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Stress gets into the belly: Early life stress and the gut microbiome

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ABSTRACT

Research has established that stress "gets under the skin," impacting neuroendocrine and neuroimmune pathways to influence risk for physical and mental health outcomes. These effects can be particularly significant for early life stress (ELS), or adverse childhood experiences (ACEs). In this review, we explore whether stress gets "into the belly," that is, whether psychosocial stress affects the gut microbiome. We review animal and human research utilizing a variety of stress paradigms (acute laboratory stressors, chronic stress, stressful life events, perceived stress, ELS, in utero stress) and their impacts on the gut microbiota, with a particular focus on ELS. We also review data on dietary interventions to moderate impact of stress on the gut microbiome. Our review suggests strong evidence that acute laboratory stress, chronic stress, and ELS affect the gut microbiota in rodents, and growing evidence that perceived stress and ELS may impact the gut microbiota in humans. Emerging data also suggests, particularly in rodents, that dietary interventions such as omega-3 fatty acids and pre- and probiotics may buffer against the effects of stress on the gut microbiome, but more research is needed. In sum, growing evidence suggests that stress impacts not only the neuroendocrine and neuroimmune axes, but also the microbiota-gut-brain-axis, providing a pathway by which stress may get "into the belly" to influence health risk.

1. Introduction

In recent decades, a large body of research has focused on how stress "gets under the skin" [1–7]. That is, how psychosocial stressors affect the body's physiological systems to influence risk for physical disease and mental health disorders [3]. Much of this work has focused on how stress impacts physical and mental health via neuroendocrine and neuroimmune pathways [8–12], finding that myriad types of stress "get under the skin" to influence the hypothalamic pituitary adrenal (HPA) axis and immune system function. The types of stress implicated include stressful life events [13–15], daily hassles [16,17], chronic stress [18–21], traumatic stress [22,23], adverse childhood experiences [24–27], and acute laboratory stressors [28–31].

Early life stress (ELS), in humans often referred to as adverse childhood experiences (ACEs), may be a particularly formative type of stress [32,33]. These significant stressors experienced in childhood or adolescence may include physical, emotional, or sexual abuse or trauma; physical or emotional neglect; chronic household dysfunction; or low socioeconomic status. McEwen referred to the "biological embedding" of early life stress, emphasizing that these early stressors may determine "operating ranges of physiological systems" for the remainder of the lifespan [3]. In other words, early experiences set the physiologic stage for how the body and brain respond to later stressors. In humans and animal models, ELS programs a dysregulated neuroendocrine-neuroimmune axis [25,33] that persists through adulthood [24]. However, relatively little is known about how ELS impacts the gut microbiome.

The gut microbiome represents a new frontier in stress research. The gut microbiome refers to the collection of microbiota (bacteria, viruses, protozoa, fungi) that inhabit the gut, as well as the genetic matter and byproducts (e.g. short chain fatty acids (SCFAs), neurotransmitters) of the microbiota. The gut microbiome is linked to the central nervous system (CNS) via the gut-brain axis, a bidirectional communication axis. The CNS also interacts with the stress-responsive neuroendocrine and neuroimmune axes [34–36]. The conceptual model of the bidirectional gut-brain-axis has been extended to encompass a "microbiota-gut-brain-axis" [37]. Communication between the microbiota and brain occurs through numerous pathways [38–42]. These pathways include the vagus nerve, immune-inflammatory mechanisms, bacterial metabolites, neurotransmitters and the HPA axis, as well as yet-unknown pathways.

In this review, we move beyond stress getting "under the skin" and

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discuss whether stress might get "into the belly," i.e. whether stress affects the gut microbiome, with an emphasis on early life stress. While other reviews have focused on the gut microbiome and psychiatric illness, in this review we focus specifically on stress. We review different types of stress and how they are related to changes in the gut microbiome, including data from animal studies, but with a strong focus on clinical research. Where available, we discuss associated data on changes in inflammatory markers. We also discuss potential dietary intervention targets.

2. Psychosocial stress impact on the gut microbiome

Studies have generally focused on the impact of stress on the richness and diversity of gut microbial community composition. Briefly, the richness refers to the number of different species present, while diversity refers to how the species are distributed. Operational taxonomic units (OTUs) refer to clusters of similar DNA sequences (e.g. a proxy for species). Alpha diversity measures variance within an individual, while beta diversity measures variance between individuals.

