

History of childhood physical abuse is associated with gut microbiota diversity among adult psychiatric inpatients

Jessica C. Rohr^{a,*}, Katelynn A. Bourassa^a, Dominique S. Thompson^{a,b},
J. Christopher Fowler^{a,c,d}, B. Christopher Frueh^e, Benjamin L. Weinstein^a, Joseph Petrosino^b,
Alok Madan^{a,c,d}

^a Department of Psychiatry & Behavioral Health, Houston Methodist, Houston, TX, USA

^b Department of Molecular Virology & Microbiology, Alkek Center for Metagenomics and Microbiome Research, Baylor College of Medicine, Houston, TX, USA

^c Houston Methodist Academic Institute, Houston, TX, USA

^d Department of Psychiatry, Weill Cornell Medical College, New York, NY, USA

^e Department of Psychology, University of Hawaii, Hilo, HI, USA

ARTICLE INFO

Keywords:

Trauma
Gut microbiota
Childhood physical abuse
Brain-gut axis

ABSTRACT

Background: Traumatic life events are associated with the development of psychiatric and chronic medical illnesses. This exploratory study examined the relationship between traumatic life events and the gut microbiota among adult psychiatric inpatients.

Methods: 105 adult psychiatric inpatients provided clinical data and a single fecal sample shortly after admission. A modified version of the Stressful Life Events Screening Questionnaire was used to quantify history of traumatic life events. 16S rRNA gene sequencing was used to analyze the gut microbial community.

Results: Gut microbiota diversity was not associated with overall trauma score or any of the three trauma factor scores. Upon item-level analysis, history of childhood physical abuse was uniquely associated with beta diversity. Linear Discriminant Analysis Effect Size (LefSe) analyses revealed that childhood physical abuse was associated with abundance of distinct bacterial taxa associated with inflammation.

Limitations: This study did not account for dietary differences, though diet was highly restricted as all participants were psychiatric inpatients. Absolute variance accounted for by the taxa was small though practically meaningful. The study was not powered for full subgroup analysis based on race and ethnicity.

Conclusions: This study is among the first to demonstrate a relationship between childhood physical abuse and gut microbiota composition among adult psychiatric patients. These findings suggest that early childhood adverse events may have long-conferred systemic consequences. Future efforts may target the gut microbiota for the prevention and/or treatment of psychiatric and medical risk associated with traumatic life events.

1. Introduction

Experience of traumatic life events, especially during childhood, increases risk for a wide range of health concerns, including nearly all psychiatric disorders (Kessler et al., 2010) and myriad chronic medical conditions (van Reedt Dortland et al., 2012; Austin and Herrick, 2014; Hughes et al., 2017; Park et al., 2016). While the mechanism of these changes is multifactorial and far from fully understood, a prevailing theory for the considerable impact of traumatic events focuses on the body's response to life stressors. Acute stressors trigger physiological changes (e.g., release of cortisol and norepinephrine (Bremner, 2006))

intended to maximize an adaptive response to the threat while minimizing the likelihood of bodily harm or death. Continued exposure to stressors or exposure to a particularly significant stressor (or trauma) can result in persistent physiological changes, resulting in a chronic state of inflammation (Boyce et al., 2021). Persistent inflammation produces enduring molecular and structural remodeling reflected in lifelong inflammatory reactivity to stressors (Carpenter et al., 2010; Chen et al., 2018; Danese and Tan, 2014; Gouin et al., 2012; Miller et al., 2011).

Animal studies suggest that much of the molecular and structural remodeling associated with chronic inflammation takes place in the gut (Bailey et al., 2011; Røytiö et al., 2017). The gut, which some have

* Corresponding author at: 6550 Fannin St, SM 2509, Houston, TX 77030, USA.

E-mail address: jrohr@houstonmethodist.org (J.C. Rohr).

<https://doi.org/10.1016/j.jad.2023.03.023>

Received 5 December 2022; Received in revised form 3 March 2023; Accepted 11 March 2023

Available online 16 March 2023

0165-0327/© 2023 Elsevier B.V. All rights reserved.

referred to as “the second brain,” is gaining recognition for its considerable involvement in regulating and integrating inflammatory, immune, and metabolic systems (Avetisyan et al., 2015). All these processes are underwritten by the microbiota of the gut and associated metabolites, completing the brain-gut-microbiome axis (Carabotti et al., 2015).

