

Review

Early Life Stress and Gut Microbiome Dysbiosis: A Narrative Review

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Abstract: Background: Exposure to early life stress significantly increases the risk of psychopathology later in life. However, the impact of early life stress on the gut microbiome and its potential role in mental health outcomes remains insufficiently understood. This narrative review examines the current knowledge on how early life stress and its associated consequences may affect the gut microbiome, with a particular focus on conditions such as anxiety, depression, and post-traumatic stress disorder. Method: A comprehensive literature search was conducted in the PubMed and Web of Science databases between January and February 2025, covering studies published between 2015 and 2025. Results: Early life stress can profoundly impact cognitive function and neurodevelopment, with maternal early-life nutrition playing a significant role in modulating the effects of prenatal and postnatal stress. Early life stress influences the gut microbiome, disrupting its composition and function by altering the synthesis of microbial metabolites, neurotransmitters, and the activation of key metabolic pathways. However, the precise role of the gut microbiome in modulating stress responses during childhood and adolescence has not yet been fully elucidated. Conclusions: Several studies have demonstrated an association between early life stress and the gut microbiome. However, causality has not yet been established due to the numerous intrinsic and extrinsic factors influencing the microbiome-gut-brain axis. In the coming years, research on key microbial regulators, such as short-chain fatty acids, amino acids, and psychobiotics, may represent a promising approach for addressing central nervous system alterations linked to early life stress. Thus, further studies will be necessary to evaluate their potential as therapeutic agents.

Keywords: early life stress; prenatal stress; postnatal stress; gut microbiome; adverse childhood experiences; anxiety; depression; post-traumatic stress disorder; key regulators



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1. Introduction

Exposure to early life stress (ELS), including early adversities, adverse childhood experiences (ACEs), or childhood trauma, during critical developmental periods significantly increases the risk of psychopathology later in life, suggesting that ELS can disrupt normal brain development and alter both its structure and function, with potential long-term consequences for mental health [1]. ELS encompasses stressors such as abuse, neglect, or family dysfunction that occur early in life and negatively impact the health and well-being of young individuals, ultimately leading to a higher risk of morbidity and mortality in adulthood [2]. In recent years, ELS has received considerable attention due to its persistent and widespread consequences [3,4]. In fact, the relationship between ELS and adult mental

health outcomes is well documented [5], with individuals exposed to ELS being more susceptible to suffer from long-lasting psychological conditions, such as anxiety, depression, and post-traumatic stress disorder (PTSD) [5–9].

Retrospective studies have shown a consistent association between ELS-related experiences and cognitive decline in adulthood via depressive symptoms and systemic inflammation [10,11]. These early experiences have also been related to neurological deficits in executive function, memory capacity, and processing speed [12–14] as they induce significant alterations in the hippocampus and prefrontal cortex (PFC) [15], thereby affecting the hypothalamic–pituitary–adrenal (HPA) axis and the neuroendocrine system, both of which are involved in the stress regulation process, mainly through the release of cortisol [16]. This hormone interacts with both cognitive and physiological processes, including immunity, inflammation, and neuroplasticity [17]. In addition, individuals exposed to ELS often exhibit psychiatric comorbidity with multiple behavioral consequences [18–20]. In this regard, although the relationships between ELS and mental health outcomes have been investigated from multiple perspectives, the impact of ELS on the gut microbiome (GM) and its potential role in these outcomes remains insufficiently understood.

The Human Microbiome Project was implemented as a decade-long, two-phase initiative to develop resources, methods, and knowledge to elucidate the links between human-microbiome interactions and health-related outcomes [21,22]. Although “microbiota” and “microbiome” are often used interchangeably, there are important differences between the two terms. The microbiome comprises the entire spectrum of microorganisms, including archaea, bacteria, fungi, and viruses, along with their collective genomes, structural components, metabolites, and surrounding environmental conditions. Microbiota is a more restricted term that refers to the community of commensal, symbiotic, and pathogenic microorganisms associated with a specific environment [23,24]. It is currently recognized that anaerobic bacteria make up approximately 95% of the GM, comprising about one thousand species [25]. The phyla Bacillota (formerly Firmicutes) (64%) and Bacteroidota (formerly Bacteroidetes) (23%) are the most abundant, although members of the phyla Pseudomonadota (formerly Proteobacteria) (8%), Actinomycetota (formerly Actinobacteria) (3%), Fusobacteriota (formerly Fusobacteria), and Verrucomicrobia have also been detected at lower percentages [26]. The dominant genera within the Bacillota are *Bacillus*, *Clostridium*, *Enterococcus*, *Eubacterium*, *Lactobacillus*, and *Ruminococcus*; while in the Bacteroidota, the most abundant genera are *Bacteroides*, *Porphyromonas*, and *Prevotella* [27,28]. In addition, archaea (*Methanobrevibacter*), fungi (*Malassezia*, *Candida*, and *Saccharomyces*), protozoa (*Blastocystis*), and viruses have been reported as common components of the human GM [29–32].

The GM has a measurable effect on the brain, influencing and being influenced by neuropsychiatric disorders, mood-related conditions, social behavior, and stress [33]. This microbiome-gut-brain (MGB) axis may be shaped by multiple mechanisms, such as endocrine, immune, and neural signaling pathways [34]. An essential step in correctly identifying the GM dysbiosis associated with ELS is to understand the characteristics of the microbiota in healthy children in whom no disorders are evident. Early childhood is a critical period for the establishment of the GM, with factors such as mode of delivery, initial feeding practices, and antibiotic exposure playing an important role [35,36]. Nevertheless, the composition and structure of the GM continuously evolve throughout life, influenced by factors such as physiological conditions, infectious diseases, drug use, diet, and lifestyle [37–39].

Given that ELS has been increasingly recognized as a critical factor influencing mental health, and considering the potential link between ELS and GM dysbiosis, this review examines the current understanding of how ELS and its associated outcomes may impact

the GM, with a particular focus on conditions such as anxiety, depression, and PTSD, as these are commonly observed in individuals affected by early life adversities. By exploring this connection, this review emphasizes the significance of various biological mechanisms underlying ELS-related mental health outcomes, which may contribute to a deeper understanding of the psychological and physiological aspects of these disorders.

2. Method

This review synthesizes current findings linking GM dysbiosis to potential outcomes of ELS. Given the complexity of the subject and the heterogeneity of the available studies, a narrative approach was deemed the most appropriate over a systematic methodology or meta-analysis. Both authors independently conducted a comprehensive literature search in the PubMed and Web of Science databases between January and February 2025, covering articles published between 2015 and 2025 without search restrictions. A combination of terms related to the research topic was used to identify relevant literature. Titles and abstracts were screened for initial selection. The remaining full-text articles were thoroughly reviewed and assessed. Studies were included if they examined the involvement of the GM in traumatic experiences, ACEs, or ELS. Those that primarily focused on substance use, physiological or genetic disorders, and psychological therapies, as well as meta-analyses and reviews were excluded. Furthermore, any studies that did not align with the research objectives were excluded from further analysis.

3. ELS and Its Impact on Mental Health

ELS has lasting and pervasive effects on development [40]. Stress is the psychological response that occurs when an individual perceives being under threat or pressure. It is typically adaptive, as it triggers a variety of behavioral and physiological reactions focused on mitigating the perceived risk [41]. However, when stress becomes chronic or excessively intense, it causes prolonged activation of physiological and psychological response systems, resulting in dysregulation and contributing to adverse mental and physical outcomes [42].

The neuropsychobiological influence of ELS represents an important developmental risk factor for the onset of mental health issues in later stages of life [43]. In terms of mental health outcomes, ELS has been strongly associated with an increased and subsequent risk of depression [44,45], PTSD [46], schizophrenia [47], suicidal tendencies [48], and maladaptive behaviors such as tobacco smoking and alcohol consumption [49].

3.1. Stress System Elements

The role of the stress system functions to preserve homeostasis by reacting to both actual and perceived stressors, whether they are short-term or long-lasting [50]. The human stress system includes both central and peripheral elements that initiate adaptive responses through a variety of hormones, neuropeptides, and neurotransmitters [51]. Central nervous system (CNS) effectors of the stress system consist of (i) corticotropin-releasing hormone (CRH) that is released by CRH neurons primarily located in brain regions, such as the paraventricular nucleus (PVN) of the hypothalamus, limbic structures, bed nucleus of the stria terminalis, cerebral cortex, central nucleus of the amygdala, dorsal root neurons of the spinal cord, cerebellum, and locus coeruleus [52]—CRH has also been identified in chromaffin cells of the sympathetic ganglia of the autonomic nervous system (ANS), adrenal medulla, and in other peripheral organs and tissues, such as the skin, gastrointestinal tract, and immune system cells [52]; (ii) arginine-vasopressin, synthesized by neurons in the hypothalamic PVN [53]; (iii) the pro-opiomelanocortin-derived peptides α -melanocyte-stimulating hormone and β -endorphin, generated within the arcuate nucleus

of the hypothalamus [54]; and (iv) norepinephrine (NE), produced in noradrenergic neuron clusters located in specific parts of the medulla oblongata [55].