2.1. Laboratory social stressors in animal models

In a key early study, mice subjected to social disruption stress for two hours daily over six days experienced a reduction in gut microbial diversity and richness [43]. The social disruption stressor involved an aggressive male mouse being placed into the home cage of the resident mice. Immediately following the stressor, levels of gut *Bacteroides* were lower and *Parabacteroides* were higher compared with non-stressed controls. At fifteen hours post-stressor, levels of bacteria in the genus *Roseburia* were increased compared with controls. The stressor also decreased levels of *Coprococcus* genus, *Dorea* species, and *Pseudobutyrivibrio* spp. As expected, the stressor acutely increased levels of proinflammatory cytokines, including interleukin-6 (IL-6) and the chemokine monocyte chemoattractant protein-1 (MCP-1). Intriguingly, these increases in proinflammatory cytokines appeared to be modulated by the gut microbiota; the aforementioned decreased levels of *Coprococcus*, *Dorea*, and *Pseudobutyrivibrio* were inversely correlated with IL-6 levels. To test whether abolishing the gut microbiota would diminish the stressor-induced increases in IL-6, the researchers administered antibiotics to reduce bacteria in the gut by 100-fold. Indeed, antibiotic administration blocked the stress-induced IL-6 increase, suggesting that gut microbiota may moderate stress-induced inflammation. Later studies in rodents have found similar stress-induced alterations in the gut microbiota. For instance, exposure to a single two-hour social disruption stressor altered gut microbial community composition, particularly reducing abundance of the genus *Lactobacillus* [44]. This social disruption stressor increased cytokine production in mice, but only in mice with intact microbiota, not in germ-free animals, similarly suggesting that gut microbiota may moderate stress-induced inflammation [45].

2.2. Laboratory psychosocial stressors in humans

Acute stressors administered in the clinical laboratory provide a standardized means of measuring physiological response to mild stress in humans. The stressor is administered in a controlled laboratory setting, usually over the course of minutes to hours. The Trier Social Stress Test (TSST), a brief stressor involving public speaking, reliably increases cortisol and proinflammatory cytokine levels in adults. To date, only one published study has examined associations between gut microbiome composition and response to an acute laboratory stressor. A sample of healthy pregnant women underwent the TSST, and cytokine and cortisol response to the TSST were assessed. Proximal to the time of the TSST, stool was sampled to assess gut microbial community composition. Cytokine and cortisol response to the acute stressor were significantly associated with several gut taxa: IL-6 response was positively associated with abundance of *Bacteroides* and negatively with *Clostridiales*, *Lachnospiraceae*, *Dialister*, and *Enterobacteriaceae*; tumor necrosis factor-alpha (TNF-α) response was positively associated with abundance of *Bacteroides*, *Prevotella*, and *Megasphaera* and negatively with *Ruminococcaceae*; C-reactive protein (CRP) response was positively associated with abundance of *Ruminococcaceae* and *Megasphaera*; and serum cortisol response was positively associated with abundance of *Rikenellaceae* and *Dialister*, and negatively with *Bacteroides* [42]. In previous studies, *Dialister* abundance was negatively associated with baseline IL-6 levels in healthy adults [46] and *Megasphaera* abundance was positively associated with stimulated IFN-γ production [47].

2.3. Chronic stress in animal models

There is evidence in rodents indicating that chronic stress (in rodents, typically over one week or more), impacts the gut microbiome. For instance, chronic stress over one month in mice increased levels of gut operational taxonomic units (OTUs) related to *Helicobacter*, Peptostreptococcaceae, *Streptococcus*, and *Enterococcus faecalis*, all taxa associated with inflammation, and decreased levels of *Rikenella*, *Roseburia*, and Lachnospiraceae [48]. The chronic stress also increased circulating white blood cell counts and activated the IL-6 /STAT3 signaling pathway. Chronic unpredictable mild stress reduced relative abundance of *Lactobacillus* and increased relative abundance of *Akkermansia* in the gut, which were associated with increases in proinflammatory markers interferon-γ (IFN-γ) and TNF-α in the hippocampus [49]. Rats that underwent chronic restraint stress for 13 days experienced changes in relative abundance of multiple gut taxa compared with non-stressed animals [50]. While changes in gut microbiota composition diminished by three weeks post-stress, differences in gut metabolites, such as amino acids, persisted.

2.4. Chronic stress in humans

In humans, chronic stress is often studied using long-term stressors (typically over weeks to months), such as caregiving for an ill relative [9, 51]. Unfortunately, there are few studies in humans examining the impact of chronic stress on the gut microbiome. One study examined the stress of entering childcare on gut microbiome composition of three-month olds, and found that after one month of childcare, there were no significant impact on the infants' gut microbiota [52]. Another study in medical students preparing for national examinations over a six-month period had a decline in *Bifidobacterium* spp. and an increase in *Streptococcus* spp [53]. Given the evidence of chronic stress impacts on the gut microbiome in animals, more human research in this area is needed.

