomes. For example, the genus *Lactobacillus* is generally considered to be beneficial and gives rise to numerous probiotics (Reid, 1999). However, this genus is consistently increased in patients with Parkinson's disease and is correlated with worsening cognition and motor symptoms (Hasuike et al., 2020; Hopfner et al., 2017; Mihaila et al., 2018; Petrov et al., 2017). *Akkermansia muciniphila* is often categorized as a commensal member of the gut microbiome that might show beneficial effect in obese patients (Zou and Chen, 2020). However, it also can degrade mucin, an important host defense mechanism to prevent bacterial translocation (Ganesh et al., 2013) and maintenance of gut barrier integrity and is increased in Alzheimer's patients (Nagpal et al., 2019; Syeda et al., 2018), Parkinson's disease (Hertel et al., 2019; Hill-Burns et al., 2017) in both cases, correlating disease progression and dysbiosis.

One of the most direct ways to alter the gut microbiome is through fecal microbiota transplantation (FMT), a process involving the delivery of stool from a healthy donor to a dysbiotic recipient (Kim and Gluck, 2019). This has successfully been used clinically to treat cases of recurrent Clostridium difficile infections. Recently, investigators are exploring the potential of this technique to treat a variety of other disorders, including but not limited to ulcerative colitis, mood disorders, autoimmune diseases, and neurological disorders (Settanni et al., 2021; Vendrik et al., 2020; Vrieze et al., 2012). FMT is a more complex intervention compared to probiotic supplementation, in that it also transfers viruses, fungi, metabolites, and genetic material. While serving as a comprehensive approach to alter the gut microbiome, FMTs can potentially expose the recipient to pathogens undetectable with 16S screening (Bibbò et al., 2020). Furthermore, its diverse composition makes identifying and developing biome targeted therapeutics difficult. This highlights the utility of in

vitro studies to investigate purified FMT components to develop a safer, synthetic FMT alternative.

Probiotics, cultures of beneficial bacteria, have also been proven to be beneficial therapeutics in specific situations (Reid, 1999); however, they cannot be universally applied, as they could potentially add to dysbiotic states. Additionally, sex is another factor to consider in the administration of probiotics (Vemuri et al., 2019). A probiotic cocktail of multiple *Lactobacillus* strains given to mice lowered IL-6, IgG2a and IgA, and increased IL-10 in female and castrated males, but there were no anti-inflammatory changes in gonadally intact males (Mu et al., 2017). Probiotic intervention is an exciting potential therapy for many conditions. However, more work must be done to understand dysbiotic changes in various disease states and in understanding if, and how, differential responses occur in male and female recipients before any meaningful contributions can be made.

5. Age related neurodegenerative disorders

Notable age-related neurodegenerative disorders include dementia (predominantly Alzheimer's, followed by vascular and Lewy body dementia), Parkinson's disease, and Huntington's disease (Mauvais-Jarvis et al., 2020). Stroke is also increasingly common with aging and leads to both acute and chronic disability (Doyle and Buckwalter, 2020). While diverse in their etiology, all these pathologies characteristically affect older individuals. All have been associated with gut dysbiosis (Cryan et al., 2020). Most neurodegenerative disorders occur after reproductive senescence in females, suggesting that female gonadal hormones, such as estrogen, may only play a small role in how the gut microbiota shape sex differences in neurodegenerative diseases. Reproductively senescence females have a microbiota and immunological behavior that is distinct from males and young females (Klein and Flanagan, 2016) and must be treated as a biological variable in study designs.

Historically, clinical research was exclusively performed using males and neglected to account for biological variability inherent to males and females skewed clinical decision making and resulted in increased health risks to women (Mauvais-Jarvis et al., 2020). Despite growing evidence defining sex differences, males are disproportionally overrepresented in gut microbiota studies. Nevertheless, several studies have either directly investigated sex differences, or included both sexes in their study design for investigating the role of the gut microbiome in neurodegenerative diseases. These studies are highlighted below (Tables 2-5).

Alzheimer's Disease (AD) is the most common type of neurodegenerative disease, is more common in women than in men, and is the 6th most common cause of death in the U.S (Alzheimers Dement, 2020). The exact etiology of AD is unknown; however, genetic factors that affect amyloid precursor protein (APP), Presilin-1, 2, and APOε4 have been associated with familial and early onset forms of AD (Jayadev et al., 2010). Diagnosis of AD is primarily clinical, and the disease is characterized by a steady decrease in cognitive function (Nelson et al., 2012). Increased phosphorylated-tau protein and decreased β-amyloid proteins (Aβ1–42) in the cerebrospinal fluid of AD patients are useful biomarkers. Brains of AD patients have cerebral atrophy in the hippocampus,

parahippocampus, axonal degeneration, and neuronal loss, notably in cholinergic neurons in the nucleus basalis of Meynert. Increasing "senile plaques", a term used to describe the extracellular deposition of β-amyloid protein, in the cortex and neurofibrillary tangles from the intracellular accumulation of tau protein are hallmarks of the disease. Cerebral amyloid can also deposit in the media and adventitia of small and medium vessels in the brain and leptomeninges, increasing the risk of hemorrhage and vascular disease (Alzheimers Dement, 2020).

Several murine models are used to model AD in the laboratory. Male and female mice differ in both biome composition throughout disease progression and in amyloid deposition during aging, with females having a higher Aβ burden (Carranza-Naval et al., 2021; Wang et al., 2003). These differences are strain dependent, with FAD mice showing sex differences in microbiota α-diversity (Maldonado Weng et al., 2019; Parikh et al., 2020). Female APP^{ps1} mice had a decreased *Ruminococcaceae* which correlated with cognitive deficits, and increased butyrate levels in females positively associated with better working- and object recognition-memory compared to males (Cuervo-Zanatta et al., 2021). Gut dysbiosis, characterized by changes in Lactobacillus and Ruminococcus, precedes accumulation of Aβ in male and female Tg2576 mice (Honarpisheh et al., 2020). Male and female germ-free APP^{ps1} mice both demonstrated an increase in plaque formation and decreased cognitive function after gut colonization with SPF APP^{ps1} mice (Colombo et al., 2021), a finding that was further supported by decreasing plaque formation by depleting the gut microbiome with long term antibiotic treatment in male and female APP^{SWE}/PS1 ^{E9} mice (Minter et al., 2016). Human gut microbiome studies have attempted to control for sex differences by balancing male and female patients to explore the role of the gut microbiota and gut integrity in the development of AD, particularly in the formation of senile plaques (see Table 2a). Additionally, researchers are exploring potential biological markers that may serve as a way to diagnose AD early, and while promising results have been found (Table 2b) more work is required to validate them. A summary of microbiome-based treatments that are being explored in an effort to develop disease modifying interventions are summarized in Table 2c. The complex interactions between the host and the microbiome also can contribute to disease phenotype, as highlighted in Table 2d.