The major peripheral effectors of the stress system are the glucocorticoids (GCs) regulated by the HPA axis and the catecholamines (e.g., NE and epinephrine) modulated by the ANS, which includes (i) the sympathetic nervous system and the sympathoadrenomedullary axis, as well as (ii) the parasympathetic system. Furthermore, a diverse array of molecules such as neuropeptides, steroid hormones, and neurotransmitters engages with traditional neuroendocrine signaling pathways to preserve homeostasis [43,56].

The ANS and the HPA axis play pivotal roles in the stress response, functioning as complementary, interdependent components within a broader network of internal neural regulation (i.e., the central autonomic network). The initial reaction to a stressor is primarily driven by ANS activation, which results in elevated catecholamine levels in peripheral tissues [46]. Concurrently, CRH is released into the hypothalamic–pituitary portal vessels, triggering the synthesis and secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary into the systemic circulation. CRH has also been implicated in triggering stress-related behaviors, influenced by the rapid activation of the ANS [57]. The adrenal cortex, the main target of ACTH, responds by releasing GCs, particularly cortisol in humans [58], which are crucial for managing the intensity, duration, and attenuation of the stress response, mainly through the binding of GCs to glucocorticoid receptors (GRs) in the hippocampus [57].

Chronic or excessive activation of the stress response system can result in sustained elevations in CRH, cortisol, and catecholamine levels. This prolonged dysregulation is thought to underlie various long-term psychological and physiological disorders linked to chronic stress, such as anorexia nervosa, depression, long-term alcohol abuse, obsessive–compulsive disorder, and panic attacks, to name a few [59–62]. In contrast, several studies have shown that chronic stress conditions, such as chronic fatigue syndrome, PTSD, fibromyalgia, nicotine withdrawal, and the postpartum phase, are often associated with a reduced activity of the HPA axis [46,60].

3.2. Neurological Alterations in ELS

3.2.1. Alterations in Prefrontal–Hippocampal–Amygdala Circuits

Studies conducted in both animal models and humans indicate that ELS leads to significant alterations in the development of prefrontal–hippocampal–amygdala networks [41]. These networks are crucial for coordinating peripheral stress responses, particularly through the release of CRH and GCs, and for regulating the ANS [42]. Moreover, they are integral to emotion and memory processing, as well as to self-regulation [63,64]. In rodent models, offspring exposed to maternal neglect or separation exhibit diminished dendritic growth in the PFC and hippocampus [65]. These structural changes are linked to epigenetic modifications and to disruptions in synaptic signaling in both the amygdala and hippocampus [66,67]. Such alterations contribute to heightened sensitivity to environmental stressors, manifesting as reduced regulation of the amygdala by the PFC and hippocampus [68]. Consequently, these changes are correlated with increased anxiety and depressive-like behaviors observed in animals after ELS exposure [69–71]. Alterations in hippocampal synaptic plasticity have also been associated with impaired spatial memory and exaggerated threat-learning responses in rodents [72,73]. These effects are likely mediated, at least partially, by prolonged exposure to CRH and GCs due to chronic stress [74,75].

Similar alterations in brain structure and function following childhood stress exposure have been reported in the amygdala, PFC, and hippocampus in humans [41], including reduced hippocampal volume [76,77], which has been linked to psychopathological symptoms and to deficits in learning processes [78–81]. In addition, changes in amygdala and

PFC responsiveness to emotional stimuli, along with disrupted connectivity between these regions, contribute to increased sensitivity to emotionally salient cues [82–84]. This atypical connectivity between these brain regions has been reported to occur in children with a history of emotional and physical maltreatment, sexual abuse, or in children growing up in poverty [85–87]. The functional connectivity between the PFC and amygdala seems to play a role in linking experiences of maltreatment with the development of anxiety and depressive symptoms [88]. Similar to animal models, evidence suggests that alterations in CRH and GC function, including epigenetic modifications, may in part mediate hippocampal alterations, psychopathological symptoms, and altered learning processes [87,89,90]. In addition, abnormal HPA responsivity has been reported to exist following a variety of ELS-related adversities, such as intrafamilial violence, low economic status, institutional neglect, and childhood abuse [87]. Prolonged exposure to GCs has been linked to hippocampal atrophy and HPA axis dysfunction [91], supporting the hypothesis that chronic HPA axis activation induces neural alterations in the PFC, hippocampus, and amygdala. These changes may contribute to impaired regulation of neural circuits involved in threat detection and adaptive responses to environmental challenges [92].

3.2.2. Alterations in Prefrontal-Striatal Dopaminergic Circuits

Emerging research indicates that ELS in animal models detrimentally impacts dopaminergic pathways implicated in motivation and reward processing [93,94], particularly within the ventral striatum, PFC, and amygdala [95]. Chronic and repeated maternal separation in rodents has been shown to disrupt dopaminergic glial cell populations, alter cell proliferation and apoptosis rates, and induce atypical dopaminergic signaling in the ventral tegmental area and substantia nigra during adulthood [96]. Other studies have linked variations in maternal care to diminished connectivity between the PFC and caudate–putamen [97], as well as structural and functional modifications in the nucleus accumbens [65,98]. These neurobiological changes have been associated with increased anhedonia-like behaviors [95] and dysregulated reward sensitivity [99].

In humans, ELS has been linked to disruptions in reward processing within the nucleus accumbens, ventral tegmental area, ventral striatum, and PFC [100,101]. These alterations have been associated with heightened vulnerability to anxiety and depressive symptoms, as well as with impairments in reward-based learning [102–104]. Notably, these neural circuits maintain strong connections with both the amygdala and PFC, which collectively regulate behavioral and psychological responses to stress, emotional and social learning, and self-regulatory mechanisms [105]. Consequently, disruptions in these pathways may contribute to an increased risk of maladaptive behaviors and adverse mental and physical health outcomes in later developmental stages [106].

4. Gut Microbiome in Early Life

Early childhood constitutes a critical period for the establishment of GM, with key factors such as early nutritional intake, the mode of birth, and antibiotic exposure influencing the development of the GM [35,107]. Thus, the composition and structure of GM changes constantly across the lifespan, influenced by both intrinsic and extrinsic factors, including physiological alterations, infectious diseases, dietary patterns, and lifestyle choices, among others [37,38,107]. Following birth, new microbial communities populate the neonatal gut, mainly determined by the gestational period and early-life factors, including birth circumstances and exposures during infancy [107–111]. The microbiome in preterm infants is often characterized by reduced diversity, a deficit in short-chain fatty acids (SCFAs), and the presence of potentially pathogenic microorganisms [112–114].

In preterm infants, the prevalent bacterial species are primarily from the Pseudomonadota and Bacillota phyla [113], with a notable presence of the *Enterobacteriaceae* and *Enterococcaceae* families [112], and of the genera *Clostridium*, *Escherichia*, *Klebsiella*, *Lactobacillus*, *Staphylococcus*, *Streptococcus*, and *Veillonella* [115,116]. The GM of infants born vaginally closely mirrors that of the maternal vaginal microbiota [117], while those delivered via cesarean section (C-section) tend to acquire a microbial profile more aligned with that of maternal skin [110,118]. For vaginally delivered infants, the most common bacteria include *Bifidobacterium* (phylum Actinomycetota), *Enterococcus* and *Lactobacillus* (phylum Bacillota), *Bacteroides*, *Parabacteroides* and *Prevotella* (phylum Bacteroidota), *Sneathia* (phylum Fusobacteriota), and *Escherichia* (phylum Pseudomonadota). Conversely, the microbiome of C-section infants is predominantly composed of *Corynebacterium* and *Propionibacterium* (phylum Actinomycetota), *Staphylococcus*, *Streptococcus* and *Veillonella* (phylum Bacillota), as well as *Enterobacter* and *Haemophilus* (phylum Pseudomonadota) [108,119–121]. Martin et al. [122] highlighted substantial differences between the meconium microbiota of vaginal and C-section births, with meconium from C-section deliveries showing lower bacterial diversity. Specifically, the C-section group had fewer *Bacteroides*, *Bifidobacterium*, and *Lactobacillus* species, but higher amounts of *Clostridium* [122,123].