2.5. Naturalistic stressors and stressful life events in humans

Naturalistic stressors, such as academic examination stress, are often used to model relatively brief (days to weeks), mild stressors in human subjects research. Among students undergoing final examinations, counts of gut lactic acid bacteria significantly decreased during the high-stress examination week compared with the lower stress early semester [36]. Exposure to stressful life events in the past year is another index of naturalistic stress exposure. In a sample of healthy children and adolescents, those with more negative life events in the past year and low heart rate variability (index of parasympathetic activity) had lower gut alpha diversity. These individuals with more past-year stressors also had lower abundance of *Firmicutes* at the phylum level, lower *Phascolarctobacterium* at the genus level, and higher *Bacteroides*, *Parabacteroides*, *Rhodococcus*, *Methanobrevibacter* and *Roseburia* [54].

2.6. Perceived stress in humans

Perceived stress is an individual's subjective appraisal of stress in

their lives, specifically how unpredictable, uncontrollable, and overloaded they feel. In a sample of physically and psychologically healthy women, perceived stress, measured by the Perceived Stress Scale (PSS), was not significantly associated with any markers of gut composition and diversity [55]. In another study, participants reported on perceived stress (PSS) and minor stressors experienced in the past week (Weekly Stress Inventory Short Form (WSI-SF)). The study found intriguing racial differences in the effect of stress on the gut microbiome. Among Caucasian women, as perceived stress increased, *Clostridium* and *Ruminococcus* abundance increased, while among Black women, as perceived stress increased, the abundance of these taxa decreased [56]. Similarly, *Fusobacterium* abundance decreased with greater exposure to weekly stressors (higher WSI-SF) among Caucasian women, but among Black women, more weekly stressors increased *Fusobacterium* abundance [56]. In a sample of individuals with inflammatory bowel disease in remission, Shannon index, a measure of alpha diversity, was reduced in those with higher levels of perceived stress compared with those who reported lower perceived stress [57]. Perceived stress was negatively correlated with the relative abundance of *Sutterella, Haemophilus, Lachnospira, Parabacteroides,* RF32 family and *Eubacterium* taxa [57]. Children with Crohn's disease who reported high levels of perceived stress in the prior two weeks had had significantly lower relative abundance of *Firmicutes* and *Anaerostipes*, and higher abundance of *Parabacteroides*, compared to those with lower perceived stress [58].

3. Early life stress impact on the gut microbiome

3.1. Early life stress in animal models

In rodents, ELS alters the gut microbiome with effects that persist into adulthood [59–62]. A key early study in rhesus macaques utilized a maternal separation stressor, in which infant macaques were separated from their mothers for one week. The separation stressor reduced fecal *Lactobacillus* levels and induced stress-indicative behaviors [35]. Another early study found that as adults, ELS-exposed rats had alterations in gut microbiota, as well as greater corticosterone, TNF-α and IFN- γ levels than non-ELS rats [61]. ELS increased levels of *Bifidobacterium bifidum*, *Lactobacillus*, *Clostridium leptum* and *Clostridium coccoides* in mice; adrenalectomy mitigated these effects [63]. An important study in rats established that ELS reduced the *Firmicutes*:*Bacteroidetes* ratio in the adult gut, and increased taxa associated with inflammation, including *Akkermansia*, *Flexibacter* and *Prevotella* [62]. In a "two-hit" model, mice experienced ELS, then as adults were subjected to chronic stress [64]. These mice experienced increases in gut *Bacteroidetes* and *Proteobacteria*, particularly *Clostridium* species.

