

## REVIEW ARTICLE

## Microbial involvement in myalgic encephalomyelitis/chronic fatigue syndrome pathophysiology

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### Abstract

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex and disabling disease related to persistent fatigue, exercise intolerance, post-exertional malaise, cognitive dysfunction, and musculoskeletal/joint pain. Gastrointestinal comorbidities, including irritable bowel syndrome, have been reported in affected individuals, indicating a potential role of gut microbiota in disease progression. In this paper, bacterial and metabolomic dysbiosis in subjects with ME/CFS are reviewed, and phenotypic, microbial, and metabolic biomarkers specific to individual cohorts are also identified. Furthermore, microbiome fluctuations or metabolic endotoxemia are proposed as possible disorder biomarkers. Based on the fact that gut microbiota dysbiosis reverts to a state of eubiosis in long-term patients with this condition, it may be hypothesized that disease progression begins with the loss of beneficial gut microorganisms, particularly short-chain fatty acid producers, leading to more widespread gastrointestinal phenotypes that are subsequently reflected in plasma metabolite levels. These alterations, specific of each individual, thereby result in metabolic and phenotypic shifts and in ME/CFS.

**Keywords:** Myalgic encephalomyelitis/chronic fatigue syndrome; Post-exertional malaise; Gut microbiota; Metabolic biomarkers; Pathophysiological phenotypes

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### 1. Introduction

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex and disabling disease related to persistent fatigue, exercise intolerance, and other symptoms aggravated by physical or cognitive efforts that may manifest immediately or typically be delayed for hours. Prolonged exacerbation of symptoms of ME/CFS, which follows physical activity and, in some cases, cognitive activity, is termed post-exertional malaise (PEM) and may last several days.<sup>1</sup> Due to this symptomatology, the quality of life of people with ME/CFS is significantly restricted in terms of social and occupational participation.<sup>2</sup>

Despite many efforts, the etiology of ME/CFS has yet to be clarified. However, several factors trigger the disease such as genetic predisposition, immune dysfunction, microbial infection, neuroendocrine imbalance, and psychological determinants.<sup>3,4</sup>

Numerous underlying biological irregularities have been recognized in subjects with ME/CFS, as exemplified by impaired energy metabolism, mitochondrial dysregulation, gastrointestinal and redox imbalances, altered immune processes (including autoimmune response), sleep disturbances, and multiple central and autonomic nervous system abnormalities.<sup>5,6</sup>

Nevertheless, not all patients experience the same clinical manifestations, suggesting the existence of ME/CFS subgroups, according to gastrointestinal disorders linked to microbial gut dysbiosis and metabolic pathways.<sup>7-9</sup> In fact, comorbid conditions such as irritable bowel syndrome (IBS) are often observed in patients with ME/CFS, thereby indicating a potential involvement of the gut microbiota in the progression of the disease.<sup>8</sup> In particular, the involvement of the gut microbiota through gut dysbiosis, the gut-brain axis, gut permeability, and bacterial translocation in ME/CFS has been repeatedly suggested.<sup>5,6,8</sup> It is widely understood that perturbation of the gut microbiota (dysbiosis) and its metabolome can affect several host processes, such as metabolism, inflammation, immunity, and brain function, and also contributes significantly to the development of multiple diseases related to the aforementioned host processes.<sup>6,10</sup>

As ME/CFS prevalence continues to grow globally,<sup>11</sup> establishing the link between the gut microbiota and ME/CFS is a pivotal aspect for delving into the disease's etiology and pathophysiology. Therefore, in the present review, we explore the potential links between the gut microbiota and ME/CFS. First, we review the evidence for bacterial and metabolomic dysbiosis in ME/CFS patients. Second, we identify potential biomarkers particular to patient cohorts across metabolic, microbial, and phenotypic domains.