Breastfeeding supplies a mixture of nutrients that contribute to several key processes, including immune system regulation and the promotion of the growth and activity of beneficial microorganisms [107,124]. The microbial composition of breast milk is diverse, typically consisting of *Staphylococcus* and *Streptococcus* species, along with other genera like *Bifidobacterium* spp., *Propionibacterium*, *Veillonella*, and lactic acid bacteria [125]. During the first three months of life, breastfeeding influences the composition of the GM, primarily by increasing the abundance of *Staphylococcus* and *Bifidobacterium*, while decreasing the abundance of *Clostridium*. Formula-fed infants, however, have a different GM composition, marked by the abundance of the bacterial genera *Atopobium*, *Bacteroides*, *Bifidobacterium*, *Clostridium*, and *Enterococcus* [121,122,126].

The administration of antibiotics during the first three years of life induces a reduction in the diversity and composition of the GM [127], resulting in a lower abundance of members of the order Clostridiales and in the genera *Bifidobacterium*, *Ruminococcus*, and *Staphylococcus* [122,128], and in an increase in members of the phyla Pseudomonadota, Actinomycetota, members of the family *Enterobacteriaceae* and the genera *Enterococcus* and *Lactobacillus* [129,130]. These alterations may have adverse effects on children's health, increasing their susceptibility to a range of microbial pathogens [131], and leading to negative mental health outcomes, such as cognitive, emotional, and behavioral difficulties, including mood-related and depressive symptoms [132]. Importantly, several CNS processes, including synaptic pruning, myelination, and synaptogenesis, which occur alongside GM maturation, may be impacted by metabolites associated with specific microorganisms [133,134].

5. Microbiological Aspects of ELS

Children who experience ELS exhibit distinct neurodevelopmental trajectories [135] and face a heightened risk of developing mental health disorders throughout their lives [136]. Studies in both animal models and human populations have shed light on the mechanisms underlying ELS-related alterations and their impact on the maturation of neural circuits and psychological processes essential for cognitive function and emotional well-being [137].

5.1. ELS in Animal Models

A few studies have examined the association between ELS and GM, and most of these are based on animal models. These preclinical studies suggest that ELS may affect the GM dysbiosis in offspring and increase their risk of developing psychiatric and physiological diseases across generations [138–140].

In animal models, ELS induces alterations in the GM that persist into adulthood [141]. An early study reported that adult mice exposed to ELS exhibited changes in the GM, with elevated levels of *Bifidobacterium bifidum*, *Clostridium leptum*, *C. coccoides*, and *Lactobacillus* spp. [142]. Another study in adult rats found that ELS decreased the Bacillota/Bacteroidota ratio, while increased taxa linked to inflammation, such as *Prevotella*, *Flexibacter*, and *Akkermansia* [143]. Mice exposed to ELS and then subjected to chronic stress as adults increased members of the Bacteroidota and Pseudomonadota phyla, and *Clostridium* species in the GM [144].

Recent research indicates that ELS may have sex-specific effects on the GM, behavior, and gene expression in the PFC of mice [145]. In males, ELS influenced the abundance of bacterial taxa from the families *Lachnospiraceae* and *Porphyromonadaceae*, as well as the genera *Alloprevotella*, *Bacteroides*, and *Lactobacillus*. In contrast, females exhibited changes primarily in the genera *Lactobacillus* and *Mucispirillum* [145]. Another study similarly reported sex-dependent differences in ELS-induced microbiota alterations, with both male and female rats showing increased *Bacteroides* and reduced *Lachnospiraceae* abundance [146]. However, males displayed an increase in *Streptococcus* and a decrease in *Staphylococcus*, whereas females exhibited a rise in *Sporobacter* and a reduction in *Mucispirillum*. These microbial shifts were linked to elevated colonic IFN- γ and IL-6, as well as higher serum IL-1 β levels in males, which corresponded to heightened anxiety-like behaviors. Furthermore, in rats, ELS was found to reduce Bacteroidota and increase Bacillota, an effect that was further modulated by serotonin transporter (5-HTT) genotype [147]. Specifically, rats with diminished 5-HTT expression exposed to ELS exhibited a microbiota profile oriented toward an inflammatory state, marked by an increased presence of taxa such as *Fusobacterium*, *Mucispirillum*, and *Desulfovibrio*.

More recently, Ke et al. [148] reviewed how the GM may contribute to PTSD by influencing inflammation (via the gut genera *Roseburia* and *Odoribacter*), neurotransmitter signaling, and stress responses, while the bidirectional gut–brain communication implies diverse pathways, mechanisms, and processes like the vagus nerve, immune system activation, and microbial metabolites. Moreover, in a preclinical study using a mouse model, Yadav et al. [149] found that recurrent exposure to social defeat stress, a well-established preclinical model for PTSD, induced GM dysbiosis that is characterized by a change in the Bacteroidota/Bacillota abundance ratio, an important factor in maintaining gut homeostasis and an increased abundance of members of the *Lachnospiraceae* family which regulate gut inflammation and gut barrier integrity. However, the decreased abundance of the members of the *Muribaculaceae* family suggests a dysregulation of dietary fiber fermentation and cholesterol metabolism.

5.2. ELS in Humans

Prenatal stress encompasses not only cases where the expectant mother experiences psychological distress, such as depression or anxiety [150,151], but also situations where maternal lifestyle or physical conditions may induce stress in the fetus, including exposure to adversity [152] or severe illness [153].

Postnatal research has examined children and adolescents who have experienced ELS, including studies on young populations within institutional settings [136,154–156], studies on adults with PTSD who have been assessed for the effects of childhood stress [157,158],

and studies across several ELS domains such as life episodes, parental factors, direct victimization, contextual risks, and interpersonal stressors [159]. Table 1 summarizes recent prenatal and postnatal studies (2019–2023) on the relationship between ELS and GM.

Table 1. Recent prenatal and postnatal studies (2019–2023) on the relationship between ELS and GM.

Study	Design	Characteristics	Outcomes
PRENATAL			
Aatsinki et al. [150]	Longitudinal	N = 446 mother–infant (2.5 months of age) pairs. Determination of prenatal psychological distress (PPD) (N = 399) and hair cortisol concentrations (HCC) (N = 115). 16S rRNA amplicon sequencing.	Both maternal PPD and HCC were linked to alterations in the GM of infants. Chronic PPD was negatively associated with the abundance of <i>Actinobaculum</i> , <i>Anaerotruncus</i> , <i>Akkermansia</i> , <i>Epulopiscium</i> , <i>Eubacterium</i> , <i>Megamonas</i> , <i>Megasphaera</i> , <i>Odoribacter</i> , <i>Parabacteroides</i> , <i>Paraprevotella</i> , <i>Phascolarctobacterium</i> , <i>Propionibacterium</i> , <i>Pseudoramibacter</i> , and <i>Slackia</i> , and positively with <i>Actinomyces</i> , <i>Coprococcus</i> , <i>Dialister</i> , <i>Dorea</i> , <i>Finegoldia</i> , <i>Rothia</i> , and <i>Veillonella</i> abundance. Maternal depression indicators were positively correlated with the abundance of <i>Butyricimonas</i> and <i>Prevotella</i> . Maternal HCC were associated with changes in the infant’s GM, showing negative correlations with <i>Actinobaculum</i> , <i>Anaerotruncus</i> , <i>Butyricimonas</i> , <i>Citrobacter</i> , <i>Enterococcus</i> , <i>Lactobacillus</i> , <i>Paraprevotella</i> , <i>Phascolarctobacter</i> , <i>Ruminococcus</i> , and <i>Slackia</i> .
Jahnke et al. [152]	Longitudinal	N = 25 mother–infant dyads. Maternal precariousness and HPA axis dysregulation were assessed both during and after pregnancy using validated scales. 16S rRNA amplicon sequencing.	Both maternal precarious exposure and HPA dysregulation were consistently linked to alterations in the infants’ GM. Maternal precarity was associated with lower diversity and higher relative abundance of <i>Enterobacteriaceae</i> and <i>Streptococcaceae</i> and a lower relative abundance of <i>Bifidobacterium</i> and <i>Lachnospiraceae</i> . Maternal HPA axis dysregulation during pregnancy was also associated with a greater relative abundance of <i>Veillonella</i> .
POSTNATAL			
D’Agata et al. [154]	Longitudinal	N = 82 infants stay in a neonatal intensive care unit, where stay can be stressful due to the separation of parents and infants as well as medical procedures. 16S rRNA amplicon sequencing.	Higher stress scores on the Neonatal Infant Stressor Scale were associated with higher relative abundances of <i>Proteus</i> and <i>Veillonella</i> .
Reid et al. [156]	Case-control	N = 17 adolescents (aged 13–21) who had been internationally adopted from orphanages, comparing them with non-institutionalized adolescents (N = 18). 16S rRNA amplicon sequencing.	The stressed group had significantly higher abundances of several bacterial taxa, including the genera <i>Bacteroides</i> , <i>Coprococcus</i> , <i>Escherichia</i> , <i>Prevotella</i> , and <i>Streptococcus</i> , compared to the non-institutionalized group.
Malan-Muller et al. [158]	Case-control	N = 79 participants with PTSD (>18 years old). 16S rRNA amplicon sequencing.	Random forest models identified a consortium of the following four genera <i>Mitsuokella</i> , <i>Odoribacter</i> , <i>Catenibacterium</i> , and <i>Olsenella</i> could distinguish PTSD status with 66.4% accuracy. The relative abundance of this consortium was higher in the PTSD group and correlated positively with CAPS-5 and CTQ scores. MDD diagnosis was also associated with increased relative abundance of the <i>Bacteroidota</i> phylum.