Parkinson's Disease (PD) involves the progressive depletion of dopaminergic neurons within the basal ganglia, specifically in the substantia nigra. The age of onset is typically 60 years, and most cases are idiopathic, with only 10–15% of cases attributed to genetic risk factors (mutations in α-synuclein, glucocerebrosidase, LRRK2, and PARK2) (Kalia and Lang, 2015; Pringsheim et al., 2014). Other risk factors for PD include environmental exposures, diet/metabolic factors (low levels of vitamin D, high iron intake, and obesity), and/or a history of traumatic brain injury. Early symptoms present as constipation, anosmia, sleep disturbance, and mood disorders such as depression, apathy, and anxiety. Eventually, this progresses to PD's hallmark motor symptoms of bradykinesia, resting tremor, rigidity, and postural instability (Kalia and Lang, 2015). Variations in PD include multiple system atrophy, which is characterized by degermation of the substantia nigra, striatum, cerebellum, inferior olivary nuclei, and/or ventromedial column of the spinal cord. Onset is ~60 years and is divided into a Parkinson form (MSA-P) and the olivopontocerebellar (MSA-C)

variant, both of which have unknown etiology (Deutschländer et al., 2018). Progressive supranuclear palsy (PSP) is another variant of PD in which atrophy of structures in the midbrain-diencephalic junction and cerebellum, as well as mid-cortical atrophy. The age of onset is also 60–80 years old. However, PSP progresses more rapidly than the other PD variants, and is often fatal within 5–10 years of onset (Deutschländer et al., 2018).

PD is the second most common neurodegenerative disease and has a 1.4–3.7 times higher incidence in males than females (Abraham et al., 2019; Cerri et al., 2019). The exact cause of the difference in incidence is not fully understood; however, there is evidence that estrogen has neuroprotective activity on dopaminergic neurons (Lee et al., 2019). The importance of estrogen in the development of PD is further supported by the increased risk of PD in females who have undergone oophorectomies before menopause (Canonico et al., 2021; Cereda et al., 2013; Rocca et al., 2008). As previously discussed, the gut microbiome can influence estrogen levels through mechanism such as β-glucuronidase levels (Baker et al., 2017). However, estrogen levels are just one of the many potential mechanisms for how the gut microbiome can influence PD development.

Gut dysbiosis promotes α-synuclein mediated motor dysfunction and enhances PD progression (Sampson et al., 2016). One study by Sampson et al. found that gut bacteria *E. coli* can produce an amyloid protein called "curli" which enhances α-synuclein pathologic changes and behavior abnormalities in mice. They determined that microbiota derived amyloid has a causative role in PD development, as monocolonization by curli producing bacteria exacerbated neurological injury which could then be alleviated with administration of a gut specific amyloid inhibitor (Sampson et al., 2020). Most clinical studies control for sex and do not pursue investigations on sex differences. There are extensive human clinical studies characterizing gut microbiome changes using 16S rRNA sequencing and its correlation with clinical presentation of motor symptoms(Table 3a). Two consistent trends in PD dysbiosis were a decrease in *Lachnospiraceae* and increased *Lactobacillaceae* (Barichella et al., 2019; Hasuike et al., 2020; Hill-Burns et al., 2017; Hopfner et al., 2017; Mihaila et al., 2018; Petrov et al., 2017; Pietrucci et al., 2019). Studies have also examined Multiple System Atrophy (MSA) and followed these patients longitudinally to assess stability/progression over time and associated pharmacological effects on the biome. Additionally, studies have investigated the role of microbial derived metabolites, such as reduced levels of SCFAs and SCFA producers (Hill-Burns et al., 2017; Tan et al., 2021), as well as the influence of the gut microbiome on other metabolic processes, such a bile acids (Li et al., 2021) and tryptophan metabolism (Cassani et al., 2015), in Parkinson's patients (Table 3b). Many of these studies have been used as the foundation of interventions at the level of the gut microbiome, by means of probiotics, prebiotics, and fecal matter transplants (Table 3c). The microbiome has been used as a potential source for biomarkers for PD that can been screened for early detection (Table 3d). Finally, the role of gut inflammation and gastrointestinal (GI) symptoms such as constipation as correlating with PD development and disease severity in both males and females (Table 3e). Unfortunately, most murine studies resulting from Pubmed searches were only performed in male mice, and so were excluded from this review. Of the animal models used to study PD, rhesus monkeys treated with MPTP are the gold standard. One study used a cohort of 5 rhesus monkeys and found males were more susceptible to PD development, and had an increased ratio of *Firmicutes* to

Bacteroidetes (Joers et al., 2020). While these results are from a small cohort, it highlights potential sex-based variations that are under investigated in human populations.

Huntington's Disease (HD) is a genetic neurodegenerative disease, resulting from CAG repeats in the Huntingtin gene on chromosome 4. Age of onset is typically ~40 years; however, due to genetic anticipation, it presents earlier in each successive generation (Walker, 2007). Less research on the microbiome is done in HD, given its heritable mechanism; however, in recent years studies have investigated the role that the gut microbiome may play in the progression of the disease. While Huntington's disease primarily manifests with brain pathology, HD is a systemic disease and mutant Huntingtin is expressed throughout the body, including the gut. Dysbiotic changes, characterized by an increase in diversity in males only (Kong et al., 2020; Wasser et al., 2020) as well as microbial derived metabolite changes both correlate with HD progression (Rosas et al., 2015). This research is new, and more is needed as gut microbiota studies in HD serve to both expand our understanding of host-microbiome interactions and may also provide more insights into understanding early and systemic presentations of HD (Table 4).