Recent research suggests that ELS may affect males and females differently. Mice exposed to multiple forms of ELS showed sex-dependent differences in gut microbiota, as well as differences in behavior and gene expression in the prefrontal cortex [65]. Specifically, ELS impacted abundance of taxa in the *Lachnospiracea*e and *Porphyromonadaceae* families, unclassified *Firmicutes*, and *Bacteroides*, *Lactobacillus* and *Alloprevotella* genera in males. ELS impacted *Lactobacillus* and *Mucispirillum* genera in females. Another study specifically examined sex differences in ELS impact on the gut microbiota. In both male and female rats, ELS increased fecal bacteria of the *Bacteroides* genus and decreased bacteria of the *Lachnospiraceae* family [66]. In males, ELS increased relative abundance of the *Streptococcus* genus and decreased relative abundance of the *Staphylococcus* genus, while in females, relative abundance of the *Sporobacter* genus was increased and abundance of the *Mucispirillum* genus was decreased. These changes in gut taxa were associated with increased colon IFN-γ and IL-6 and serum IL-1β in males, but not females. Intriguingly, the males also had increased anxiety behaviors. The researchers proposed that one potential pathway is lipopolysaccharide production by *Bacteroides*, which can induce local or systemic inflammation. Rincel and colleagues followed up to examine the impact of pharmacological inhibition of myosin light chain kinase, an enzyme involved in intestinal permeability, on ELS. They found that by pharmacologically restoring the gut barrier in ELS-exposed rats, they were able to normalize relative abundance of several taxa in adulthood [67]. Restoring the gut barrier of the rat pups also normalized behaviors and corticosterone levels in adulthood. Beyond sex, genotype may also play a role in vulnerability to effects of ELS. In rats, ELS reduced *Bacteroidetes* and increased *Firmicutes*, an effect that was potentiated by serotonin transporter (5-HTT) genotype [68]. Specifically, rats with diminished 5-HTT expression exposed to ELS experienced a shift in microbiota composition toward an inflammatory profile characterized by higher abundance of taxa including *Desulfovibrio*, *Mucispirillum*, and *Fusobacterium* [68].

3.2. Adverse childhood experiences in humans

Some studies have examined associations between childhood adversities and the gut microbiome in real time, examining proximal relationships. A study examining the earliest stages of life focused on infants in the neonatal intensive care unit (NICU) during the first six weeks of life. NICU stays can involve stress from parent-infant separation and medical procedures. The researchers operationalized stress with the Neonatal Infant Stressor Scale (NISS) which captures interventions performed in the NICU. They found that higher NISS stress scores were associated with smaller probabilities of *Proteus* and *Veillonella* being present in the gut, but when *Proteus* and *Veillonella* were present, greater stress scores were associated with higher relative abundances of both genera [69]. A study of healthy five-to-seven year-old children examined associations between socioeconomic risk, behavioral dysregulation, caregiver behavior, and the gut microbiome [70]. The study revealed significant associations between taxonomic composition and parent-child dysfunction, and that caregiver behavior moderated associations between socioeconomic risk covariates and the microbiome. In these children, abundance of gut *B. fragilis* was associated with lower reported incidents of family turmoil and fewer events on the Life Events Checklist. *B. fragilis* abundance was also associated with reduced levels of aggressive behavior, emotional reactivity, externalizing behavior, sadness, and impulsivity [70]. Finally, adolescents who had recently been in institutional care had increased abundance of genera *Prevotella*, *Bacteroides* (family Bacteroidaceae), *Coprococcus*, *Streptococcus*, and *Escherichia*, compared with non-institutionalized adolescents [71]. *Bacteroides* (f_Ruminococcaceae) abundance was significantly associated with CD^{8+} CD^{57+} T cells.

Other studies have examined associations between childhood adversity and the gut microbiome in adulthood, exploring distal relationships. A study of psychiatrically healthy women examined a low ACE control group and a high ACE group that had experienced multiple adversities in childhood. Women in the high ACE group had higher differential abundance of *Prevotella* and a trend toward lower abundance of *Erysipelotrichaceae* (species previously in *Eubacterium* genus) and *Phascolarctobacterium* than low ACE participants [42]. Importantly, these women were psychiatrically healthy, suggesting that ACE, independent of current stress or psychiatric function, may affect the gut microbiota. These findings align with rodent models demonstrating increased *Prevotella* and reduced *Firmicutes:Bacteroidetes* among rodents exposed to ELS [62]. Another study examined a shorter timeframe, measuring impact of adversity in infancy, operationalized as institutional or foster care, on gut microbiome composition in adolescence [72]. Early childhood adversity altered diversity of gut microbiome composition in adolescence, compared with controls who had not experienced childhood adversity. Another study found that adults with a history of trauma who developed PTSD had lower total gut abundance of the phyla *Actinobacteria*, *Lentisphaerae*, and *Verrucomicrobia*, compared with those with trauma exposure who did not develop PTSD [73]. However, it was difficult to isolate the effects of childhood trauma exposure as it was confounded with PTSD diagnosis. Finally, a recent study examined associations between childhood adversity and, not gut

microbiome community composition itself, but gut metabolites. History of childhood adversity, measured by the Early Traumatic Inventory Self Report, was associated with four gut metabolites: 5-oxoproline, malate, urate, and glutamate gamma methyl ester [74]. Notably, these changes in gut metabolites of ACE-exposed adults were also associated with alterations in functional brain connectivity.