The gut microbiome is composed of trillions of bacteria, archaea, viruses, and protozoa and has influence on early development, intestinal homeostasis, and vulnerability to and recovery from diseases (Lerner et al., 2017). The gut and its microbiome together are associated with healthy immune functioning, inflammatory responses, and metabolic regulation, and they are uniquely integrated with stress systems (Boyce et al., 2021). The gut microbiome is almost immediately established at birth and has demonstrated malleability at critical and sensitive time periods throughout development, suggesting that traumatic events, especially during these time periods, may have significant impact on both the gut microbiome and the systems it communicates with and regulates (Baldwin et al., 2018; Boyce et al., 2021; Gensollen et al., 2016).

Though direct modeling of the relationship between early life stress and the gut microbiome is predominantly relegated to animal research at this time, these models have demonstrated that these effects can persist into adulthood (Jašarević and Bale, 2019; Jašarević et al., 2015; O’Mahony et al., 2017). Preliminary data in humans have demonstrated an association between traumatic life events and functional gastrointestinal distress (a proxy for gut dysbiosis; Park et al., 2016). As a result, the gut microbiome is gaining recognition as a mechanism through which both resiliency and risk for future pathology to occur (Boyce et al., 2021). The current study aims to contribute to models linking traumatic events and gut health by exploring the association between stressful events across the lifespan and gut microbiota composition among an adult inpatient psychiatric sample.

2. Method

2.1. Participants & setting

Between January 1, 2015 and December 31, 2016, self-collected fecal samples were provided by 105 adult psychiatric inpatients at a freestanding, nonprofit hospital located in the American Southwest. Patients at the facility received personalized psychiatric and medical treatment over an extensive duration of stay (average length of stay = 49.7 ± 14.5 days). Psychiatric care included a personalized care plan with a comprehensive medical evaluation, psychotropic drug optimization, psychotherapy, milieu therapy, psychoeducation, and family involvement (Madan et al., 2020). Data from this sample have been published elsewhere (Madan et al., 2020; Thompson et al., 2021; Thompson et al., 2023).

2.2. Procedure

Data were collected as part of a hospital project to evaluate treatment outcomes (Allen et al., 2009; Fowler et al., 2013) and as part of a larger study to identify biomarkers of psychiatric illness and response to treatment (Sharp et al., 2016; Madan et al., 2017; Ambrosi et al., 2017; Madan et al., 2020; Thompson et al., 2021; Thompson et al., 2023). Participants completed baseline psychiatric measures (within 72 h of admission) and provided a fecal sample shortly thereafter.

2.3. Measures

2.3.1. Clinical variables

Demographics, health records, and psychiatric history were collected using a standardized patient information survey (Allen et al., 2009; Fowler et al., 2013).

2.3.1.1. Diagnosis. A gold standard semi-structured interview, the Structured Clinical Interview for DSM-IV Disorders (SCID-I/II [First et al., 1997; First et al., 2002]) was used to determine Axis I and Axis II diagnoses. The SCID-I/II were modified for research purposes and administered by master’s level researcher staff.

2.3.1.2. Trauma. Trauma history was assessed with a modified version Stressful Life Events Screening Questionnaire (SLESQ [Allen et al., 2015; see Goodman et al., 1998 for the original]). This 14-item, self-report questionnaire assesses lifetime trauma exposure, including trauma type, age of occurrence, and trauma duration. Responses to the first 13 items are dichotomous “yes/no” to indicate exposure to a category of traumatic event. Item 14 provides additional information about the identified most distressing event (age at exposure, chronicity, current distress). The modified measure has been validated in a sample of over 1500 psychiatric inpatients and demonstrated good internal consistency ($\alpha = 0.87$) with a three-factor structure (sexual trauma, physical assaults, emotional distress (Allen et al., 2015)).

2.4. Ethics

The present study adheres to the guidelines and ethical principles outlined in the Declaration of Helsinki. Participants provided written informed consent following a full explanation of all procedures. Through informed consent, study participants attested to the voluntary nature of their participation. Study design was approved by the Institutional Review Board (IRB) at Baylor College of Medicine.

2.5. Data analysis

2.5.1. Analytic plan

Given the exploratory nature of this study, we first sought to examine the potential relationship between overall traumatic load (summation of all SLESQ items) and gut microbiota composition.

Subsequently, we examined the relationship between the three factors of the SLESQ (sexual trauma, physical assaults and emotional distress) and gut microbiota composition.

We then explored item level associations (specifying specific categories of traumatic experience) and microbiota composition. Lefse analyses (see description below) were applied to items of significance to identify bacterial taxa. Finally, we used PubTator (Wei et al., 2019), to quantify the number of publications associated with specific taxa and an a-priori list of MeSH terms.