Stroke is the 5th cause of death in the United States (Virani et al., 2020). Unlike the aforementioned diseases, there are many known modifiable risk factors for stroke prevention. Risk factors such as obesity and atherosclerotic disease also are strongly influenced by the gut microbiome in women (Haro et al., 2016). Female reproductive senescence is associated with poorer outcomes after stroke when compared to pre-menopausal women and in animal models (Haast et al., 2012; Manwani et al., 2013; Park et al., 2020). The mechanism for these differences in recovery are not fully understood; however, the gut microbiome may contribute. Reproductively senescent female Sprague-Dawley rats showed baseline elevation in Firmicutes/Bacteroidetes (F:B), decreased α-diversity, and significant shifts in β-diversity which worsened after stroke as compared to younger female adult rats (Park et al., 2020). This study also performed a fecal matter transplant between ovariectomized females, with and without estrogen supplementation, and intact females. Adult and middle-aged, estrogen-treated, ovariectomized (OVX + E) females had increased *Prevotella* and *Lactobacillus,* with decreased SFCA and increased LPS levels. This indicates that the gut biome and microbial metabolites are affected by estrogen. Most importantly, when the middle aged, reproductively senescent rat's dysbiotic biome was transplanted by an adult OVX + E female, there was a significant improvement in infarct volume and behavioral outcomes. The importance of examining the role of the biome is further supported by increased mortality after stroke in female mice with antibiotic depleted microbiome (Winek et al., 2016); however this study was only conducted in females, and so it cannot be determined if this was a sex specific effect. Studies evaluating interventions at the level of the gut microbiome for stroke are detailed in Table 5a. Gut dysbiosis after stroke is often investigated in parallel to gut functional changes (Table 5b) and worsening gut function is useful in determining the role of gut inflammation in gut microbiota-brain communications (Ahnstedt et al., 2020; Li et al., 2019; Roth et al., 2020; Stanley et al., 2016). Once a stroke has occurred, there is an increase in gut permeability and decreased mucin production (Crapser et al., 2016). Furthermore, gut and microbiome disruptions lead to changes in microbiota diversity and metabolite production (Table 5c). Microbially derived

TMAO negatively impacts the outcomes of atherosclerotic diseases, such as stroke (Jones et al., 2020a). Collectively the baseline microbiome diversity, immunity, and gut function in reproductively senescent females results in increased mortality and morbidity after stroke when compared to non-senescent females. In addition to susceptibility and incidence, there are sex differences in post stroke recovery, with aged males fairing worse than aged females as measured by mortality and hemorrhagic conversion two weeks after an induced stroke (Ahnstedt et al., 2020). These changes were associated with more persistent changes in gut integrity, microbiome composition, and inflammation in males. However, studies specifically investigating sex differences in clinical populations have not yet included the examination of human gut microbiome. Therefore, more work should be done to determine if female dysbiosis influences stoke incidence and outcomes in humans.

5.1. Future directions

The gut microbiome is a major factor in both the development and progression of neurological diseases, and its effects and interactions with the immune system differs in a sex specific manner. The potential to develop new treatments for these age-related neurological disorders, many of which have no cure, by targeting the microbiome is an area of active investigation. While this literature review focused primarily on post-menopausal females, the impact of the gut microbiome begins long before senescence. The gut microbiome also has effects that are transmitted from mother to fetus and has the ability to impart transgenerational effects (Gohir et al., 2014). Understanding the effects of the gut microbiome in the mother can lead to a better appreciation of the risk for neurological disability and stroke predisposition in offspring. By improving our awareness of the effects of the gut microbiome in females, we may better predict, prevent, and treat various neurodegenerative diseases in aged women, as well as in young women who will give rise to the next generation.

Acknowledgements

Figures created in Biorender.com

Abbreviations:

AD	Alzheimer's disease
EAE	Experimental autoimmune encephalomyelitis
PD	Parkinson's disease
HD	Huntington's disease

MCI	Stroke, Mild cognitive impairment
SPF	Specific Pathogen Free
SCFA	Short chain fatty acids
TMAO	Trimethylamine N-oxide
APP	Amyloid precursor protein
MSA	Multiple System Atrophy
PSP	Progressive supranuclear palsy

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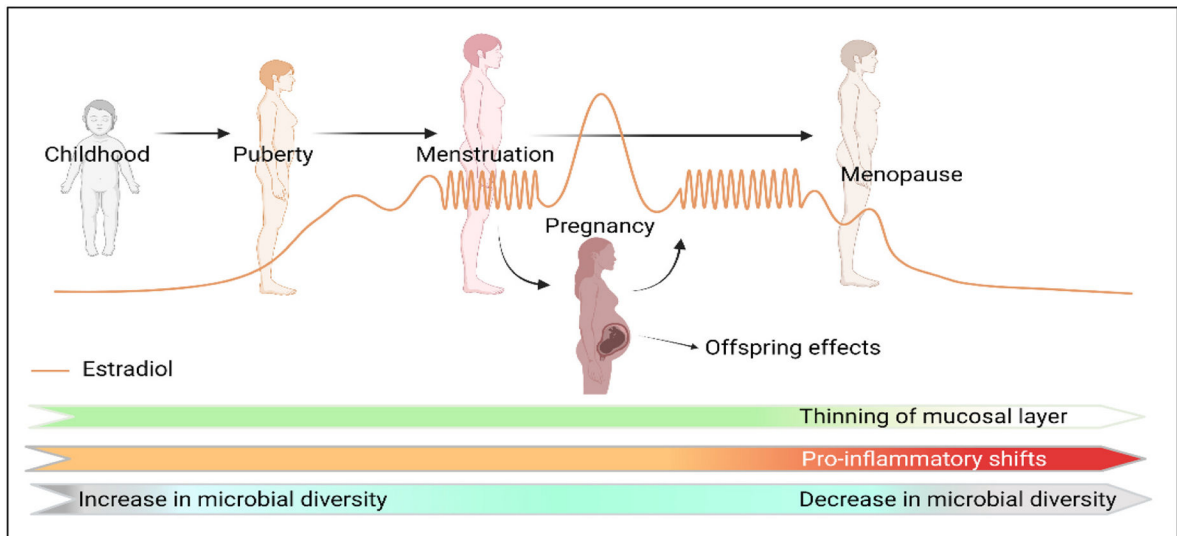**Fig. 1.**
Graphical depiction of change in estradiol levels, gut integrity and biome over the lifespan on females.
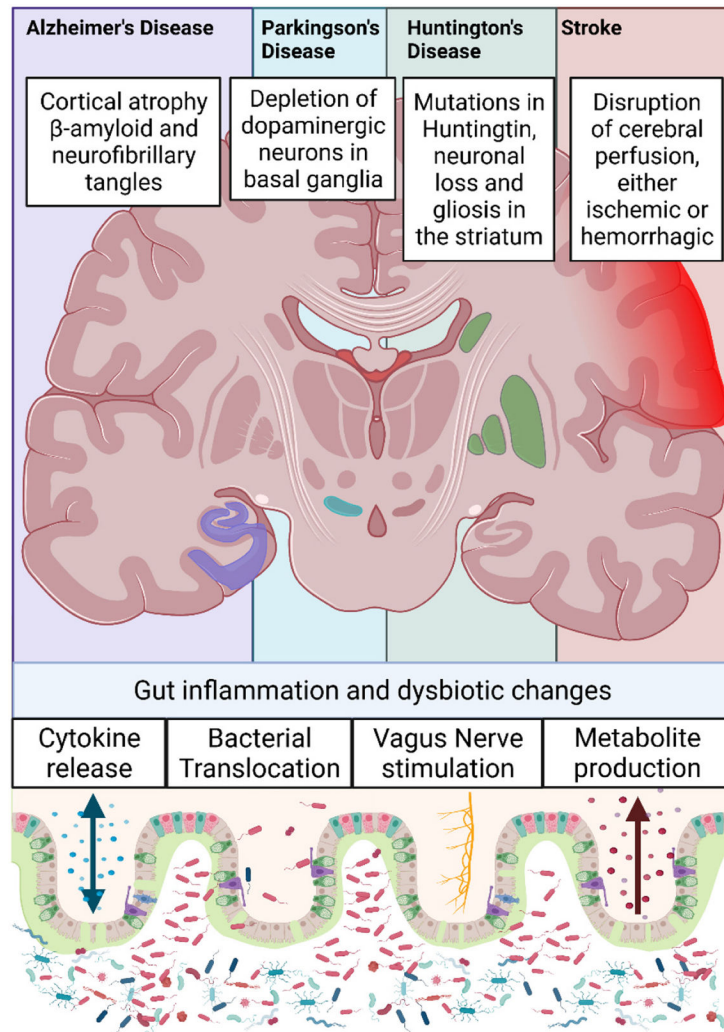
Fig. 2.
Graphical depiction of the microbiota-gut-brain axis in the context of neurodegenerative diseases.