Table 1. Cont.

Study	Design	Characteristics	Outcomes
Hantsoo et al. [160]	Longitudinal	N = 48 of healthy women between 20 and 26 weeks of gestation compared a low ACEs control group with a high ACEs group. 16S rRNA amplicon sequencing.	Women in the high ACEs group exhibited a higher differential abundance of <i>Prevotella</i> and a lower abundance of <i>Erysipelotrichaceae</i> and <i>Phascolarctobacterium</i> compared to those in the low ACEs group
Michels et al. [161]	Cross-sectional	N = 93 children-adolescents (8–16 years old) with psychosocial stress. 16S rRNA amplicon sequencing.	High stress was associated with lower <i>Bacillota</i> at the phylum level and higher <i>Bacteroides</i> , <i>Parabacteroides</i> , <i>Rhodococcus</i> , <i>Methanobrevibacter</i> , and <i>Roseburia</i> but lower <i>Phascolarctobacterium</i> at genus level.
Flannery et al. [162]	Cross-sectional	N = 40 children (mean age 6.12 years). Shotgun metagenomics analyses using Illumina GAIIx platform, taxonomically profiled using MetaPhlAn,	Both socioeconomic risk exposure and child behaviors associate with the relative abundances of specific taxa, such as <i>Bacteroides</i> spp. and <i>Bifidobacterium</i> spp. as well as functional modules encoded in their genomes (e.g., monoamine metabolism) that have been linked to cognition and health. <i>B. fragilis</i> was associated with reduction in aggressively, emotional reactivity, sadness, and impulsivity. <i>Coproccoccus comes</i> and <i>Eubacterium rectale</i> were associated with increase in anxious depression and less inhibitory control. <i>Roseburia inulinivorans</i> was associated with reduced depressive problems.
Keskitalo et al. [163]	Case-control	N = 193 infants (2.5-month-old) with both fecal sample and salivary stress response measurement. 16S rRNA amplicon sequencing.	The findings indicated that a reduced cortisol response to the stressor was weakly linked to GM diversity, while stronger associations were observed between cortisol levels and the specific taxonomic composition of the children's fecal microbiome.
Laue et al. [164]	Longitudinal	N = 260 children. 16S rRNA amplicon sequencing.	The findings indicated that while most outcomes were not linked to changes in beta-diversity, a higher diversity in the microbiome at 6 weeks was associated with lower depression levels in the entire sample, as well as reduced anxiety and improved internalizing behaviors, particularly in boys. In boys, better adaptive functioning scores correlated positively with <i>Bifidobacterium</i> spp., <i>Bacteroides vulgatus</i> , and <i>Streptococcus</i> spp. abundance, but negatively with the abundance of <i>Klebsiella oxytoca</i> , <i>Clostridium</i> spp., and <i>Haemophilus</i> spp. Better depression score was associated with the abundance of <i>Tyzzereella nexelis</i> , and negative relationship with <i>Eggerthella lenta</i> abundance. In girls, <i>Granulicatella</i> was associated with higher anxiety scores at 6 weeks, while <i>Streptococcus peroris</i> was linked to better internalizing behavior at 1 year. Furthermore, certain <i>Blautia</i> spp. were related to higher hyperactivity scores, with a stronger association observed in girls.

Table 1. Cont.

Study	Design	Characteristics	Outcomes
Kraaij et al. [165]	Cross-sectional	N = 1784 children (10-year-old) with mental problems. 16S rRNA amplicon sequencing.	Lower GM diversity and richness was related to internalizing problems and anxious/depressed conduct problems. Although a definitive evidence linking GM diversity, taxonomic traits, or functions, and mental health problems in the pediatric population was not established, a reduction in the genera that have previously been related to psychiatric disorders, including <i>Anaerotruncus</i> , <i>Hungatella</i> , and <i>Oscillospiraceae</i> was found.

CAPS-5: Clinician-administered PTSD Scale for DSM-5; CTQ: Childhood Trauma Questionnaire.

5.2.1. Prenatal Stress Studies

A longitudinal study tracked Dutch children from the third trimester of pregnancy through to 110 days after birth [151]. It was found that prenatal stress, which was measured via surveys and basal salivary cortisol, was associated with offspring GM composition for at least three months. Participants experiencing high levels of cumulative prenatal stress showed an increased relative abundance of genera belonging to the phylum Pseudomonadota (*Enterobacter*, *Escherichia*, and *Serratia*), and a lower relative abundance of genera from the phyla Bacillota (*Aerococcus*, *Lactococcus*, and *Lactobacillus*) and Actinomycetota (*Bifidobacterium*, *Collinsella*, and *Eggerthella*), suggesting an association with the GM dysbiosis.

Aatsinki et al. [150] conducted a longitudinal study in Finland. The authors found that both maternal prenatal psychological distress (PPD) and hair cortisol levels were linked to alterations in the GM of infants at 2.5 months of age ($N = 446$ mother–infant pairs). Chronic PPD, as assessed by various questionnaires, was negatively associated with *Actinobaculum*, *Anaerotruncus*, *Akkermansia*, *Epulopiscium*, *Eubacterium*, *Megamonas*, *Megasphaera*, *Odoribacter*, *Parabacteroides*, *Paraprevotella*, *Phascolarctobacterium*, *Propionibacterium*, *Pseudoramibacter*, and *Slackia* abundance, and positively with *Actinomyces*, *Coprococcus*, *Dialister*, *Dorea*, *Finegoldia*, *Rothia*, and *Veillonella* abundance. Maternal depression indicators were positively correlated with the abundance of *Butyricimonas* and *Prevotella*. On the other hand, maternal hair cortisol levels were associated with changes in the infant's GM, showing negative correlations with *Actinobaculum*, *Anaerotruncus*, *Butyricimonas*, *Citrobacter*, *Enterococcus*, *Lactobacillus*, *Paraprevotella*, *Phascolarctobacter*, *Ruminococcus*, and *Slackia*.

Another longitudinal study of 25 mother–infant dyads in the Galapagos Islands (Ecuador) found correlations between exposure to precariousness and peripartum changes in the HPA axis and in the offspring GM [152]. Maternal precariousness was assessed both during and after pregnancy using validated scales, while HPA axis activity was measured through maternal salivary cortisol levels collected during and after pregnancy. In addition, saliva, and stool samples were obtained from newborns at three days and two months of age. The authors found that both maternal precarious exposure and HPA dysregulation were consistently linked to alterations in the infants' GM. These changes were characterized by reduced species diversity, a decrease in *Bifidobacterium* abundance at the genus level, and an increased presence of potential pathogens within the *Enterobacteriaceae* family. Figure 1 shows changes in the GM at the genus level in several prenatal stress studies.