Demographic and clinical data were analyzed using the R stats package (R Core Team, 2018). Descriptive statistics were used to summarize the characteristics of the sample. Descriptive statistics were used to determine any significant group differences among groups characterized by specific trauma exposures.¹

2.5.2. Microbiota-related procedures

Self-collected fecal swabs were provided shortly after admission (20.1 ± 12.8 days) by each participant and subsequently transported to the study laboratory where they were stored in a -80°C freezer prior to sequencing procedures. MO BIO PowerSoil DNA Isolation Kit was used to extract bacterial genomic DNA from fecal samples. An Illumina MiSeq system was used to sequence the 16S rDNA V4 region was PCR-

¹ Many participants in the study were taking psychotropic medications, which are related to gut microbiota diversity in the empirical literature (Maier and Typas, 2017). In this particular sample, there is a non-significant association between specific pharmacologic agents (e.g. antibiotics, probiotics, antidepressants, antipsychotics, and opioids) and gut microbiota bacterial richness and alpha diversity (see Madan et al., 2020 for full analysis). Due to this non-significant association, psychotropic medications were not included as potential covariates in the current analyses.

amplified. The amplification primers (515F-806R) contain MiSeq adapters and single-end barcodes supporting sample pooling and PCR products sequencing. This pipeline employs both phylogenetic and alignment-based methods. Read pairs were demultiplexed using unique molecular barcodes before being merged using USEARCH v7.0.1090. The UPARSE algorithm allowed clustering of 16S rDNA sequences into Observed Operational Taxonomic Units (OTUs) at the 97 % similarity cutoff value. Detected OTUs were annotated by mapping to a SILVA Database version that contained only the 16S v4 region. Abundance subsequently was quantified by mapping demultiplexed reads to OTUs. Based on a minimum rarefaction depth of 4815, no samples were omitted due to insufficient reads. Alpha-diversity, beta-diversity, and phylogenetic analysis relied on the final OTU table.

To improve bacterial DNA yield and reduce background amplification, genomic bacterial DNA (gDNA) extraction methods were refined for Whole Genome Shotgun Sequencing (WGS) (The Human Microbiome Project Consortium, 2012a; The Human Microbiome Project Consortium, 2012b). We filtered paired-end sequencing reads for low quality sequences and for Illumina phix sequences. Subsequently, bbdutk (BBMap version 37.58; Bushnell et al., 2017) was used to remove Illumina adapters. The resulting sequences were mapped to the human hg38 reference database using bowtie2 v.2.3.4.3 (Langmead and Salzberg, 2012) completely and with high-stringency, resulting in the removal of sequence-level host contamination. MetaPhlan2 (Truong et al., 2015) allowed for inferences of taxonomic profiles, and HUMAnN2 (Franzosa et al., 2018) allowed for functional profiling of the microbial community. Final output files were represented in biom format (McDonald et al., 2012).

2.5.3. 16s microbiome analysis

As stated above, we conducted the following analyses examining the relationship between gut microbiota and (1) SLESQ total score, (2) the three factors of the SLESQ (sexual abuse, physical assault and emotional distress), and (3) individual items of the SLESQ.

2.6. Envfit analysis

The Envfit function, a component of the R Package Vegan (Oksanen, 2012; Oksanen et al., 2013) was used to identify environmental variables that have maximum correlation with the 16s sequencing data. Binary, item level responses (yes/no) from the SLESQ were factorized and used as the environmental variables in the analyses. First, non-metric multidimensional scaling using Bray-Curtis ordination was used to create a dissimilarity matrix for the samples. Next, the 'Envfit' function was used to fit the environmental factors onto the Bray-Curtis ordination. The significance of each factor was determined using 999 permutations for each variable. R^2 was used to determine the goodness of fit of the model.

2.7. Alpha diversity

Differences in microbial richness and evenness of 16 s sequencing data at admission was measured using the Shannon Index. The sample was grouped by a covariate of interest (i.e., response to a binary, single item on the SLESQ) which emerged in Envfit analysis. A Kruskal-Wallis (KW) rank-sum test was used to determine the significance of the Shannon Index scores. Full alpha diversity analysis was performed using the R packages, 'Phyloseq' (McMurdie and Holmes, 2013) and 'stats' (R Core Team, 2018).

2.8. LefSe

To further explore the relationship between the identified covariate of interest and gut microbiome composition, Linear Discriminant Analysis (LDA) Effect Size (LefSe (Segata et al., 2011)), a biomarker discovery method, was used to identify significant microbial taxa

associated with the presence or absence of exposure to a specific trauma. In LefSe, a Kruskal-Wallis (KW) rank-sum test is used to statistically rank taxa abundance differences between the two groups. Taxa with a LDA score of 2.0 or higher and a p value of <0.05 was considered statistically significant.