Table 1

Gut microbiome studies throughout the female lifespan.

Pre-pubertal	Pre-menopausal		Post-Menopausal
	Menstruation	Pregnancy	
Microbiota changes at puberty in mice (Steegenga et al., 2014)	Estrus cycle show no biome changes in changes in mice (Wallace et al., 2018)	Alterations during pregnancy in humans (Koren et al., 2012)	Changes in microbiota diversity in postmenopausal women (Fuhrman et al., 2014)
Sex differences and microbiota changes at puberty in humans (Yuan et al., 2020)	Follicular and luteal phase microbiota composition, and hormonal contraceptive effects in humans (Mihajlovic et al., 2021)	Microbiota changes in preeclampsia and abnormal placenta growth in humans (Huang et al., 2021)	
Pediatric gut microbiome (Hollister et al., 2015)	Irregular estrus cycle and gut microbiota changes in rats (Guo et al., 2016)		

Table 2a

Literature review of Alzheimer's disease and gut microbiome in females.

Key effect	Proposed mechanism	Bacteria	Model	Sex	References
Observational Gut Microbiome Alterations					
APOE-associated differences present in male/female EFAD mice Sex differences in E3FAD and E4FAD		↑*Prevotella* and *Ruminococcus* in Female E4FAD vs Female E3FAD ↑*Sutterella* in Male E4FAD vs Male E3FAD	E3FAD and E4FAD mice	F/M	(Maldonado Weng et al., 2019)
α-diversity ↔ w/APOE, 5xFAD status and sex,β -diversity associated with APOE genotype, not sex or 5xFAD status	APOE genotype		FAD mice	F/M	(Parikh et al., 2020)
Direct impact on brain amyloid-β pathology in males, but not in females	↓ Butyrate in Female	↓*Ruminococcaceae* in Female	APP^{PS1} mice	M/F	(Cuervo-Zanatta et al., 2021)
Cognitive decline(M > F), working and object recognition memory Cognitive advantage of females was lost in APP^{PS1}					
↓Density of small plaques	Bacterial colonization ↑ plaque formation SCFA ↑ plaque formation	Germ-free	Germ-free APP^{PS1} mice	F/M	(Colombo et al., 2021)
↑Amyloid deposition ↓Cognitive function	MAPK pathway	↑*Bacteroides acidifaciens*, ↑SCFA producers	APP^{swe}/PS1 ^{E9} (PAP) mice	F	(Li et al., 2020)
Correlation with disease progression	Divergence of biome began at 6 months	↔→*Bacteroidetes*, ↑*Proteobacteria* (*sutterella*) (*Betaproteobacteria*), *Erysipeotrichaceae* family	APP/PSS1 (TG) and C57BL/6 mice	F	(Bäuerl et al., 2018)
APOE genotype has specific gut microbiome profiles in both humans and APOE-TR mice.		↑*Prevotellaceae, Ruminococcaceae* and several butyrate-producing genera w/APOE genotypes	Human, APOE-targeted replacement (TR) mice	F/M	(Tran et al., 2019)
↓Microbial diversity in AD		↓*Firmicutes*, ↑*Bacteroidetes*, and ↓*Bifidobacterium* in AD	25 AD, 25 Control	F/M	(Vogt et al., 2017)
↑TMAO in CSF of individuals with MCI and AD dementia	CSF TMAO are associated with CSF biomarkers of AD pathology and neuronal degeneration	Gut microbiota-derived metabolite TMAO	40 AD 35 MCI 335 cognitively-unimpaired individuals	F/M	(Vogt et al., 2018)
↑Peripheral inflammatory state ↑Brain amyloidosis ↑Cognitive impairment		↑*Escherichia/Shigella*, ↓ *Eubacterium rectale*	CI with and with no brain amyloidosis (n = 33, Amy−) (n = 40, Amy+) 10 controls	F/M	(Cattaneo et al., 2017)
↓Butyrate synthesizers ↑Proinflammatory taxa in AD	P-glycoprotein pathway	↑*Bacteroides, Alistipes, Odoribacter, Barnesiella*↓*Lachnoclostridium* in AD ↑*Odoribacter,Barnesiella*↓*Eubacterium, Roseburia Lachnoclostridium*, and *Collinsella* in other dementia types	Human fecal prospective cohort study, T84 intestinal epithelial cells	F/M	(Haran et al., 2019)
	Aluminum sulfate significantly induces the generation of BF-LPS	*Bacteroides fragilis* generates pro-inflammatory glycolipid lipopolysaccharide (BF-LPS)	*B. fragilis* (*B. fragilis*, ATCC 23745	–	(Alexandrov et al., 2020)

Table 2b

Literature review of Alzheimer's disease and gut microbiome in females.