4. Intergenerational effects

The association between maternal stress during pregnancy and effects on offspring gut microbiome suggests potential intergenerational effects of stress. Stress during pregnancy, including stressful life events, chronic stress, and traumatic stress, have all been associated with poor offspring neuropsychiatric outcomes [75]. Similarly, maternal childhood adversity has been associated with increased offspring risk for psychiatric diagnoses or symptoms, altered brain development [76–81], and dysregulated stress response [82]. While there are numerous factors that may influence intergenerational transmission of stress, the maternal gut microbiome is a potential target as it not only influences maternal inflammation [47], but produces metabolites necessary for the developing fetus [83].

4.1. Prenatal stress in animal models

In utero stress may be considered the earliest form of ELS. Several studies have examined the influence of maternal stress during pregnancy on the offspring, who experienced the stressor while in utero. Male mice that were exposed to prenatal stress showed multiple sequelae in adulthood, including decreased *Bacteroides* and *Parabacteroides* abundance, reduced social behavior, increased corticosterone following social interaction, neuroinflammation, decreased oxytocin receptor expression, and decreased cortical serotonin metabolism [84]. In a similar study, male rats exposed to prenatal stress had altered gut microbiota in adulthood including decreased abundance of the *Lactobacillus* genus, and elevated abundance of the *Oscillibacter*, *Anaerotruncus* and *Peptococcus* genera, compared with non-ELS controls [85].

A potential mechanism by which rodents exposed to prenatal stress experience alterations in gut microbiome may be alterations to the maternal gut or vaginal microbiome, which are then passed to the offspring. This passing of microbiota from mother to offspring is known as vertical transmission [86,87]. Generally, the gut microbiome composition of neonates is similar to the maternal vaginal microbiome, and later at weaning, the offspring gut microbiome composition is similar to the maternal gut microbiome [88,89]. In pregnant mice, chronic stress exposure altered vaginal microbiome composition, preventing a bloom of the *Firmicutes* and *Bacteroidetes* phyla, resulting in expansion of Proteobacteria and reducing relative abundance of *Lactobacillus* [60]. In the offspring, males who experienced prenatal stress had significant differences in gut community composition compared with control males and prenatal stress-exposed females at the same age.

4.2. Prenatal stress in humans

Few studies have examined associations between maternal stress during pregnancy and offspring gut microbiome. Maternal stress during pregnancy, operationalized by both self-report and cortisol levels, was associated with altered gut microbiome composition in human infants [90]. In this sample, maternal stress was assessed via a sum of subjective stress measures including general anxiety, pregnancy-related anxiety, daily hassles and pregnancy-related daily hassles; salivary cortisol awakening response was also assessed as an objective measure. Both subjective and objective stress measures were significantly associated with the relative abundances of over 60 % of bacterial groups at the genus level at at least one timepoint during the first four months of offspring life. During pregnancy, maternal daily hassles were associated positively with *Erwinia, Haemophilus,* and *Serratia* in the offspring gut at 2.5 months of age [91]. Similarly, maternal hair cortisol, reflecting cortisol levels of the first five months of pregnancy, was associated with the abundance of several bacterial genera in the offspring stool at 2.5 months. Specifically, maternal hair cortisol was negatively associated with the genera *Slackia*, *Actinobaculum*, *Paraprevotella*, *Butyricimonas, Citrobacter*, *Ruminococcus*, *Phascolarctobacter*, *Anaerotruncus, Enterococcus,* and *Lactobacillus* in offspring stool [91]. Pregnancy-related anxiety in the second trimester was significantly associated with lower diversity in newborn fecal matter (meconium), and was correlated with lower abundance of the *Enterococcaceae* family [92]. However, second trimester symptoms of depression, general anxiety, perceived stress, nor stressful life events experienced during the 2nd trimester were associated with newborn meconium bacterial composition. Another study did not significant associations between maternal self-reported stress during the third trimester and maternal fecal microbiota composition, although this study did not examine offspring gut microbiome composition [93].

5. Dietary interventions

Because the gut microbiome is modifiable by diet, this presents a potential intervention point for stress-disrupted microbiota. A number of dietary interventions, including omega-3 polyunsaturated fatty acids (PUFAs), prebiotics and probiotics have been examined in terms of ameliorative effects on stress exposure, particularly ELS, in animal models.