## 2. Human gut microbiota and microbial metabolites

The human gut tract is composed of a broad microbial community, with a density of around 10 – 100 trillion of microbial cells.<sup>12</sup> The gut microbiota encompasses the microbial community in the gastrointestinal tract and consists of several microbial taxa, including bacteria, archaea, viruses, protozoa, and fungal species, being the most prevalent the bacteria domain,<sup>13</sup> which form a symbiotic relationship with the human gut.<sup>14</sup> Archaeal genera are present at reduced levels in the healthy human gut microbiota, with *Methanobrevibacter smithii* being the most abundant species.<sup>15</sup> The eukaryotic microorganisms most frequently detected in the gut tract are fungi, such as the genera *Candida* and *Saccharomyces*.<sup>16</sup> Protozoa such as *Blastocystis* have been identified in the human gut microbiota and their presence has been often linked

to a decrease in gastrointestinal diseases.<sup>17</sup> The human virome is mainly composed of bacteriophages, and the role that they play in the gut is related to modulating the bacteriome.<sup>18</sup> Typical microorganisms in the human gut are represented by approximately 100 bacterial species that belong to the following eight phyla: Actinomycetota, Bacillota, Bacteroidota, Campylobacterota, Fusobacteriota, Pseudomonadota, Thermodesulfobacteriota, and Verrucomicrobiota.<sup>12,14,19</sup>

Diverse intestinal compartments are characterized by a specific spatial distribution of the microorganisms.<sup>20-22</sup> The human gut microbiota composition differs both functionally and taxonomically based on aspects such as age, antibiotic intake, and diet,<sup>23-25</sup> and the predominant genera within the human gut microbiota are *Bacillus*, *Blautia*, *Clostridium*, *Dorea*, *Enterococcus*, *Eubacterium*, *Faecalibacterium*, *Lactobacillus*, *Roseburia*, and *Ruminococcus* (phylum Bacillota); *Bacteroides* and *Prevotella* (phylum Bacteroidota); *Bifidobacterium* (phylum Actinomycetota); and *Escherichia* (phylum Pseudomonadota).<sup>12,14,26</sup>

The gut microbiota exerts beneficial effects for the human host, including metabolic and immunological functions.<sup>12,27</sup> Intestinal microorganisms constitute essential regulators of the digestion process through the absorption of nutrients, and also through the synthesis of diverse metabolites, such as amino acids, lipids, short-chain (2-6 C) fatty acids (SCFAs), and vitamins.<sup>28,29</sup> Furthermore, the gut microbiota exerts a pivotal function in the maintenance of the intestinal epithelium integrity.<sup>27</sup> Moreover, the gut microbiota generates a broad diversity of secreted biologically active compounds from undigested foods,<sup>30</sup> such as histamine, polyamines, SCFAs, and tryptophan catabolites.<sup>31,32</sup> The metabolic products of tryptophan (5-hydroxytryptamine, indole, and kynurenine) have been identified as inhibitory compounds of neuroinflammation.<sup>33</sup> SCFAs, such as acetate, butyrate, and propionate, constitute signaling molecules that locally modulate the gut function via enteroendocrine cells, influencing the metabolism of the brain, liver, and muscle, as well as the host energetic homeostasis.<sup>34,35</sup> In addition, SCFAs exert neuroactive effects via the induction of neuroinflammatory responses.<sup>36</sup>

The state related to the loss of gut homeostasis due to endogenous and exogenous factors is known as dysbiosis, which triggers chronic inflammation and changes in the release of microbial metabolites, including mucin, secondary bile acids, and SCFAs, which are pivotal for the regulation of both the immune and physiological functions of the host.<sup>37</sup> The gut microbiome homeostasis is essential for preserving brain health, such as cognitive function and

synaptic plasticity,<sup>38</sup> thereby inhibiting neuroinflammation processes and safeguarding from neurodegenerative diseases by maintaining microglial cells in a healthy mature condition.<sup>33</sup>

### 3. Gut microbiota dysbiosis and ME/CFS

Alterations in the gut microbiome have been linked to diminished microbial diversity, a reduction of commensal gut microbiota, and an increase in proinflammatory molecules leading to a dysregulated host immune response or adjustment of the gut in individuals with ME/CFS.<sup>39</sup> In addition, several recent studies have reported comorbidity with gastrointestinal disorders, such as IBS.<sup>8</sup>