Key effect	Proposed mechanism	Bacteria	Model	Sex	References
Therapeutics					
Antibiotics ↓Aβ plaque deposition, attenuated plaque-localized glial reactivity, and significantly altered microglial morphology	↑ Soluble Aβ	Prolonged shifts in gut microbial composition and diversity induced by long-term broad-spectrum combinatorial antibiotic treatment	APP^{SWE}/PS1 ^{E9} mice	F/M	(Minter et al., 2016)
Brain pathology ↑w/ gut inflammation/leakiness	VSL#3 * Altered levels of bile acids and prostaglandins in the serum and brain		AppNL-G-F mice	F	(Kaur et al., 2020)
Probiotics ↓intestinal inflammation/ leakiness, ↔ amyloid-β, cytokine, or gliosis in the brain.					
Lactobacillus sakei Probio 65 and Lactobacillus paracasei 0291 alleviated eye neurodegeneration	Probiotic treatment **	↓ Wolbachia ↑ Stenotrophomonas, Acetobacter	GMR-OreR (Control) GMR-Aβ42 Drosophila	F/M	(Liu et al., 2020)
↓Cognitive decline	Long-term calorie restriction	↓ Bacteroides	Tg2576 mice	F	(Cox et al., 2019)
↓ Aβ aggregates, tau hyperphosphorylation, ↓MDA levels, astrocyte and microglial activation, PSD-95, synaptophysin, GluR1 and ARC protein levels, and ↑levels of pGSK-3. ↑ cognition	Fed BF *** for 7 months	↑Prevotella copri, Lactobacillus ruminis, Streptococcus anginosus, Actinobacillus parahaemolyticus, and Haemophilus parainfluenzae vs WT. BF ↓these abundances and ↑Bacteroides uniformis, Faecalibacterium prausnitzii, and Akkermansia miciniphila	3xTg-AD (TG) mice	F	(Syeda et al., 2018)
MMKD **** modulates the gut microbiome and metabolites in association with improved AD biomarkers in CSF.	MMKD and AHAD **** intervention for 6-weeks	↑ Enterobacteriaceae, Akkermansia, Slackia, Christensenellaceae and Erysipelotriaceae ↓Bifidobacterium and Lachnobacterium in MMKD, ↑Mollicutes with AHAD	11 MCI 6 Control	F/M	(Nagpal et al., 2019)
Specific gut microbial signatures may depict the mild cognitive impairment					
No significant changes		F. prausnitzii	20 AD outpatients	F/M	(Leblhuber et al., 2018)

* = f8 strains of lactic acid-producing bacteria: L. plantarum, Lactobacillus delbrueckii subsp. Bulgaricus, L. paracasei, Lactobacillus acidophilus, Bifidobacterium breve, Bifidobacterium longum, B. infantis, and Streptococcus salivarius subsp. Thermophilus.

** = seven different LAB strains (L. paracasei 0291, Lactobacillus helveticus 1515, Lactobacillus reuteri CDV, L. reuteri 8513d, Lactobacillus fermentum 8312, Lactobacillus casei Y, L. sakei Probio65).

*** = a combination of dried nopal, soy, chia oil, and turmeric.

**** = MMKD (Mediterranean-style ketogenic diet) and AHAD (American Heart Association Diet).

Table 2c

Literature review of Alzheimer's disease and gut microbiome in females.

Key effect	Proposed mechanism	Bacteria	Model	Sex	References
Diagnostic Markers					
Actinobacteria concentrations		↓Relative abundances of *Actinetobarteria* and TM7 in 3xTg-AD	3xTg-AD mice	F	(Bello-Medina et al., 2021)
miRNAs are regulators in bacterial pathways relevant to AD or PD.	miRNAs	*Ruminococcaceae*	Human meta-analysis	F/M	(Hewel et al., 2019)
Serum-based bile acid metabolites			1562 AD, meta-analysis	F/M	(Nho et al., 2019)
↑White matter hyperintensity and cortical and hippocampal atrophy		↑*Bacteroides* associated with MCI in patients without dementia	82 patients, cross sectional	F/M	(Saji et al., 2019)
Microbiome associated w/ AD compared with pre-onset stage amnestic mild cognitive impairment (aMCI) and healthy subjects. Correlation between the severity scores of AD and the abundance of altered microbes		↓ *Firmicutes* ↑ *Proteobacteria* in AD ↑*Gammaproteobacteria Enterobacteriales*, *Enterobacteriaceae* in aMCI and AD	33 AD 32 aMCI 32 controls	F/M	(Liu et al., 2019)

Table 2d

Literature review of Alzheimer's disease and gut microbiome in females.

Key effect	Proposed mechanism	Bacteria	Model	Sex	References
Gut health and contributing factors					
↓Serum primary BA (cholic acid CA) and ↑ secondary BA, deoxycholic acid (DCA) ↑Ratio of DCA:CA, which reflects 7α–dehydroxylation of CA by gut bacteria, strongly associated with ↓cognition	Bile acid levels		370 control, 284 early MCI, 505 late MCI, 305 AD	F/M	(MahmoudianDehkordi et al., 2019)
Gut inflammation ↑ Aβ deposition in the intestine ↑ IL-9, VEGF and IP-10.	Gut dysfunction	↓*Ruminiclostridium* (early) ↑ *Lactobacillus* (late)	Tg2576 mice	F/M	(Honarpisheh et al., 2020)
↓Butyrate and IL-10 Endothelial dysfunction ↑ with pro-inflammatory cytokines, acetate and valerate and ↓ with butyrate and IL10 levels	Endothelial dysfunction		89 AD patients, PET and blood collection	F/M	(Marizzoni et al., 2020)
AD patients had higher CLEC-2 and zonulin levels compared with MCI patients. In addition, CLEC-2 levels ↑ w/ zonulin levels ↑ CLEC-2 and zonulin ↓ w/ (MMSE) score.	CLEC-2 and zonulin levels		110 AD, 110 MCI, 110 control	F/M	(Wang et al., 2020)
IBS ↑risk of dementia in 50 years old.	Inflammatory bowel		IBS patients	F/M	(Chen et al., 2016)

Table 3a

Literature review of Parkinson's Disease and gut microbiome in females.