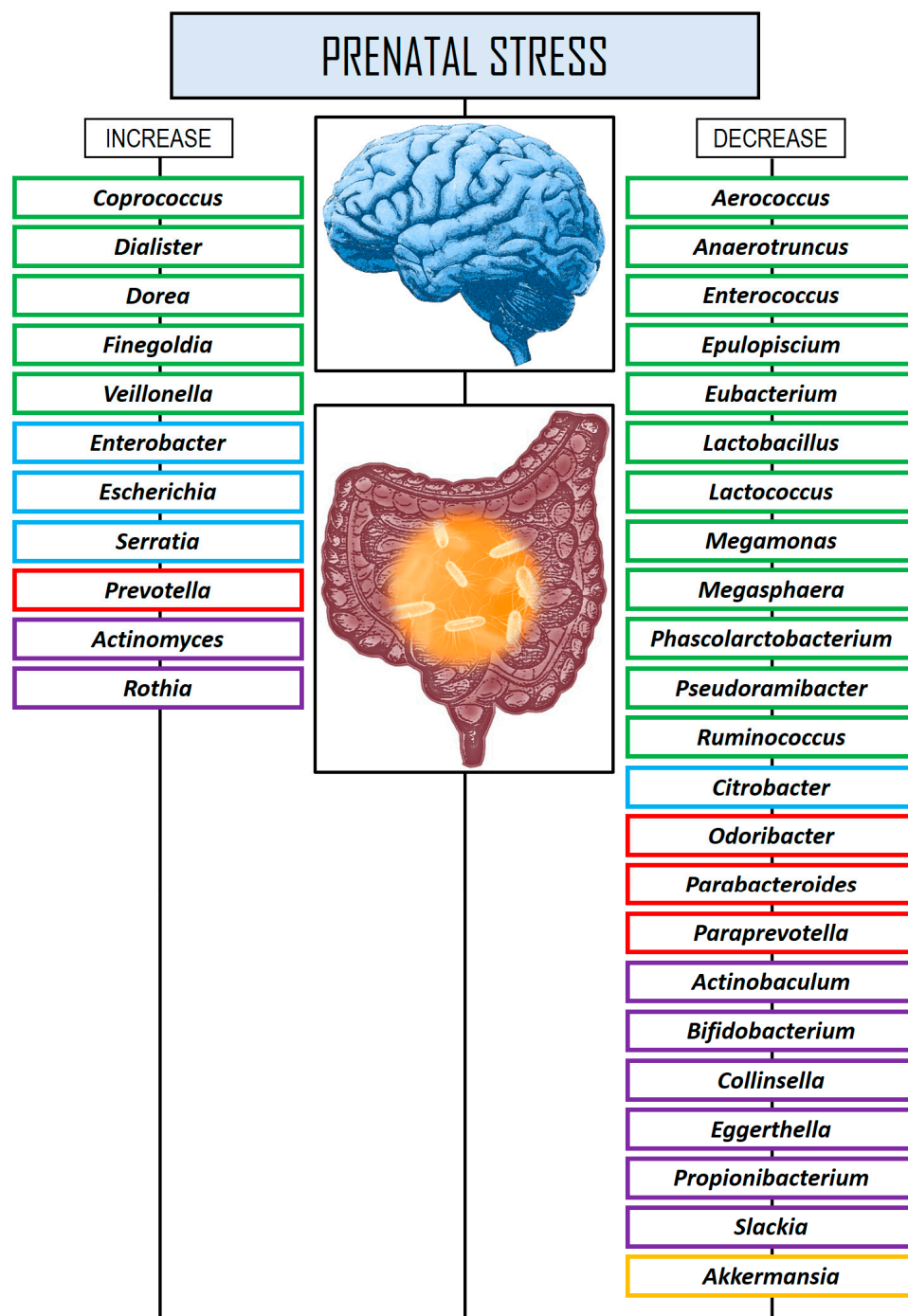


Figure 1. Changes in the GM at the genus level in several prenatal stress studies. Rectangles in green color: phylum Bacillota. Rectangles in blue color: phylum Pseudomonadota. Rectangles in red color: phylum Bacteroidota. Rectangles in violet color: Actinomycetota. Rectangles in yellow color: phylum Verrucomicrobiota.

5.2.2. Postnatal Stress Studies

An exploratory study involving adults ($N = 18$) with a history of trauma and PTSD revealed a reduced overall gut microbiota abundance of taxa from the phyla Actinomycetota, Lentisphaerota, and Verrucomicrobiota in individuals who developed PTSD, compared to those who were exposed to trauma but did not develop the disorder [157]. However, no significant differences were observed between the PTSD and control groups in terms of alpha- or beta-diversity measures.

A longitudinal study examined the first six weeks of life of 82 infants stay in a neonatal intensive care unit, where stay can be stressful due to the separation of parents and infants as well as to medical procedures [154]. The authors found that higher stress scores on the Neonatal Infant Stressor Scale were associated with higher relative abundances of *Proteus* and *Veillonella*.

A study involving psychiatrically healthy women ($N = 48$) between 20 and 26 weeks of gestation compared a low ACEs control group with a high ACEs group, where participants had experienced multiple childhood adversities. Women in the high ACEs group exhibited a higher differential abundance of *Prevotella* and a lower abundance of *Erysipelotrichaceae* and *Phascolarctobacterium* compared to those in the low ACEs group [160]. Importantly, these women were psychiatrically healthy, suggesting that ACEs might affect the GM independently of current stress or psychiatric status. This study also indicates an association between GM composition and the acute glucocorticoid-immune response to stress and suggests that women with high ACEs who consume higher amounts of ω -3 polyunsaturated fatty acids may experience a reduced inflammatory response to acute stress.

A cross-sectional study conducted by Michels et al. [161] in young participants ($N = 93$, 8–16 years old) explored the relationship between the GM in feces and psychosocial stress, measured via questionnaires and cortisol levels. The findings revealed that elevated levels of stress were linked to a decrease in alpha-diversity, to a higher abundance of *Bacteroides*, *Methanobrevibacter*, *Parabacteroides*, *Roseburia*, and *Rhodococcus*, and to a lower abundance of the genera *Phascolarctobacterium* and the phylum Bacillota. Several genera exhibited conflicting results across different stress measures, such as *Ruminococcaceae* UCG014, members of the phylum Mycoplasmatota (formerly Tenericutes), *Christensenellaceae* R7, *Prevotella* 9, and *Eubacterium coprostanoligenes*.

Another longitudinal study focused on a shorter time frame and measured the impact of childhood adversity, specifically institutional or foster care, on the GM composition during adolescence ($N = 344$ participants, ages 3–18 years) [136]. Early childhood adversity was related to shifts in alpha- and beta-diversity, and decreases in *Lachnospiraceae*, whether related to adversity or not, were associated with brain reactivity, particularly in the PFC, during emotional processing.

A cross-sectional study involving healthy children aged 5 to 7 years ($N = 40$) explored the relationships between behavioral dysregulation, socioeconomic risk, diet, caregiver behaviors, and GM [162]. The findings indicated that higher levels of *Bacteroides fragilis* and *Bifidobacterium* spp. were linked to lower instances of aggression, emotional reactivity, externalizing behaviors, sadness, and impulsivity, as well as fewer family conflicts. On the other hand, two butyrate-producing bacteria, *Coproccoccus comes* and *Eubacterium rectale*, were associated with greater anxiety and depression, alongside reduced inhibitory control. Interestingly, *Roseburia inulinivorans*, another butyrate producer, showed an inverse correlation, being linked to fewer depressive symptoms.

Keskitalo et al. [163] investigated the association between the GM composition and the cortisol response to stress in children. The study used data from the FinnBrain Birth Cohort, a large transgenerational prospective observational study that initially included 3808 mothers, 2623 fathers, and 3837 children. The nested case-control analysis focused on children who had both a fecal microbiome profile and salivary cortisol measurements at 2.5 months of age. Following exposure to a mild acute stressor, cortisol levels were assessed at four intervals: 0, 15, 25, and 35 min. The findings indicated that a reduced cortisol response to the stressor was weakly linked to GM diversity, while stronger associations were observed between cortisol levels and the specific taxonomic composition of the children's fecal microbiome.

Reid et al. [156] examined the GM of adolescents ($N = 35$, aged 13–21) who had been internationally adopted from orphanages into the United States, comparing them with non-institutionalized adolescents. The study found that the stressed group had significantly higher abundances of several bacterial taxa, including the genera *Bacteroides*, *Coprococcus*, *Escherichia*, *Prevotella*, and *Streptococcus*, compared to the non-institutionalized group. Furthermore, notable associations were observed between the relative abundance of *Escherichia*, specific T-cell subsets in circulation, and cytomegalovirus seropositivity. These findings suggest a potential connection between the GM and immune system alterations resulting from early life adversity.

Laue et al. [164] carried out a 3-year prospective longitudinal study to investigate sex-specific relationships between the GM and behavioral outcomes. The study involved stool samples from 260 children taken at 6 weeks, 1 year, and 2 years of age. When the children reached approximately 3 years old, their parents completed a behavioral assessment survey to evaluate various phenotypes. The findings indicated that while most outcomes were not linked to changes in beta-diversity, a higher diversity in the microbiome at 6 weeks was associated with lower depression levels in the entire sample, as well as reduced anxiety and improved internalizing behaviors, particularly in boys. Specifically, in boys, better adaptive functioning scores correlated positively with *Bifidobacterium* abundance and negatively with *Klebsiella* abundance. In girls, *Granulicatella* was associated with higher anxiety scores at 6 weeks, while *Streptococcus peroris* was linked to better internalizing behavior at 1 year. Furthermore, certain *Blautia* species were connected to higher hyperactivity scores, with a stronger association observed in girls.

In a case-control study by Malan-Muller et al. [158], the relationship between the GM and mental health outcomes was examined in adults with PTSD, comparing them to trauma-exposed individuals without PTSD. The study also involved several questionnaires to assess anxiety disorders, past traumatic events, and major depressive disorder (MDD). Fecal samples were collected within the same week as the clinical assessments. The results identified a specific group of four genera (i.e., *Catenibacterium*, *Mitsuokella*, *Odoribacter*, and *Olsenella*) that were positively correlated with PTSD. Moreover, MDD was associated with a higher relative abundance of bacteria from the Bacteroidota phylum. These findings suggest that early life trauma could set the stage for microbiome alterations, which may contribute to a pro-inflammatory response, potentially increasing susceptibility to PTSD later in life.