Diverse studies have shown gut dysbiosis in ME/CFS (Table 1), although the results vary depending on the characteristics of the trials. Wang *et al.*<sup>10</sup>, in a retrospective review, reported that the proportions of gut microbial phyla between patients with ME/CFS and healthy controls are distributed as Bacillota (67.1% vs. 78.9%), Bacteroidota (21.2% vs. 10.8%), Actinomycetota (1.8% vs. 2.6%), and other phyla (10.2% vs. 8.9%); therefore, a decrease of the Bacillota/Bacteroidota may be associated with ME/CFS. In addition, the microbial  $\alpha$ -diversity (*i.e.*, the observed number in taxa or the relative abundances in those taxa of an average sample within a habitat type) of the gut microbiome was reduced and there was a significant disparity within the general configuration of the gut microbiome  $\beta$ -diversity (*i.e.*, the variability in community composition or the identity in taxa observed among samples within a habitat) in individuals with ME/CFS compared to the non-affected controls. Thus, the role of the gut microbiota in the pathogenesis of ME/CFS is not yet clarified.

Several studies showed differing results regarding the abundance of the bacterial phyla in the gut microbiome. Increased abundance was found in the phyla Bacteroidota (genera *Alistipes*, *Bacteroides*, and *Paraprevotella*),<sup>5,8,40,46</sup> Bacillota (genera *Blautia*, *Clostridium*, *Coprobacillus*, *Enterocloster*, *Eggerthella*, *Erysipelatoclostridium*, *Lachnoclostridium*, *Phascolarctobacterium*, *Ruminococcus*, *Ruminococcaceae\_UCG\_014*, *Ruthenibacterium*, *Sellimonas*, and *Tyzzrella*),<sup>5,41,44-46</sup> and in the phylum Pseudomonadota.<sup>42</sup> In contrast, a decrease of the abundance was reported in the following phyla: Actinomycetota (genus *Bifidobacterium*),<sup>40,42</sup> Bacteroidota (genera *Bacteroides*, *Coprobacter*, and *Phocaeicola*),<sup>8,41,45</sup> and Bacillota (genera *Anaerostipes*, *Eubacterium*, *Faecalibacterium*, and *Roseburia*).<sup>5,8,40,42,44,45,47</sup>

It has been suggested that gut dysbiosis can cause immunometabolic disturbances (*e.g.*, diminished generation of antimicrobial peptides and SCFAs, perturbed tryptophan/kynurenine pathway metabolism), giving

rise to a disrupted gut barrier (“leaky gut”), bacterial translocation, subsequent systemic chronic inflammation, along with neuroinflammation and neuroimmune impairment that may impact the brain and lead to ME/CFS.<sup>6</sup> While the precise mechanism underlying this phenomenon remains unclear, one proposed explanation is that the rise in *Enterobacteriaceae* associated with dysbiosis might drive intestinal inflammation and increased permeability, potentially due to elevated concentrations of lipopolysaccharide (LPS) produced by these bacteria, causing metabolic endotoxemia, which has been reported in ME/CFS.<sup>48</sup> The inquiry into whether a leaky gut also plays a role in ME/CFS has been addressed by Shukla *et al.*,<sup>40</sup> who found greater bacterial translocation and heightened levels of IgA and IgM to LPS in patients with ME/CFS than in healthy controls. Considering that bacterial translocation can induce systemic inflammation, disrupt blood-brain barrier, and lead to neuroinflammation, diverse researchers speculate that this process may account for the development of neurological anomalies in ME/CFS.<sup>49,50</sup> Figure 1 shows the hypothetical pathways regarding the relationship between gut microbiome and ME/CFS.