Key omega-3 PUFAs include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), found in fish oil, and alpha-linolenic acid (ALA), found in nuts and seeds. Mice subjected to chronic stress had reductions in gut *Lactobacillus*, which was prevented by concomitant fish oil treatment but not olive oil treatment [94]. When fecal matter was transplanted from mice that had experienced unpredictable chronic mild stress over eight weeks, to germ-free mice, the recipient animals developed depressive symptoms, an effect that was seemingly moderated by omega-3 fatty acids [95]. Mice who received an omega-3 deficient diet had an elevated gut *Firmicutes:Bacteroidetes* ratio and blunted immune responsiveness, while omega-3 supplemented mice had higher fecal *Bifidobacterium* and *Lactobacillus* abundance and dampened HPA axis activity [96].

Rodent studies suggest that dietary intake of omega-3 PUFAs may reverse the impact of ELS-induced changes to the gut microbiome and inflammation. In rodents with an ELS-induced reduced *Firmicutes*:*Bacteroidetes* ratio, supplementation with EPA and DHA in adulthood corrected the ratio to that of non-ELS rats [62]. Rats subjected to ELS had altered gut microbiota composition and intestinal permeability, yet a diet including PUFAs (arachidonic and docosahexaenoic acids), prebiotics (galacto- and fructo-oligosaccharides) and probiotics (Lactobacillus paracasei NCC2461), restored intestinal permeability but not gut microbiome composition [97]. Another study examined the influence of a fish oil supplemented diet, with or without fluoxetine, on rats subjected to ELS [98]. ELS reduced *Lachnospiraceae* sp., *Christensenellaceae*, *Caldicoprobacteraceae* and *Caldicoprobacter*, and significantly reduced total SCFA in stool, including acetate, propionate, iso-butyrate and iso-valerate. Fish oil reduced the *Firmicutes*: *Bacteroidetes* ratio, and increased ratios of *Prevotellaceae* in groups that received fish oil alone or with fluoxetine. Fish oil also significantly reduced levels of butyrate in stool. In addition, SCFAs, which are produced by gut bacteria via fermentation of dietary fiber and starches [99], may also be a dietary intervention. Chronic social stress over three weeks altered composition of the gut microbiome in mice, but these changes were corrected by treatment with oral SCFAs [100].

Polyphenol supplementation has also showed effects in mitigating impact of ELS on the gut microbiome. ELS altered abundance of gut taxa, including *Streptococcus, Ruminococcus, Parabacteroides, Rothia,* and *Christensenellaceae*, and induced depressive behaviors and altered HPA axis function in the adult. Supplementation with quercetin significantly increased *Enterorhabdus* abundance and xanthohumol changed the

abundance of *Asteroplasma, Lachnospiraceae*, and *Coprococcus* [101]. Supplementation was also associated with reduction in depressive behaviors and corticosterone production.

Finally, prebiotics and probiotics impact gut microbiome composition, and may protect against stress-induced changes. Treatment with the probiotic *Bifidobacterium bifidum* G9-1 prevented the deleterious effects of ELS on gut microbiome composition, and prevented a hypersensitive corticosterone response to restraint stress [102]. Chronic stress decreased the relative abundance of gut taxa including *Bifidobacterium*, but in mice pretreated with prebiotics, the effects of stress on the gut microbiome, as well as corticosterone and proinflammatory cytokine levels and depression-like and anxiety-like behavior, were limited [103]. In humans, medical students preparing for examinations who received the probiotic *Lactobacillus gasseri* CP2305 for 24 weeks did not experience the changes in abundance of *Bifidobacterium* spp. and *Streptococcus* spp that their colleagues who received placebo did [53].

6. Conclusion

In this review, we discussed not how stress gets "under the skin," but

Table 1
Impact of various stressors on the gut microbiome in animal and human research.