Key findings	Study type	Model	Sex	References
Observational Gut-Microbiome Alterations				
MPTP[*] administration has a greater effect in males than females with ↓ *Firmicutes*, ↓*Firmicutes* to *Bacteroidetes* ratio, and ↑ *Verrucomicrobia*		5 rhesus monkeys (*Macaca mulatta*, 5–7 yrs. of age, 3 females, 2 males)	F/M	(Joers et al., 2020)
↑ opportunistic[**] oral pathogens were detected in males, both with and without PD. ↔nasal microbiota PD patients		PD patients (oral: *n* = 72, nasal: *n* = 69) control (oral: *n* = 76, nasal: *n* = 67)	F/M	(Pereira et al., 2017)
↓*Lachnospiraceae* family in **PD** ↓*Prevotellaceae* ↑*Verrucomicrobia, Lactobacillaceae, Verrucomicrobiaceae* in **MSA** ↓*Lachnospiraceae, Streptococcaceae,*and ↑*Verrucomicrobia, Christensenellaceae, Verrucomicrobiaceae* in **PSP**	Observational	PD (*n* = 193, 39 drug naïve) PSP (*n* = 22), MSA (n = 22), HC (*n* = 113)	F/M	(Barichella et al., 2019)
↓ *Clostridium coccoides, C. leptum*, and *Bacteroides fragilis* ↑ Lactobacillus ↓ antiparkinsonian drug dosage, serum TG and bilirubin levels in Small intestinal overgrowth (SIBO+) patients ↔caloric intake	Prospective investigation	39 PD 19 SIBO+, 16 SIBO–, 4 equivocal	F/M	(Hasuike et al., 2020)
Differentially abundant gut microbes (*Akkermansia*) and no differences in nasal microbiota in PD 80% of differential gut microbes in PD versus healthy controls showed similar trends in idiopathic rapid eye movement sleep behavior disorder (*Anaerotruncus* and several *Bacteroides spp.*, and correlated with nonmotor symptoms)		Stool and nasal wash from 76 PD, 21 idiopathic rapid eye movement (REM) sleep behavior disorder patients, 78 controls	F/M	(Heintz-Buschart et al., 2018)
↑ *Lactobacillaceae, Barnesiellaceae* and *Enterococcacea* with PD		29 PD, 29 age-matched controls	F/M	(Hopfher et al., 2017)
Different abundances of *Lactobacillus, Gordonibacter, Phascolarctobacterium*, and *Haemophilus* in feces and of *Leucobacter*, and *Bacteroides* in blood between MSA patients and healthy controls (HC). ↓ *Phascolarctobacterium, Ruminococcus* in MSA-P than those in MSA-C *Blastococcus, Bacillus*, and *Acinetobacter* in blood were different between MSA subtypes. The differential genera were associated with disease duration, anxiety, and autonomic dysfunction		40 MSA patients (23 MSA-P, 17 MSA-C) and spouses (HC)	F/M	(Du et al., 2019)
↑*Akkermansia muciniphila* and *Bilophila wadsworthia* drive PD-specific patterns in microbial-host sulfur co-metabolism that may contribute to PD severity	Longitudinal de novo Parkinson's disease (DeNoPa)	PD and healthy controls	F/M	(Hertel et al., 2019)
↑*Akkermansia*, ↓ *Megamonas, Bifidobacterium, Blautia*, and *Aggregatibacter* in MSA		15 MSA 15 controls	F/M	(Wan et al., 2019)
↓ *Tenericutes, Euryarchaeota, Firmicutes* ↓*Lachnospiraceae* in PD ↑ *Rikenellaceae, Deferribacteraceae* ↓*Phytobacterium* in PD for more than five years. ↔ *Ruminococcaceae* ↔α- and β-diversity not significantly different between early and late PD onset		75 patients with PD and 45 age-matched controls	F/M	(Lin et al., 2018)
Significant changes in a set of 9 host miRNAs, correlating with some of the significantly changed microbial taxa. Robust correlations between many microbiota and cognition, balance, and disease duration ↑*Bifidobacteriaceae* and *Lactobacillaceae*		Saliva of 8 PD subjects and 36 healthy controls	F/M	(Mihaila et al., 2018)
↓*Dorea, Bacteroides, Prevotella, Faecalibacterium, Bacteroides massiliensis, Stoquefichus massiliensis, Bacteroides coprocola, Blautia glucerasea, Dorea longicatena, Bacteroides dorei, Bacteroides plebeus, Prevotella copri, Coprococcus eutactus*, and *Ruminococcus callidus* ↑ *Christensenella, Catabacter, Lactobacillus, Oscillospira, Bifidobacterium, Christensenella minuta, Catabacter hongkongensis, Lactobacillus mucosae, Ruminococcus bromii*, and *Papillibacter cinnamivorans*.		89 PD 66 controls (patients w/out severe somatic pathology w/parkinsonism)	F/M	(Petrov et al., 2017)
↑*Clostridium IV, Aquabacterium, Holdemania, Sphingomonas, Clostridium XVIII, Butyricicoccus* and *Anaerotruncus*		Feces of 45 patients and their healthy spouses	F/M	(Qian et al., 2018)

Key findings	Study type	Model	Sex	References
↓*Escherichia/Shigella* correlates w/ ↑disease duration. ↓*Dorea and Phascolarctobacterium* correlates w/ ↑levodopa equivalent doses (LED). ↑ *Butyricicoccus* and *Clostridium XIVb* correlates w/ ↓ cognition				
↑*Lactobacillus, Akkermansia*, and *Bifidobacterium* ↓*Lachnospiraceae* family and the Faecalibacterium genus, most consistent PD gut microbiome alterations	Meta-analysis re-analyzing 16S microbiome datasets	23 studies on microbiome of PD using metagenomics		(Romano et al., 2021)

*=
1-Methy-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) is a potent neurotoxin extensively used to model Parkinson's disease (PD).

**=
Lactobacillus, Capnocytophaga, Leptotrichia, Veillonella, Aggregatibacter, Porphyromonas, and Prevotella.

Table 3b

Literature review of Parkinson's disease and gut microbiome in females.

Key findings	Study type	Model	Sex	References
Gut-Microbiome derived metabolite differences				
↓ N-acyl-phosphatidylethanolamines (NAPEs) in plasma of PD patients, with sex-specific profiles		319 controls; 268 PD, mouse strain undisclosed	F/M/M	(Hamid et al., 2019)
Urinary indican ↑ in PD and DPD (tryptophan metabolism is characteristically impaired in PD patients, with a significant reduction in its metabolites)	Case-control study	Urine 68 PD with levodopa (PD) 34 de novo PD (DPD) 50 control	F/M	(Cassani et al., 2015)
↓SCFAs ↓cognition and low BMI. ↓ butyrate ↓postural instability–gait disorder scores. ↑*Akkermansia*, *Bifidobacterium*, *Lactobacillus*, *Clostridium saccharolyticum*, *Veillonella*, and *Coriobacteriia*		Stool from 104 PD and 96 controls	F/M	(Tan et al., 2021)
↑*Akkermansia*, *Lactobacillus*, and *Bifidobacterium* and ↓*Lachnospiraceae* in PD, consistent with SCFA depletion		197 PD and 130 controls	F/M	(Hill-Burns et al., 2017)
↑*Burkholderia* ssp. encode the rate-limiting enzyme for secondary bile acid synthesis (bile-acid dehydratase)		Appendix of PD patients	F/M	(Li et al., 2021)
Parkin dysfunction may perturb several metabolic pathways, signifying common pathomechanisms in PARK2 and iPD subjects Profiles from PARK2 patients ↑ of fatty acid (FA) metabolites and oxidized lipids, and ↓antioxidant, caffeine, and benzoate-related metabolites		15 PARK2 patients, 19 healthy controls	F/M	(Okuzumi et al., 2019)
↑*Lactobacillaceae*, *Enterobacteriaceae* and *Enterococcaceae* in PD patients ↓ *Lachnospiraceae* ↓*Lachnospiraceae* and ↑*Enterobacteriaceae* families also correlated with ↑disease severity and motor impairment Metagenomics indicated a significant variation of genes involved in the metabolism of short chain fatty acids amino acids, and in lipopolysaccharide biosynthesis		80 PD and 72 healthy controls	F/M	(Pietrucci et al., 2019)

Table 3c

Literature review of Parkinson's disease and gut microbiome in females.