Other studies reported increased oxidative stress in ME/CFS.<sup>51</sup> Increased oxidative stress and decreased resting antioxidant levels during periods of rest have been noted in patients with ME/CFS when compared to healthy controls.<sup>52</sup> Furthermore, heightened urinary 8-hydroxydeoxyguanosine (8-OHdG) levels, an indicator of oxidative DNA degradation, have been associated with symptoms of malaise and depression in individuals with ME/CFS.<sup>53</sup> In addition to dysbiosis and metabolic endotoxemia, other factors may be also involved in an oxidant/antioxidant imbalance, such as viral infection, stress, depression, and reduced antioxidants.<sup>54,55</sup>

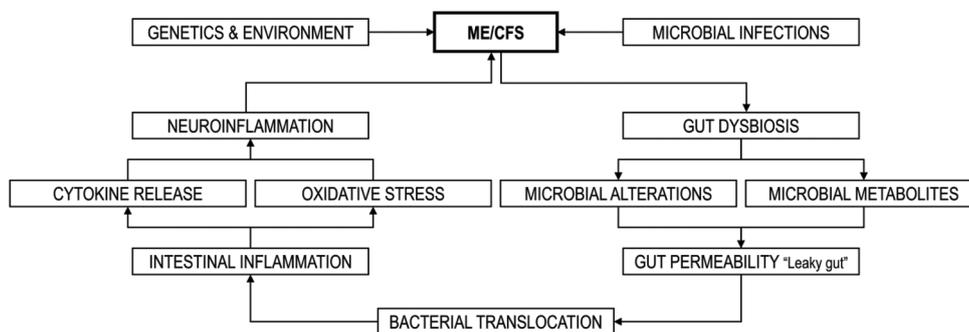
Gut microbiota also possesses the capacity to generate neurotransmitters and influence their signaling pathways. Dysbiosis can interfere with the synthesis and equilibrium of neurotransmitters, including gamma-aminobutyric acid and serotonin, which are crucial for cognitive function, mood regulation, and other brain activities. Disruptions in neurotransmitter production and signaling processes might play a role in the neurological and psychological manifestations observed in subjects with ME/CFS.<sup>56</sup> Abnormalities in the levels of tryptophan, a neurotransmitter modulated by the microbiome, have been associated with ME/CFS.<sup>57</sup> In addition, the gut microbiome directly impacts vagal nerve stimulation, although this relationship may be bidirectional, as the vagal nerve also innervates the colon.<sup>6</sup>

Finally, dysbiosis can modify the synthesis and accessibility of various metabolites such as SCFAs and