Stressor	Model	Gut microbiome	Inflammatory markers
Laboratory Stressor			
Social disruption	Animal	Reduced gut microbial diversity and richness [43]	Increased IL-6, MCP-1
Social disruption	Animal	Reduced abundance of genus *Lactobacillus* [44]	Increased cytokine production
Chronic Stress			
Chronic restraint stress	Animal	Increased OTUs related to *Helicobacter*, Peptostreptococcaceae, *Streptococcus*, *Enterococcus faecalis;* decreased *Rikenella*, *Roseburia*, Lachnospiraceae [48]	Increased circulating white blood cell counts, activated IL-6 /STAT3 signaling
Chronic unpredictable mild stress	Animal	Reduced relative abundance of *Lactobacillus,* increased relative abundance of *Akkermansia* [49]	Increased IFN-γ, TNF-α in the hippocampus
Childcare stress	Human	No significant impact [52]	
Examination preparation	Human	Decline in *Bifidobacterium* spp., increase in *Streptococcus* spp [53]	
Naturalistic Stressor			
Academic examination stress	Human	Decreased gut lactic acid bacteria [36]	
Stressful life event (past year)	Human	Reduced alpha diversity; lower *Firmicutes* and *Phascolarctobacterium;* higher *Bacteroides*, *Parabacteroides*, *Rhodococcus*, *Methanobrevibacter, Roseburia* [54]	
Minor stressor (past week)	Human	*Fusobacterium* abundance decreased with greater exposure to weekly stressors among Caucasian women, increased *Fusobacterium* abundance among Black women [56]	
Perceived Stress			
Perceived stress	Human	No significant associations [55]	
Perceived stress	Human	Perceived stress associated with increased *Clostridium* and *Ruminococcus* abundance in Caucasian women, reduced abundance of these taxa in African American women [56]	
Perceived stress	Human	Lower abundance of *Firmicutes*, *Anaerostipes;* higher abundance of *Parabacteroides* [58]	
Perceived stress	Human	Reduced Shannon index; Lower abundance of *Sutterella, Haemophilus, Lachnospira, Parabacteroides,* RF32 family, *Eubacterium* taxa [57]	
Early Life Stress			
Early life stress	Animal	Reduced fecal *Lactobacillus* levels [35]	
Early life stress	Animal	Population-based microbiota alterations [61]	
Early life stress	Animal	Increased levels of *Bifidobacterium bifidum*, *Lactobacillus*, *Clostridium leptum, Clostridium coccoides* [63]	
Early life stress	Animal	Reduced *Firmicutes*:*Bacteroidetes* ratio; increased *Akkermansia, Flexibacter, Prevotella* [62]	
Early life stress	Animal	In males, impacted abundance of *Lachnospiraceae* and *Porphyromonadaceae* families, *Firmicutes*, *Bacteroides*, *Lactobacillus, Alloprevotella*. In females, impacted *Lactobacillus* and *Mucispirillum* [67]	
Early life stress	Animal	Higher *Desulfovibrio*, *Mucispirillum*, *Fusobacterium* [68]	
Early life stress	Animal	Higher *Bacteroides* genus, lower *Lachnospiraceae* family. In males, higher *Streptococcus* genus and lower *Staphylococcus* genus; in females higher *Sporobacter* genus and lower *Mucispirillum* genus [66]	Increased colon IFN-γ, IL-6, increased serum IL-1β in males. Increased hippocampal IL-1β.
Trauma (lifetime including childhood)	Human	Lower *Actinobacteria*, *Lentisphaerae*, *Verrucomicrobia* [73]	
Trauma (Early Traumatic Inventory - Self Report)	Human	Lower levels of gut metabolites 5-oxoproline, malate, urate, glutamate gamma methyl ester [74]	
ACE	Human	Higher *Prevotella* [42]	Proinflammatory cytokine response to TSST was significantly associated with several gut taxa
NICU exposure	Human	Higher *Proteus, Veillonella* [69]	
Caregiver behavior	Human	Lower *B. fragilis* [70]	
Institutional care	Human	Lower alpha diversity and observed richness, lower *Lachnospiraceae* [72]	
Institutional care	Human	Increased abundance of *Prevotella*, *Bacteroides* (family Bacteroidaceae), *Coprococcus*, *Streptococcus*, and *Escherichia*, compared with non-institutionalized adolescents [71]	*Bacteroides* (f_Ruminococcaceae) abundance was significantly associated with CD^{8+} CD^{57+} T cells
In Utero Stress			
In Utero stress	Animal	Decreased *Lactobacillus*, elevated *Oscillibacter*, *Anaerotruncus, Peptococcus* [85]	
In Utero stress	Animal	Decreased *Bacteroides* and *Parabacteroides* abundance [105]	Neuroinflammation
Daily hassles, cortisol	Human	Relative abundances of over 60 % of bacterial groups [90]	
Pregnancy-related anxiety, PSS, stressful life events	Human	Elevated pregnancy-related anxiety was associated with lower *Enterococcaceae* [92]	
Daily hassles, cortisol	Human	Elevated *Erwinia, Haemophilus, Serratia;* lower *Slackia*, *Actinobaculum*, *Paraprevotella*, *Butyricimonas, Citrobacter*, *Ruminococcus*, *Phascolarctobacter*, *Anaerotruncus, Enterococcus, Lactobacillus* [91]	

whether stress may get "into the belly," with an emphasis on early life stress. We have focused on psychosocial stressors' impact on the gut microbiome, which may ultimately influence health risk via the microbiota-gut-brain-axis. The complexity of the microbiota-gut-brain-axis communication system is vast, and data from animal and human studies suggest that this axis may be impacted in multiple ways by various forms of stress. Studies have demonstrated the long-lasting effects of intergenerational, *in utero* and early life stress on health outcomes, and more recently, on the gut microbiota. Insight into how stress perturbs the microbiota-gut-brain-axis has profound importance as it may illuminate avenues for intervention to alleviate the health consequences of early life exposure to psychosocial stress.