More recently, Kraaij et al. [165] conducted a cross-sectional study of 1784 ten-year-old children from the Netherlands to characterize associations of the GM with child mental health problems. Although lower gut microbial diversity and richness was related to internalizing problems and anxious/depressed conduct problems, these associations were not significant. These authors did not find definitive evidence linking GM diversity, taxonomic traits or functions, and mental health problems in the pediatric population. However, they noted suggestive findings indicating a reduction in the genera that have previously been related to psychiatric disorders, including *Anaerotruncus*, *Hungatella*, and *Oscillospiraceae*. Figure 2 shows changes in the GM at the genus level in several postnatal stress studies.

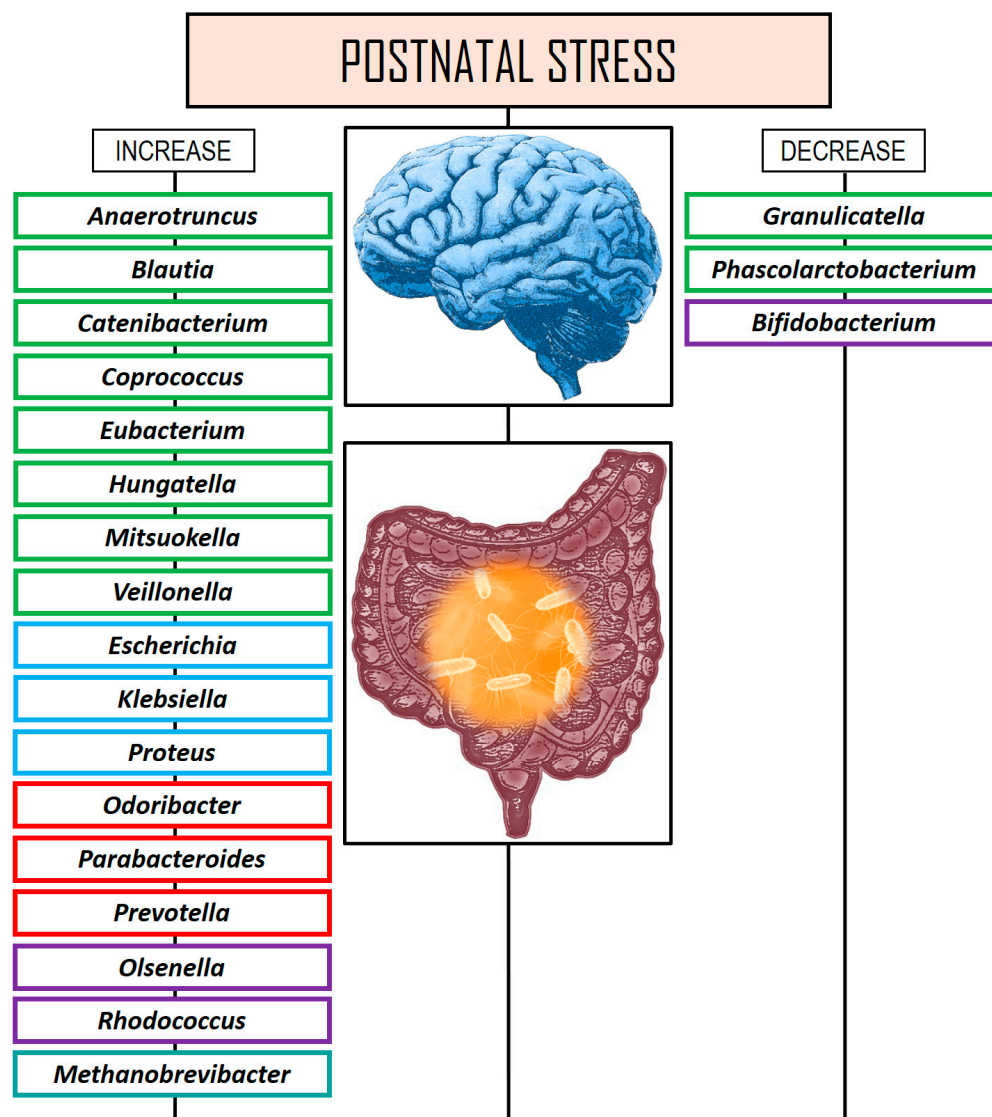


Figure 2. Changes in the GM at the genus level in several postnatal stress studies. Rectangles in green color: phylum Bacillota. Rectangles in blue color: phylum Pseudomonadota. Rectangles in red color: phylum Bacteroidota. Rectangles in violet color: Actinomycetota. Rectangles in turquoise color: phylum Euryarchaeota.

6. Microbial Key Regulators of ELS

6.1. The Role of SCFAs in ELS

SCFAs, derived from microbial fermentation of dietary fibers, are considered a pivotal mechanism by which the GM influences the effects of maternal stress on offspring neurodevelopment [166]. These SCFAs, primarily acetate, propionate, and butyrate, are efficiently absorbed into the bloodstream and can reach the brain parenchyma [167]. They have the potential to impact brain function both prenatally and postnatally, as maternal microbiota-derived SCFAs can enter the maternal bloodstream and subsequently reach the fetal brain during pregnancy [168]. In rodent models, chronic restraint stress has been shown to reduce fecal SCFA levels [169]. Furthermore, supplementation with SCFAs has been found to mitigate social defeat stress-induced deficits in reward-seeking behavior, highlighting their potential therapeutic benefits [170].

SCFAs also influence the developing fetus by impacting the microglia, which play a key role in neuromodulation throughout development and into adulthood [171]. During

embryonic development, microglia gain the ability to respond to environmental cues, and disruptions in the presence of maternal microbial metabolites can hinder their proper function and maturation [172]. While microglia do not directly express receptors for SCFAs, these molecules can diffuse into the cells, influencing gene expression by inhibiting histone deacetylase activity and preventing NF- κ B nuclear translocation in response to LPS treatment in vitro [173]. Notably, acetate, which is a key SCFA derived from the microbiome, has been shown to be essential for microglial maturation. In germ-free mice, acetate regulates the microglial metabolic state and has also been found to modulate microglial phagocytosis and influence disease progression in neurodegenerative conditions [174].

6.2. The Role of Amino Acids in ELS

In a study using maternally separated (MS) mice, Zhu et al. [175] reported that decreased levels of amino acid transporters in the gut of MS mice led to lower blood glutamine (Gln) levels and synaptic dysfunction in the medial PFC. Reduced blood Gln availability limits its use in the brain for the reuptake of presynaptic neurotransmitters like glutamate (Glu) and γ -aminobutyric acid (GABA). In addition, MS mice exhibited GM dysbiosis, specifically a decrease in the relative abundance of *Limosilactobacillus* (formerly *Lactobacillus*) *reuteri*. Supplementation with *L. reuteri* alleviated neurobehavioral deficits in MS mice by enhancing intestinal amino acid transport and restoring synaptic transmission in the medial prefrontal cortex. Moreover, supplementation with other amino acids like tryptophan (Trp) altered the GM, with increased levels of *Intestinimonas* and decreased levels of *Turicibacter* in adult offspring at 12 weeks of age in Sprague–Dawley rats [176]. These authors also observed that Trp supplementation provided protection against hypertension induced by maternal chronic kidney disease. Stress during pregnancy in mice disrupted placental Trp metabolism and reduced the availability of Trp during fetal neurogenesis, partly by diminishing the maternal Trp-metabolizing microbiota [177]. Key gut microbes involved in Trp metabolism, such as *Parasutterella* and *Bifidobacterium*, were reduced in both the dams and their offspring following prenatal stress [177]. This suggests that maternal malnutrition or drug exposure during pregnancy may influence placental Trp availability, alter the kynurenine (Kyn) metabolic pathway, and/or decrease the abundance of Trp-metabolizing microbes in the gut, potentially contributing to neuropsychiatric disorders in offspring.

In humans, Trp is primarily derived from diet and serves as a precursor of serotonin (5-HT), which is associated with metabolic disorders [178], and is also directly and indirectly implicated in regulating brain functions [179], playing a central role in the development of social and emotional behaviors in offspring [180]. Alterations in Trp metabolism are a fundamental biological marker of prenatal maternal stress induced by intrauterine inflammation [181], which increases the potential risk for neurodevelopmental disorders [36,182,183] and is associated with peer victimization in adolescents [184–186]. Children with autism spectrum disorder (ASD) have been found to have impaired Trp metabolism in the gut, CNS, and blood, which may underlie the pathophysiology of ASD [187,188].