**Table 1. Recent studies on gut microbiota dysbiosis of patients with ME/CFS compared to healthy controls**

Study/Country	Characteristics	Increased microbial taxa	Decreased microbial taxa
Shukla <i>et al.</i> <sup>40</sup> /USA	N=10 ME/CFS and N=10 HC. Age: 20 – 60 years. Blood and stool samples. 16S rRNA. Pyrosequencing	Blood: Pseudomonadota and Bacillota. Stool: Bacteroidota	Blood: Bacteroidota. Stool: Actinomycetota and Bacillota
Armstrong <i>et al.</i> <sup>41</sup> /Australia	N=34 ME/CFS and N=25 HC. Mean age: 34.9 years ME/CFS and 33.0 years HC. Stool samples. Culture method. MALDI-TOF	<i>Clostridium</i>	<i>Bacteroides</i>
Giloteaux <i>et al.</i> <sup>42</sup> /USA	N=46 ME/CFS and N=34 HC. Stool samples. 16S rRNA. Illumina MiSeq	Pseudomonadota	<i>Faecalibacterium</i> and <i>Bifidobacterium</i>
Nagy-Szakal <i>et al.</i> <sup>8</sup> /USA	N=50 ME/CFS (21 with IBS and 29 without IBS) and N=50 HC (without IBS). Mean age: 51 years. Stool samples. Shotgun metagenomic sequencing. Illumina HiSeq 4000	<i>Alistipes</i> in patients with IBS and unclassified <i>Bacteroides</i> in patients without IBS	<i>Faecalibacterium</i> in patients with IBS and <i>Phocaeicola</i> (formerly <i>Bacteroides</i> ) <i>vulgatus</i> in patients without IBS
Mandarano <i>et al.</i> <sup>43</sup> /USA	N=49 ME/CFS and N=39 HC. Mean age: 53.0 years ME/CFS and 44.0 years HC. Stool samples. 18S rRNA. Illumina MiSeq	Basidiomycota/Ascomycota fungal phyla ratio	Gut eukaryotic diversity
Kitami <i>et al.</i> <sup>44</sup> /Japan	N=48 ME/CFS (11 with IBS) and N=52 HC. Stool samples. 16S rRNA. Illumina MiSeq	<i>Blautia</i> , <i>Coprobacillus</i> , and <i>Eggerthella</i>	<i>Faecalibacterium</i>
Lupo <i>et al.</i> <sup>5</sup> /Italy	N=35 ME/CFS and N=70 HC. Mean age: 46.4 years ME/CFS and 55.2 years HC. Stool and saliva samples. 16S rRNA. Illumina MiSeq	Stool: <i>Bacteroides</i> and <i>Phascolarctobacterium</i> . Oral: <i>Rothia dentocariosa</i> and <i>R. mucilaginosa</i>	Stool: <i>Anaerostipes</i>
Guo <i>et al.</i> <sup>45</sup> /USA	N=106 ME/CFS (without IBS) and N=91 HC. Mean age: 47.4 years. Stool samples. Shotgun metagenomic sequencing. Illumina MiSeq	<i>Blautia sp.</i> , <i>Clostridium scindens</i> , <i>Enterocloster</i> (formerly <i>Clostridium</i> ) <i>bolteae</i> , <i>Erysipelotoclostridium ramosum</i> , <i>Lachnoclostridium sp.</i> , <i>Ruminococcus gnavus</i> , <i>Ruthenibacterium lactatiformans</i> , <i>Sellimonas intestinalis</i> , and <i>Tyzzeraella nexilis</i>	<i>Coprobacter secundus</i> , <i>Eubacterium rectal</i> , and <i>Faecalibacterium prausnitzii</i>
He <i>et al.</i> <sup>46</sup> /China	UK Biobank GWAS: N=2076 ME/CFS and N=460857 HC. Mendelian study of 25 cohorts from populations of European ethnicity in 11 countries	<i>Paraprevotella</i> and <i>Ruminococcaceae_UCG_014</i>	Not established
Xiong <i>et al.</i> <sup>47</sup> /USA	N=75 short-term ME/CFS, N=79 long-term ME/CFS, and N=79 HC. Mean age: 43 years. Stool samples. Shotgun metagenomic sequencing	Short-term patients showed significant microbial dysbiosis, while long-term patients had largely resolved microbial dysbiosis	Microbial diversity: <i>Roseburia</i> and <i>F. prausnitzii</i>

Abbreviations: IBS: Irritable bowel syndrome; HC: Healthy control; MALDI-TOF: Matrix-assisted laser desorption/ionization time-of-flight; ME/CFS: Myalgic encephalomyelitis/chronic fatigue syndrome.



**Figure 1.** Hypothetical pathways on the relationship between gut microbiome and ME/CFS  
Abbreviation: ME/CFS: Myalgic encephalomyelitis/chronic fatigue syndrome.

cytokines, which may interfere with gut-brain interaction and contribute to the symptoms of ME/CFS.<sup>44,58</sup> An alternative hypothesis suggests that bacterial metabolites could influence ME/CFS by interfering with the pathways of estrogen and Vitamin D receptors. The Vitamin D receptor has been linked to the onset of autoimmune disorders that commonly present alongside ME/CFS. However, this potential connection remains insufficiently explored.<sup>55,59</sup> Several investigations have identified possible variations in metabolite levels between individuals with ME/CFS and controls.<sup>10</sup> In particular, SCFAs (such as butyrate, acetate, or isobutyrate) were significantly reduced in feces, blood, and urine of patients with ME/CFS.<sup>44</sup> A substantial decrease in serum  $\alpha$ -tocopherol (vitamin E), an antioxidant that may be metabolized by specific gut microorganisms, was also noted in patients with ME/CFS.<sup>10</sup>

#### 4. Modulation of gut microbiome as a potential therapy for ME/CFS

Based on its lower biodiversity compared to healthy subjects, it is believed that the gut microbiome may be a novel therapeutic target for patients with ME/CFS,<sup>41</sup> leading to several potential therapies, including probiotics, diet, and fecal microbiota transplantation (FMT).<sup>6,55</sup>