2.8.1. Literature search of microbial features

PubTator (Wei et al., 2019), a text-mining tool, was used in conjunction with the taxa identified in the LefSe analysis to determine the relevance of our findings in the existing literature. Specifically, PubTator was used to comprehensively explore PubMed abstracts and PMC full-text articles using the seven bacterial taxa identified as associated with the covariate of interest. We searched for articles mentioning any of the seven features and a list of previously determined MeSH terms associated with inflammation, dysbiosis, short chain fatty acids, butyrate, the gut-brain axis, and trauma.

3. Results

3.1. Participant characteristics

The patient cohort ($N = 105$) in this study consisted of predominantly Caucasian younger adults. The sample was well-educated and less than half had been employed within the 30 days preceding the hospitalization. They presented with multiple Axis 1 diagnoses, of which a diagnosis of a mood disorder was most common. They had significant past psychiatric treatment histories. Of the 105 participants, 75 % ($n = 79$) endorsed exposure to a stressful life event at any point in their life. Of this 75 %, >72 % ($n = 57$) endorsed experiencing at least two stressful life events. Of the 79 who endorsed lifetime stressful life events, 35 % ($n = 28$) endorsed childhood physical trauma.

3.2. EnvFit analysis

In the EnvFit analysis, the overall trauma score (the total score on the SLESQ) was not significantly related to gut richness or biodiversity ($p > .05$). Three constructs representing different types of trauma were analyzed in relation to gut richness and biodiversity, and none produced significant results (SLESQ sexual trauma factor, SLESQ physical assault factor, and SLESQ emotional distress factor, all $p > .05$).

Item-level analysis from the SLESQ revealed that childhood physical abuse was the only significant predictor for differences in microbiome composition ($p < .05$; see Table 1). See Fig. 1 for a visualization of the gut microbiome by the report of childhood physical abuse using a non-metric multidimensional scaling (NMDS) plot.

Because this variable was significant, we first determined whether there were any demographic differences between those who had endorsed childhood physical abuse and those who did not. Those with a

Table 1

Envfit analysis identifying associations between 16s sequencing data and stressful life events questionnaire (SLESQ) items.

Items on stressful life events questionnaire	r^2	p value
Life-threatening illness	0.0011	0.95
Life-threatening accident	0.0188	0.27
Physical force/weapon used	0.0047	0.74
Family member/close friend died	0.0082	0.58
Physical force used to have sex	0.0028	0.83
Physical force/threat to try to have sex	0.0226	0.23
Childhood: touched your body private parts	0.004	0.75
Childhood physical abuse by parent/caregiver	0.0486	0.04*
Partner/date physically harmed you	0.0339	0.09
Threatened with a weapon	0.0182	0.29
Present when someone was killed, injured, or assaulted	0.0025	0.83
Other situation: seriously injured/ life in danger	0.006	0.69
Other situation: extremely frightening/horrifying	0.0015	0.91