The fetal-placental unit controls Trp metabolism, primarily via two pathways: 5-HT and Kyn. The Kyn pathway, which is active in the brain, liver, intestine, and placenta, degrades over 95% of Trp and plays a role in neurotransmission and inflammation, as well as in immune modulation and responses during pregnancy [189]. Key enzymes in the Kyn pathway include indoleamine-2,3-dioxygenase type 1 and type 2, and Trp-2,3-dioxygenase [190]. The 5-HT pathway uses up to 5% of Trp, primarily in pancreatic cells, adipose tissue, the gut, and the CNS, regulating responses to environmental stimuli such as feeding behavior, cognition, and sleep. Key enzymes in this pathway include tryptophan hydroxylase type 1 in the enterochromaffin cells of the gastrointestinal tract, adipose tissue,

and β -cell pancreatic cells, whereas tryptophan hydroxylase type 2 hydrolyzes Trp in central neurons [191].

The GM plays a critical role in the Trp metabolism, directly converting it to various molecules such as indole and its derivatives, indole acrylic acid, indole-3-acetic acid, indole-3-propionic acid, indole-3-acetaldehyde, and tryptamine [192]. These products help maintain intestinal balance by regulating the expression of pro- and anti-inflammatory cytokines [193,194]. The specific gut bacteria involved in Trp metabolism include the genera *Anaerostipes*, *Bacteroides*, *Bifidobacterium*, *Clostridium*, *Lactobacillus*, and *Ruminococcus*. Other bacteria, like *Providencia*, *Pseudomonas*, and *Staphylococcus*, mediates the conversion of Trp to Kyn [195]. Indole and its derivatives play important roles in gastrointestinal function, inflammation control, antioxidation, and immune system regulation. Indole also promotes the release of glucagon-like peptide-1, which slows down gastric emptying and reduces appetite. Moreover, tryptamine encourages the secretion of 5-HT from enterochromaffin cells, stimulating gastrointestinal movement by influencing intestinal neurons [193,195,196].

Interestingly, the excess of Trp supply during pregnancy may reduce the aggressiveness in the male offspring via modification of the MGB axis function [197]. In addition, probiotics may prevent aggressive behavior by modifying the central serotogenic system, and thus the GM may act as a complementary endocrine organ [198]. Trp exposure may also increase catecholamine concentrations in the thalamus and in the hypothalamus, affecting energy homeostasis and social interaction, which may be related to changes in the GM and in the GB axis' function [199]. Stress-induced HPA axis overactivity is related to reactive aggression [200], and the HPA axis has been involved in several adverse mental conditions, such as attention deficit hyperactivity disorder (ADHD), anxiety, and depression [201,202].

Striatal dopamine (DA) synthesis is elevated in ASD and has been linked to social defeat [203]. DA serves as the precursor for NE and EP, both of which play key roles in the reward system by contributing to feelings of satisfaction [204]. Functionally, EP and NE possess strong similarities as neurotransmitters or hormones, both acting to regulate the response to stress [205]. An NE reuptake inhibitor, viloxazine, by blocking the actions of the DA receptors and transporters, enhances the presence of DA and NE [206], thereby alleviating symptoms of impulsivity and inattention in ADHD, which is directly linked to bullying behavior in males [207,208]. The 5-HT and DA systems interact at a neurophysiological level in the regulation of impulsive aggression, which is central to several mental health disorders, such as borderline personality disorder and antisocial personality disorder [209,210].

6.3. The Role of Psychobiotics in ELS

The modulation of the GM and its metabolites via psychobiotic administration appears to be a highly promising strategy for addressing CNS alterations resulting from ELS [211]. Psychobiotics consist of probiotics, prebiotics, synbiotics, and postbiotics that provide mental benefits by acting on the GM and reducing symptoms of stress, anxiety, and depression [212]. With respect to ELS, few studies have been performed using probiotics to minimize the effects on mental health and CNS function, through the ability of probiotics to synthesize neuroactive compounds, such as GABA, 5-HT, DA, NE, and acetylcholine [33,213].

Male Sprague–Dawley rats subjected to MS were exposed to probiotics (i.e., *Lactobacillus helveticus* and *Lactocaseibacillus rhamnosus*) through the maternal drinking water during the stress period [214]. The study revealed that the stressed rat pups exhibited premature activation of the medial PFC during fear regulation, a phenomenon that could be mitigated by probiotic treatment.

Stressful social experiences in early life were investigated by Karen et al. [215] by examining how they can induce changes in the MGB axis. These authors found that the supplementation with the probiotic *Lactocaseibacillus paracasei* strain HT6 had a significant beneficial effect on anxiety-like behavior in stressed rats, along with normalized levels of ACTH, corticosterone, GRs, 5-HT, DA, and NE.

De Santa et al. [216] explored the effects of prolonged consumption of a multi-strain probiotic mixture on behavioral alterations in a MS mouse model, focusing on adult male mice. The study found that probiotic treatment, which included strains such as *Bifidobacterium animalis* subsp. *lactis* BL03, *B. animalis* subsp. *lactis* BI04, *B. breve* BB02, *Lactobacillus acidophilus* BA05, *L. helveticus* BD08, *L. paracasei* BP07, *Lactiplantibacillus plantarum* BP06, and *Streptococcus thermophilus* BT01, successfully reversed anxiety- and depressive-like behaviors. Moreover, it normalized the neuroinflammatory state by restoring the quiescent state of microglia and induced a proneurogenic effect. Additionally, the probiotic treatment significantly influenced the production of SCFAs, particularly increasing butyrate levels.

7. Discussion

This review examined ELS-related outcomes and their association with the GM. Traumatic experiences during childhood or adolescence constitute major negative life events that profoundly affect the cognitive function and development, and can lead to adverse mental conditions such as anxiety, depression, and PTSD. In turn, there are various ways through which the GM can impact human psychological processes, including the nervous system (i.e., autonomic nervous system, enteric nervous system, and vagus nerve), the immune system, and the HPA axis [217]. The effect of GM on mental disorders is mainly mediated via the synthesis of neurotransmitters and microbial metabolites, as well as through the activation of certain metabolic pathways such as Trp metabolism. Nevertheless, the precise role of the GM in modulating stress responses and influencing social behavior in children and adolescents has not yet been fully elucidated and remains as a widely debated topic. For this reason, research should aim at determining to which extent ELS is associated with alterations in the GM and whether dysbiosis early in life may induce the onset and development of various mental disorders later in life. This will highlight the GM as a novel biological factor influencing vulnerability versus resilience to stress and potentially identify new treatment targets for several mental disorders.

The influence of prenatal stress on the infant GM is supported by longitudinal evidence showing that both psychological and physiological markers of maternal distress are associated with specific microbial alterations in early life. Aatsinki et al. [150] and Jahnke et al. [152] independently demonstrated that maternal stress, HPA axis dysregulation, and hair cortisol concentrations were linked to changes in the composition of the infant GM. Notably, *Veillonella* abundance was consistently elevated in association with maternal stress markers in both cohorts, suggesting a potential role for this bacterial genus as a microbial correlate of prenatal stress exposure. Nevertheless, there are divergences between both studies. Aatsinki et al. [150] identified broad shifts, including reductions in beneficial genera such as *Anaerotruncus*, *Phascolarctobacterium*, and *Ruminococcus*, as well as elevations in *Coproccoccus* and *Prevotella*, with associations varying depending on whether distress was assessed psychologically or via cortisol biomarkers. In contrast, Jahnke et al. [152] reported a reduction in alpha-diversity and increased relative abundance of pro-inflammatory taxa such as members of the families *Enterobacteriaceae* and *Streptococcaceae*, emphasizing compositional changes potentially linked to immune modulation. These differences may reflect the distinct stress metrics used, as well as methodological variability or statistical power given the much smaller sample in Jahnke et al. [152]. Postnatal studies, in turn, present significant variability in the results, but also reveal common patterns. In the study by

D'Agata et al. [154], neonatal stress, measured by the Neonatal Infant Stressor Scale, was associated with higher relative abundances of the genera *Proteus* and *Veillonella*. Reid et al. [156] found that adolescents who experienced stress during childhood, as a result of being internationally adopted from orphanages, exhibited higher abundances of the genera *Bacteroides* and *Prevotella*. Flannery et al. [162] and Michels et al. [161] identified higher abundances of *Bacteroides*, *Rhodococcus*, and *Roseburia*. Interestingly, Laue et al. [164], found that greater diversity in the infant microbiome was associated with lower levels of depression and anxiety, particularly in boys, suggesting that GM diversity may play a protective role against psychosocial stress. In contrast, the study by Kraaij et al. [165], in a larger sample of children, reported that lower GM diversity and richness were related to internalizing problems and anxious/depressed conduct problems. These findings highlight the complexity of the relationship between GM and mental health, with results varying depending on the context, age, and nature of the stress experienced. However, a trend is observed, particularly a reduction in *Phascolarctobacterium* and an increase in the *Bacteroides* genus being associated with greater emotional and behavioral difficulties. Therefore, while prenatal exposures appear to more consistently influence taxa associated with immune maturation and colonization resistance, potentially reflecting early disruptions in vertical transmission and gut-immune crosstalk, postnatal stress exposures, particularly during sensitive periods of neurodevelopment, seem to associate more with genera linked to emotional regulation and cognition, such as *Roseburia*, *Bacteroides*, and *Coprococcus*, as well as functional pathways involved in monoamine metabolism [162]. Furthermore, while prenatal stress studies identified a potential reduction in microbial diversity [152], postnatal studies present a more variable pattern, with some of them reporting reduced richness [165] and others highlighting taxonomic shifts without diversity loss [164].