As we described here and summarized in Table 1, multiple manifestations of psychosocial stress, in both human and animal models, are associated with alterations in the gut microbiota. In animal models, stress due to social disruption results in both short and long term effects on microbial composition [43,44]. There is also ample evidence in animal models that ELS impacts the gut microbiome [35,61–63,65,68]. Manipulation of the gut microbiota in animal experiments involving germ-free mouse models or antibiotics lends further proof of the effect of social stress on gut microbiota, and downstream consequences. For example, when subjected to social disruption stress, only mice with intact microbiota, not germ-free mice, experienced an increase in proinflammatory cytokines [45]. This suggests the gut microbiome may be a key moderator in the well-known association between stress and inflammation.

In humans, understanding the relationship between stress and gut microbiome is far more challenging. We examined different models of stress, showing that perceived stress [56–58], early life stress [69,72] or ACEs [42], and *in utero* stress [90–92] have been associated with altered microbial composition and/or diversity. The majority of studies demonstrate alterations in specific bacteria, microbial composition or diversity in association with stress exposure or perceived stress. These studies direct our attention to the microbiome-gut-brain axis, but the mechanisms by which these stress-induced alterations in the gut microbiome are in a *causal* pathway that links stress with the immune and central nervous systems remains to be determined. Future studies should move beyond measuring just stress-associated taxonomic changes in the gut microbiota, and assess potential mechanistic markers such as proinflammatory cytokines or short-chain fatty acids.

That is, future studies should examine the causal mechanisms by which the gut microbiome influences downstream effects of stress. As summarized by Cryan et al., the microbiota trigger production of entities including cytokines, chemokines, neurotransmitters, neuropeptides, endocrine messengers, and microbial by-products that enter the bloodstream or interact with the vagal and spinal afferent neurons to interface with the CNS [37]. Particularly in humans, far more research is needed to understand how stress affects microbiota-gut-brain interactions, and to identify targets for intervention to ameliorate the adverse effects of stress through the microbiota-gut-brain axis. Future studies should also investigate how these relationships between stress and the microbiota-gut-brain axis may be moderated by factors such as sex, age, and psychiatric disorders, as well as potentially protective factors such as social support. While the present review focused on stress and the gut microbiome, and specifically excluded psychiatric illness, stress and psychiatric illness are closely linked and should be studied in conjunction in future research.

However, dietary interventions in animal models and observational studies in humans hold promise for modifying the gut microbiome and shifting the cascade of microbiota-gut-brain interactions in ways that might ameliorate the effects of stress. PUFAs, which are generally anti-inflammatory [104], show particular promise in ameliorating stress-induced changes to the gut microbiome [94,96]. As we described, rodent studies suggest that dietary intake of PUFAs may reverse the impact of ELS-induced changes to the gut microbiome, inflammation and intestinal permeability [62,97,98]. In humans, ω-3 PUFA intake was associated with reduced inflammation in women with high scores for adverse childhood experiences [42]. Fish oils, polyphenols and probiotics have also been tested in animal models, and in addition to restoring gut microbiome composition, reduce depressive behaviors and improve HPA axis function [101–103]. Dietary manipulation or supplementation with specific compounds may offer low cost and low risk strategies to ameliorate the adverse effects of stress through the microbiota-gut-brain axis.

In sum, evidence from animal and human research suggests that varied types of stress get "into the belly," impacting the gut microbiome in multiple ways. ELS may be a particularly potent form of stress, as it is embedded in the development of stress-responsive systems such as the neuroendocrine-neuroimmune axes [25,33]. Data in both animals and humans, reviewed here, suggests that ELS may also embed its effects in the gut microbiome. Further research is needed to clarify the effects of specific stressors on the gut microbiome as well as downstream outcomes, such as proinflammatory markers. In addition, translational research is needed to clarify the mechanisms by which stress impacts the microbiota-gut-brain axis. Finally, dietary interventions should be explored as treatment targets to buffer the impacts of stress on the microbiota-gut-brain axis.

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Declaration of Competing Interest

None.

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