Key findings	Study type	Model	Sex	References
Therapeutics				
Consumption of a multi-strain probiotic (Hexbio®) over 8 weeks improved bowel opening frequency and whole gut transit time in PD patients with constipation.		PD patients with constipation (ROME III criteria)	F/M	(Ibrahim et al., 2020)
B. subtilis probiotic strain PXN21 inhibits α-synuclein aggregation and clears aggregates in *C. elegans* model of synucleinopathy, partly mediated by DAF-16. *B. subtilis strains* protect via spores, vegetative cells, biofilm formation, and sphingolipid metabolism (genes lagr-1, asm-3, and sptl-3)		*C. elegans* strain NL5901	–	(Goya et al., 2020)
The UDPRS III significantly improved and the levodopa-equivalent daily dose ↓ after vegetarian diet and fecal enema in a one-year follow-up Significant correlation between the gut microbiome diversity and the UPDRS III and the abundance of *Ruminococcaceae*. ↓ *Clostridiaceae* after enema.	Case-control study	54 PD 32 healthy controls (HC)	F/M	(Hegelmaier et al., 2020)
Inconclusive rifaximin treatment for SIBO	Single-center, double-blind, placebo-controlled, randomized clinical trial (NCT02470780)	SIBO-positive PD	F/M	(Vizcarra et al., 2018)

Table 3d

Literature review of Parkinson's disease and gut microbiome in females.

Key findings	Study type	Model	Sex	References
Predictive/ Diagnostic ↓ Dysbiosis correlates with clinical phenotypes and severity. Altered plasma cytokine profiles associated with gut microbiome composition alterations suggest aberrant immune responses may contribute to inflammatory processes in PD ↑*Verrucomicrobia, Mucispirillum, Porphyromonas, Lactobacillus*, and *Parabacteroides* ↓Prevotella ↑*Bacteroides* were increased in patients with non-tremor PD subtype than patients with tremor subtype			**F/M**	(Lin et al., 2019)
PD predicted based on selected OTUs after the binary transformation, age, and sex	Computational	Predictive modeling **OTUs**	**F/M**	(Dong et al., 2020)
↓*Bifidobacterium* and *Bacteroides fragilis* at year 0 associated with worsening of UPDRSI scores in 2 years. ↓*Bifidobacterium* at year 0 ↑ hallucinations/delusions in 2 years ↓ *B.fragilis* at year 0 ↓motivation/initiative in 2 years Deteriorated group ↓*Bifidobacterium*, B. fragilis, and *Clostridium leptium* than the stable group at year 0 but not year2		36 patients	**F/M**	(Minato et al., 2017)
↑ WP_087393524.1 protein of *Akkermansia muciniphila*, ↔Prevotellaceae/Prevotella in PD	Case-control study	Feces from 40 PD and healthy spouses Cohort of 78 PD, 75 control subjects, 40 MSA and 25 AD.	**F/M**	(Qian et al., 2020)

Table 3e

Literature review of Parkinson's disease and gut microbiome in females.

Key findings	Study type	Model	Sex	References
Gut integrity				
↑GI-symptoms ↓performance on letter fluency, visuospatial, learning and memory tests. Cognitive performance was uniquely associated with GI-symptoms and unrelated to non-GI autonomic symptoms.	Secondary analysis of Parkinson's Progression Markers Initiative (PPMI)	423 newly diagnosed PD patients followed for up to 5 years.	**F/M**	(Jones et al., 2020b)
PD may have colonic dysfunction beyond constipation as part of a dysautonomic non-motor phenotype IBS-like symptoms had more non-motor symptoms and ↓ *Prevotella*	Case–control study	74 PD patients with 75 controls	**F/M**	(Mertsalmi et al., 2017)
GI infections correlated with ↑ risk for PD	Prospective cohort study, human		**F/M**	(Nerius et al., 2020)
SIBO was highly prevalent in PD, and nearly one-third was detected. SIBO was associated with worse gastrointestinal symptoms and worse motor function.		82 PD, and 200 controls	**F/M**	(Niu et al., 2016)

Table 4

Literature review of Huntington's disease and gut microbiome in females.

Key Findings	Bacteria	Model	Sex	References
Microbiota composition coincided w/ ↓weight and ↑food intake, ↑motor deficits, ↑fecal water content in HD mice at 12 weeks of age	↑ *Bacteriodetes* ↓*Firmicutes* ↑ diversity in M ↔diversity in F	R6/1 mice	**F/M**	(Kong et al., 2020)
↔*Bacteroidetes, Firmicutes* ↑*E. halli* correlated to ↑Huntington's disease progression and ↓cognition. ↔*Verrucomicrobia, Bacteroidetes, Proteobacteria* correlated to ↔cognition	↓α-diversity and β-diversity ↓*Firmicutes, Lachnospiraceae* and *Akkermansiaceae* in HDGEC males ↔ Phylum and Family in F	19 HD, 23 Premanifest HD 36 healthy controls	**F/M**	(Wasser et al., 2020)
Gut-microbiome-derived metabolites differed in PHD metabolome Metabolites reflecting mutant huntingtin toxicity and neurodegeneration differed in symptomatic HD metabolome	↓Indole-3-propionic acid in PHD ↓Serotonin in PHD and HD ↓5-hydroxyindoleacetate in PHD ↓2-hydroxyphenylacetate in HD ↓3-hydroxyphenylacetate in HD ↓4-hydroxyphenylacetate in HD ↔Hypoxanthine, guanosine ↓Xanthosine in HD, ↓Xanthine in PHD and HD	Plasma from 52 pre-manifest HD(PHD), 102 early symptomatic HD, and 140 healthy controls	**F/M**	(Rosas et al., 2015)

Table 5a

Literature review of stoke and gut microbiome in females.