Probiotics are live bacteria that are thought to foster health.<sup>60</sup> A pilot study showed that the consumption of five different mixtures of probiotics (Enterelle: *Enterococcus faecium* and *Saccharomyces boulardii*; Bifiselle: *Bifidobacterium longum*, *Bifidobacterium breve*, *Bifidobacterium bifidum*, and *Bifidobacterium infantis*; Rotanelle: *Bifidobacterium longum* strain AR81; Citogenex: *Lactobacillus casei* and *Bifidobacterium lactis*; and Ramnoselle: *Lactobacillus rhamnosus* strain GG and *Lactobacillus acidophilus*) over an 8-week period led to changes in overall welfare, along with alterations in inflammatory and oxidative indices in subjects with ME/CFS, culminating in a decrease of inflammatory indicators.<sup>61</sup> In another study, Sullivan *et al.*<sup>62</sup> investigated the impact of *Lactocaseibacillus* (formerly *Lactobacillus*) *paracasei* subsp. *paracasei* strain F19, *Lactobacillus acidophilus* strain NCFB 1748, and *Bifidobacterium animalis* subsp. *lactis* strain Bb12 on fatigue and physical activity in 15 patients with ME/CFS. After 4-week period, neurocognitive functions showed a significant improvement, while fatigue and physical activity scores did not change. Finally, the administration of *B. longum* subsp. *infantis* strain 35624 to 48 ME/CFS cases demonstrated the capability of probiotics to downregulate levels of systemic proinflammatory markers, such as C-reactive protein (CRP), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interleukin 6 (IL-6).<sup>63</sup>

Dietary modification is a quick, consistent, and straightforward approach to modify the gut microbiota.<sup>64</sup>

Diet, similar to prebiotics, has been linked to some disease pathophysiology, and is able to alter the balance of microbiota composition and attenuate inflammation.<sup>65</sup> Patients with IBS, obesity, and Crohn's disease have seen positive outcomes with diet therapy, and dietary interventions have also been investigated within the neuropsychiatric field.<sup>23</sup> Intake of omega-3 polyunsaturated fatty acids enhances microbiota diversity and reduces metabolic endotoxemia, while consumption of polyphenols and fibers is also advantageous, due to their protective effects of polyphenols in obesity, neurodegenerative diseases, Type 2 diabetes, and cardiovascular diseases.<sup>65-68</sup> Eicosapentaenoic acid, prevalent in omega-3-rich oil, may mitigate symptoms in patients with ME/CFS.<sup>69</sup> Combining a diet aimed at reducing intestinal permeability with anti-inflammatory and antioxidant agents led to marked improvements in leaky gut, indicating a novel therapeutic strategy for ME/CFS.<sup>70</sup> Similar findings have been observed in individuals with depression, suggesting that gut permeability and the associated heightened immune response might elucidate a connection between major depressive disorder and the cognitive symptoms of ME/CFS.<sup>71</sup>

Recently, FMT has gained attention as a potential treatment for ME/CFS. This approach aims to reestablish a balanced gut microbiota by transferring fecal matter from a healthy donor into the recipient's gastrointestinal tract.<sup>72</sup> About 70% response rate was achieved when 13 non-pathogenic bacteria were delivered through colonoscopy to 60 patients with ME/CFS. After 15 – 20 years of follow-up, 58% of cases were documented to have maintained response without relapse.<sup>73</sup> Kenyon *et al.*<sup>74</sup> conducted an FMT trial in which each patient received 10 FMTs delivered via a rectal catheter into the lower part of the sigmoid colon. Of the 21 patients treated with FMT, 17 reported 65 – 95% improvement, with seven patients describing a normalization of their quality of life. However, a recent study showed that FMT was safe, but did not enhance the health-related quality of life for subjects suffering from CFS.<sup>75</sup>

#### 5. Discussion

While gut microbiome homeostasis has been associated with diverse diseases, its role in the pathogenesis and progression of ME/CFS is still not fully defined. However, several factors implicating the gut-brain axis may explain the connection between gut dysbiosis and ME/CFS.