In essence, across the reviewed literature, there is growing evidence linking psychosocial stress, both prenatal and postnatal, with alterations in the GM composition across developmental stages. Despite methodological heterogeneity among studies (e.g., variations in sample sizes, age ranges, stress assessments, and sequencing techniques), the genera *Veillonella*, *Prevotella*, and *Coprococcus* were repeatedly associated with stress-related exposures in both infant and adolescent populations, suggesting a potential shared microbial signature of psychosocial stress. Specifically, *Veillonella* was positively associated with maternal HPA axis dysregulation [152] and neonatal stress exposure [154], while *Prevotella* was consistently elevated in individuals with high adversity exposure across different age groups [150,156,160]. Conversely, taxa such as *Phascolarctobacterium* and *Anaerotruncus* tended to show decreased abundance in relation to stress or psychopathology [150,161,165], possibly reflecting a stress-induced depletion of beneficial commensals. On the other hand, while *Coprococcus* was enriched in adolescents exposed to early institutionalization [156]; it was also associated with increased anxiety symptoms in younger children [162], pointing to potential developmental or contextual moderators. In addition, while some studies [163,164] reported associations between GM diversity and psychological outcomes, others found no clear links, highlighting ongoing debate regarding the role of diversity per se as a biomarker of stress resilience or vulnerability.

It is pivotal to acknowledge the limitations inherent in the studies reviewed, as these must be carefully considered when interpreting the findings of this review. First, several of these studies adopt a cross-sectional design, often resulting in small sample sizes that reduce statistical power and increase susceptibility to confounding bias. Second, most GM studies have been conducted at the genus and phylum levels, despite evidence suggesting that species-level differences are critical for inferring functional variations in the GM. Third, 16S rRNA gene sequencing, the predominant method used, has limited taxonomic resolution and does not account for other key microbial components, such as protozoa,

viruses, and fungi. Fourth, the bacterial sequencing techniques employed are unable to reliably differentiate between beneficial and pathogenic taxa. Consequently, whole-genome metagenomics, such as shotgun sequencing, is expected to surpass 16S rRNA gene sequencing in future research. Finally, diet represents a major confounding factor in the association between the GM and ELS, and it is often not adequately controlled in these studies.

A recent systematic review of human studies [218] identifies emerging patterns and significant gaps in the relationship between ELS and the GM. Prenatal stress appears consistently associated with increased abundance of Proteobacteria (currently Pseudomonadota), particularly the family *Enterobacteriaceae*, and decreased levels of *Bifidobacterium*, a genus with well-documented immunomodulatory and neuroactive properties. These changes were linked to maternal cortisol levels and early infant stress markers, suggesting potential mechanistic pathways linking maternal stress physiology to microbial colonization. However, postnatal studies present more conflicting findings, partly due to variability in stress definitions, microbiome assessment methods, and population characteristics. While some studies report reductions in alpha-diversity and shifts in beta-diversity among institutionalized or traumatized children, others fail to replicate these results, highlighting the need for greater taxonomic resolution and longitudinal designs. Moreover, discrepancies in the abundance of taxa such as *Bacteroides*, *Eubacterium*, and *Coprococcus*, which are variably associated with both protective and detrimental outcomes, underscore the limitations of current approaches and the influence of confounding factors such as sex, medication, diet, and socioeconomic conditions. The present narrative review and the systematic review by Agusti et al. [218] identify specific microbial genera, including *Veillonella*, *Prevotella*, and *Coprococcus*, as being associated with psychosocial stress across developmental stages, suggesting a potential shared microbial signature. However, the implications of these findings remain uncertain due to methodological variability across studies. Both reviews acknowledge key limitations, such as the predominance of 16S rRNA sequencing with limited taxonomic resolution, the absence of species-level analysis, and insufficient control over confounding factors like diet and socioeconomic conditions. While the review by Agusti et al. [218] emphasizes the need for longitudinal studies and a deeper understanding of the role of maternal cortisol in microbial colonization, our review also underscores the biological pathways through which the GM may influence psychological processes, particularly through neurotransmitter synthesis, microbial metabolites, and metabolic pathways such as tryptophan metabolism. Furthermore, our review highlights the roles of SCFAs, amino acids, and psychobiotics as key microbial regulators in the context of ELS.

A more comprehensive understanding of the GM and its effects on human behavior is essential to clarify its implications in the field of psychosocial sciences. In this sense, Maes et al. [219] have recently introduced a novel clinimetric approach, known as “precision nomothetic psychiatry”, which facilitates the exploration of causal relationships between causome/protectome factors, recurrence of illness index (ROI), cognitive deficits, and a quantitative score of the phenotype of depression. This model shows that ACEs and the increased translocation of Gram-negative bacteria are robustly related to depression, with these effects being mediated by ROI, reduced antioxidant defenses such as lowered high-density lipoprotein cholesterol and the activation of immune and oxidative stress pathways. Nevertheless, there is currently no evidence revealing whether ACEs and ROI affect the GM, nor whether compositional dysbiosis may mediate the effects of ACEs on the depression phenotype, which encompasses cognitive deficits and suicidal behavior.

ELS can contribute to the perpetuation of social disparities and cycles of mental health vulnerability, placing a considerable strain on public resources, healthcare systems, and overall societal well-being. To mitigate these undesirable effects, it is essential to implement

public policies that promote safe and supportive environments for children and adolescents. This includes raising awareness about the impact of ELS and educating about the potential factors influencing its onset, which should be prioritized in health professional training and community programs. Research focused on understanding the psychological processes and emotional states involved in early adversities, such as the role of humiliation in the context of bullying victimization [220], could offer valuable insights for addressing ELS and its long-term consequences. Furthermore, interdisciplinary studies on the GM and its interaction with physiological, psychological, and environmental factors may be promising to shape and regulate human behavior from infancy.

8. Conclusions

ELS can profoundly impact cognitive function and neurodevelopment, with maternal early-life nutrition playing a significant role in modulating the effects of prenatal and postnatal stress. ELS influences the GM, disrupting its composition and function by altering the synthesis of microbial metabolites, neurotransmitters, and the activation of key metabolic pathways. However, the precise role of the GM in modulating stress responses during childhood and adolescence has not yet been fully elucidated.

Although several studies have demonstrated an association between ELS and the GM, causality has not yet been established due to the numerous intrinsic and extrinsic factors influencing the MGB axis. In the coming years, research on key microbial regulators, such as SCFAs, amino acids, and psychobiotics, may represent a promising approach for addressing CNS alterations linked to ELS. Thus, further studies will be necessary to evaluate their potential as therapeutic agents.

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Abbreviations

The following abbreviations are used in this manuscript:

ACTH	Adrenocorticotropin
ACEs	Adverse childhood experiences
ADHD	Attention deficit hyperactivity disorder
ASD	Autism spectrum disorder
ANS	Autonomic nervous system
CNS	Central nervous system
CRH	Corticotropin-releasing hormone
C-section	Cesarean section
DA	Dopamine
ELS	Early life stress
EP	Epinephrine
GABA	γ -aminobutyric acid
Gln	Glutamine
Glu	Glutamate
GM	Gut microbiome
GCs	Glucocorticoids
GRs	Glucocorticoid receptors
5-HT	Serotonin

5-HTT	Serotonin transporter
HPA	Hypothalamic–pituitary–adrenal
IFN	Interferon
IL	Interleukin
Kyn	Kynurenine
LPS	Lipopolysaccharide
MDD	Major depressive disorder
MS	Maternally separated
MGB	Microbiome-gut-brain
NE	Norepinephrine
NF- κ B	Nuclear factor kappa B
PVN	Paraventricular nucleus
PTSD	Post-traumatic stress disorder
PFC	Prefrontal cortex
PPD	Prenatal psychological distress
ROI	Recurrence of illness index
SCFAs	Short-chain fatty acids
Trp	Tryptophan

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