Outcomes	Bacteria	Markers	Model	Sex	Reference
Treatments					
Fecal transfer from adult ovariectomized and estrogen-treated (OVX + E) to middle-aged OVX + E ↓ infarct volume, and ↑behavioral recovery	OVX + E ↔ phyla, ↑*Prevotella* and *Lactobacillus* ↓Butyrate baseline in the middle-aged OVX + E ↑LPS in OVX + E post-stroke	↑serum endotoxin ↓ SCFAs ↑ IL-17A	Sprague-Dawley rats (a) gonadally intact adult and middle-aged, (b) OVX + E (c) in middle-aged OVX + E after fecal microbiome transfer	**F**	(Park et al., 2020)
↔infarct volumes ↓ survival in microbiota-depleted mice compared to MCAO-SPF and sham-microbiota-depleted mice. All microbiota-depleted animals developed severe colitis. This was rescued by continuous Abx or colonization with SPF microbiota pre-op	Antibiotic depleted gut biome		C57BL/6 J mice after an 8-week decontamination with quintuple broad-spectrum antibiotic cocktail. Microbiota-depleted animals were subjected to 60 min middle cerebral artery occlusion or sham operation (ABX stopped 3 days pre MCOA)	**F**	(Winek et al., 2016)

Table 5b

Literature review of stoke and gut microbiome in females.

Outcomes	Bacteria	Markers	Model	Sex	Reference
Gut Function					
Mortality (50% vs 14%, $p < 0.05$) and hemorrhagic transformation (44% vs 0%) ↑males than in females	Stroke induced non-reversible alterations in microbiota diversity in males	Stroke induced greater gut permeability in males at day 3 ($p < 0.05$)	Aged (20-22 months) C57BL/6 N mice	**F/M**	(Ahnstedt et al., 2020)
Stroke-induced gut barrier permeability and dysfunction preceded the dissemination of bacteria to peripheral tissues 37.5% mortality in stroke patients w/ infections	>70% of microorganisms in the infected stroke patients were commensal (*Enterococcus spp., Escherichia coli* and *Morganella morganii*)		36 stroke patients, 36 controls, (7- to 10-week-old male C57BL/6 J mice)	**F/M/M**	(Stanley et al., 2016)
↑ CVA risk with disorders of the stomach, and functional, inflammatory, and infectious GI disorders. ↔diseases of the anus, rectum, or neoplastic GI disorders			Retrospective cohort study (claims data between 2008 and 2015) from a 5% sample of Medicare beneficiaries 66 years of age	**F/M**	(Roth et al., 2020)
CI patients showed significant dysbiosis of the gut microbiota	↑*Odoribacter, Akkermansia*		30 CI and 30 healthy control	**F/M**	(Li et al., 2019)

Table 5c

Literature review of stroke and gut microbiome in females.

Outcomes	Bacteria	Markers	Model	Sex	Reference
Observational Gut Microbiome Alterations					
↑risk of myocardial infarction, recurrent stroke and cardiovascular death **in males and females** > 66 years of age, and in patients with hypertension		TMAO level > 4.86 μM TMAO dose-dependently related ↑ risk of recurrent stroke and subsequent cardiovascular events in patients after 1st stroke	$n = 78$, Second independent validation cohort ($n = 593$)	F/M	(Haghikia et al., 2018)
Stroke and TIA patients had ↑ opportunistic pathogens and ↓commensal or beneficial genera. Correlating w/ disease severity	↑ *Enterobacter, Megasphaera, Oscillibacter,* and *Desulfovibrio* ↓*Bacteroides, Prevotella,* and *Faecalibacterium*	TMAO level in stroke and TIA patients was significantly ↓ than asymptomatic group.	322 stroke/TIA, 231 controls did not use an age- and sex-matching, age range from 18 to 80 years	F/M	(Yin et al., 2015)
	↑opportunistic (Enterobacteriacea, Veillonellaceae) ↑lactate-producers (*Bifidobacterium, Lactobacillus*) ↓butyrate-producers (Lachnospiraceae, Ruminococcaceae) in high vs low-risk.	↓Butyrate in high-risk group ↔acetate, propionate, isobutyrate, isovalerate, and valerate among the three groups	141 participants 60 years w/o prior history of stroke. Divided into low, medium, and high-risk	F/M	(Zeng et al., 2019)
3 months after admission, patients with ↑TMAO levels were more likely to have ↑risks of poor functional outcome		Median TMAO concentration was 3.8 μM	225 acute ischemic stroke patients	F/M	(Zhai et al., 2019)
↑TMAO was an independent predictor for cognitive impairment in post-stroke patients		Mean TMAO level was 5.6 ± 2.4 μM,	256 total, 86 (33.6%) patients were diagnosed as PSCI	F/M	(Zhu et al., 2020)
Patients with END showed ↑TMAO at admission Levels of TMAO predicted of early neurological deterioration (END) in patients with ischemic stroke.		Median TMAO concentrations were 4.8 μmol/L	362 patients END was diagnosed in 97 subjects	F/M	(Hou et al., 2020)
↑Christensenellaceae, Erysipelotrichaceae associated w/ ↑ risk of death ↑Enterobacteriales and Enterobacteriaceae in 1st week in the neuro ICU associated w/92% ↑ risk of 180-day mortality	↓α-diversity ↓Ruminococcaceae and Lachnospiraceae over time in patients followed longitudinally. ↑Enterobacteriaceaawas associated with ↑Rankin Scale at discharge.		98 patients and 84 age- and sex-matched healthy subjects	F/M	(Xu et al., 2019)
	↑Actinobacteria in control group ↑Coriobacteriales, Vagococcus, Sphingobacteriales and Adlercreutzia in CI	↑IL-4, TNF-β, IL-1β and C-reactive protein in CI group ↑myeloperoxidase, malondialdehyde ↑homocysteine ↓Adiponectin	30 control group, 28 cerebral infarction (CI) and 28 patients with OSAHS complicated by CI (OSAHS+CI)	F/M	(Zhang et al., 2020)
	OSAHS+CI ↑Bifidobacterium, Parascardovia, Metascardovia and Anaerostipes caccae.	In Control vs CI and OSAHS+CI vs CI			
↑SVD scores were associated with ↑cognitive decline and behavioral and psychological	Enterotype-I (Bacteroides >30%)	Fecal metabolites were significantly ↑in patients with	87 patients without dementia or a history of stroke, 64 of	F/M	(Saji et al., 2021)

Outcomes	Bacteria	Markers	Model	Sex	Reference
symptoms. Certain gut microbes may double the risk of white matter hyperintensity.	↑cognitive decline and cerebral SVD and ↑VSRAD scores	↑total SVD scores	whom exhibited mild cognitive impairment		
	Escherichia, Bacteroides, Megamonas, Parabacteroides, Akkermansia, Prevotella, Faecalibacterium, Dialister, Bifidobacterium and *Ruminococcus* were significantly different of CI and IS patients compared with controls	CI and IS were closely associated with internal glucose metabolism	8 patients with CI, 2 patients with IS and 10 healthy volunteers as controls	**F/M**	(Ji et al., 2017)