As changes in the gut microbiome have also been reported in postulated autoimmune diseases such as Crohn's disease, systemic lupus erythematosus 2, and Type 2 diabetes, it would be valuable to explore whether the microbiome could be associated with autoimmune

manifestations of ME/CFS.<sup>5,76</sup> In addition, both genetic and environmental factors can affect the gut microbiome, and shifts in local gut microbiota composition should be evaluated in ME/CFS.<sup>77</sup> Although the significance of the gut microbiome in health and disease is becoming increasingly clear,<sup>78</sup> limitations must be addressed regarding studies of the gut microbiota and ME/CFS, such as differing results, small sample sizes, confounding variables, and lack of homogeneity of the microbial gene sequencing platforms.<sup>45,55</sup>

Butyrate and its precursor acetate are two of the most important SCFAs of microbial origin. Both metabolites are reduced in ME/CFS patients likely due to the decrease of *F. prausnitzii*, *Ruminococcus* spp., *Eubacterium rectale*, and *C. secundus* in their gut microbiome (Table 1). Thus, a deficiency of these intestinal homeostatic metabolites could contribute to a number of detrimental physiological perturbations, including a weakened epithelial barrier and increased intestinal inflammation, which results in elevated plasma LPS levels in ME/CFS, indicative of microbial translocation.<sup>42</sup> In addition, *F. prausnitzii* and *Lachnospira* (formerly *Lactobacillus*) *rogosae* are the major bacterial species associated with the symptoms of ME/CFS and with individual and total Multidimensional Fatigue Inventory (MFI) scores.<sup>45</sup>

The cognitive problems detected in ME/CFS subjects could be related to alterations in the gut microbiota and also to a substantial decrease in Vitamin E levels. Tryptophan, a precursor for serotonin, can be degraded by determined gut microorganisms, which may exert influence on brain function,<sup>79</sup> and on the pathophysiology of ME/CFS.<sup>80</sup> Thus, studying the changes in gut microbiome composition and function may clarify how tryptophan metabolism affects serotonin concentrations, which may contribute to various symptoms of ME/CFS, such as depression and restless sleep.

Considering the impact of ME/CFS on mental health, the exploration of psychobiotics as a therapeutic option for patients with ME/CFS holds considerable promise. Psychobiotics, which target the gut-brain axis, have demonstrated potential in modulating anxiety, depression, and stress-related disorders through gut microbiome adjustments.<sup>60</sup> Diet also offers possibilities for ME/CFS symptom management. Specifically, vegetarian diets, rich in antioxidant and fiber, are known to enhance gut health, lower inflammatory markers, and reduce oxidative stress,<sup>65</sup> which may be beneficial to mitigate the physiological responses commonly reported by patients with ME/CFS. In addition, vegetarian diets may exert a positive influence on mental health.<sup>81</sup>

Another interesting aspect related to ME/CFS is to delineate the role of microbial infections, both bacterial

(e.g., *Coxiella burnetii*) and mainly viral (e.g., Epstein-Barr, Ross River, SARS-CoV-2), in triggering this disease.<sup>82-84</sup> The recent pandemic of COVID-19 caused a serious impairment in quality of life<sup>85</sup> and led to long COVID-19 in numerous patients who “recovered” but did not return to full health.<sup>86</sup> In this regard, long COVID-19 shares many phenotypic abnormalities with ME/CFS following viral infections, including persistent chronic fatigue and myalgia.

## 6. Conclusion

Research on patients with ME/CFS has revealed variable findings on alterations in gastrointestinal processes that involve microbiota. Microbiome changes or metabolic endotoxemia may be potential biomarkers of ME/CFS. The progression of ME/CFS may begin with the loss of beneficial gut microorganisms, especially SCFA producers that are reflected in plasma metabolite levels. These alterations may result in metabolic and phenotypic shifts and in ME/CFS. Randomized controlled trials in well-identified patients with ME/CFS, using diet, FMT, and other approaches may benefit these patients and establish causality.

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## Conflict of interest

The authors declare that they do not have competing interests.

## Author contributions

*Conceptualization:* Alejandro Borrego-Ruiz

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*Writing – review & editing:* Alejandro Borrego-Ruiz

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## Consent for publication

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