* $p < .05$

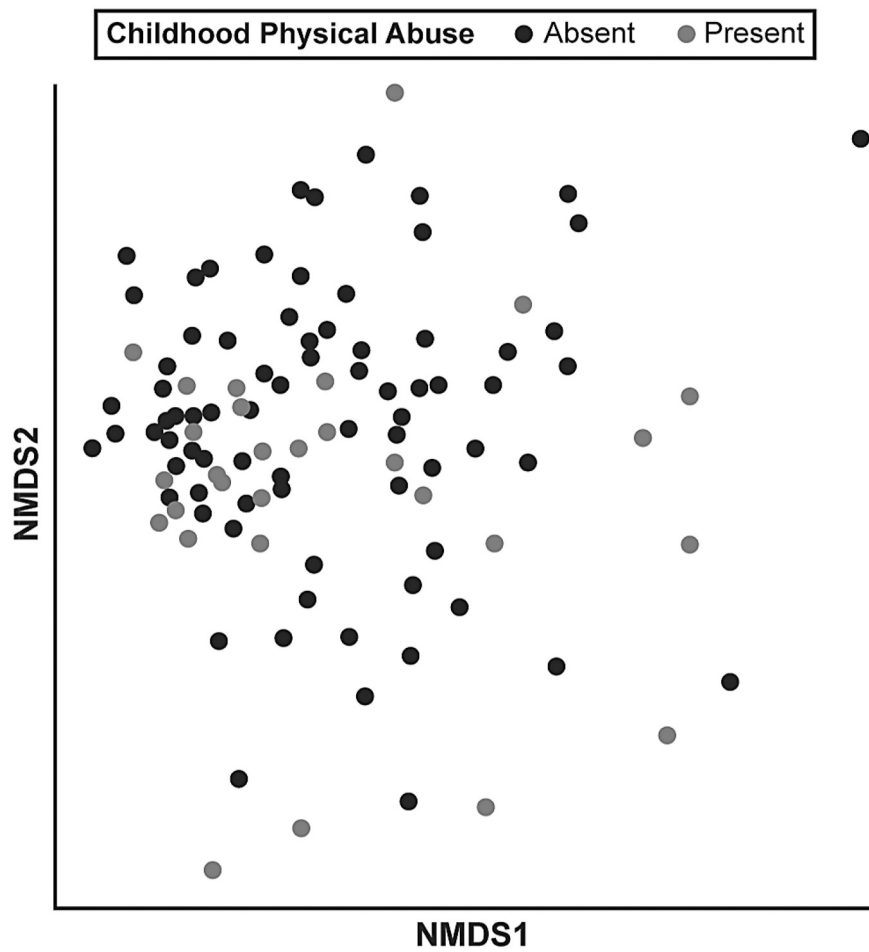


Fig. 1. Envfit analysis NMDS visualization. Note. Bacterial community clustering is associated with the presence of childhood physical abuse. Non-metric multi-dimensional scaling (NMDS) plot of individual microbiome sample dissimilarities using 16s abundance data at admission (genus level resolution) correlated with the presence/absence of childhood physical abuse.

history of childhood physical abuse were more racially diverse than those without a history of childhood physical abuse, $p = .01$. Additionally, those with a history of childhood physical abuse were more likely to have been married compared to those without a history of childhood physical abuse, $p = .04$. See [Table 2](#) for details.

3.3. Alpha diversity analysis

Again, the analyses of the relationships between the total trauma score and the three trauma factors and gut microbiota were non-significant ($p < .05$), as was the relationship between all item-level variables and gut microbiota ($p > .05$).

Table 2
Association of childhood physical abuse and baseline demographics/burden of illness characteristics within cohort.

Variable	Childhood PA Mean (SD)	No childhood PA Mean (SD)	Childhood PA n (%)	No childhood PA n (%)	p value
Age, years	37.86 (13.22)	35.53 (13.66)			0.43
Gender, female			11 (39.29)	37 (48.05)	0.43
Race, Caucasian			22 (78.57)	73 (94.81)	0.01
Never married			8 (28.57)	39 (50.65)	0.04
Education, bachelor's degree or greater			16 (57.14)	48 (62.33)	0.85
Employed last 30 days			12 (42.86)	36 (46.75)	0.72
Total Axis I	2.61 (1.35)	2.68 (1.35)			0.78
Psychotic spectrum			0 (0)	2 (26.31)	0.39
Bipolar spectrum			7 (25)	9 (11.84)	0.10
MDD spectrum			18 (64.29)	57 (75)	0.28
Mood disorder			25 (89.29)	61 (80.26)	0.28
PTSD			9 (32.14)	5 (6.49)	<0.001
Alcohol use disorder spectrum			12 (42.86)	27 (35.53)	0.49
Substance use disorder spectrum			9 (32.14)	24 (31.58)	0.96
Any personality disorder			14 (50)	24 (31.58)	0.08
Total psychiatric hospitalizations	2.68 (2.71)	1.77 (2.81)			0.14

Note. Childhood physical abuse subsample N = 28; No childhood physical abuse subsample N = 77; PA = physical abuse; t-test used continuous variables and Pearson's Chi-squared test used for categorical variables.

3.4. LefSe analysis

LefSe analysis again revealed no significant differences in the relative abundance of bacterial taxa based on overall trauma score ($p > .05$) or the three trauma factors ($p > .05$).

Upon item-level analysis, significant differences in the relative abundance of several bacterial taxa were found between those who did and did not report childhood physical abuse. Notably, taxa from the Clostridiales order, including the *Peptococcus* and *Murdochiella* genera, were significantly increased in individuals who reported childhood physical abuse (Fig. 2). The *Peptoniphilus* genus and an uncultured genus, both also belonging to the Clostridiales order were significantly increased in individuals who did not report childhood abuse (Fig. 2). The differential association of microbial taxa belonging to the same order indicates possible functional differences that exist at a lower phylogenetic level. Additionally, abundance differences in the *Dialister* and *Prevotella* genera were found to be significantly associated with childhood physical abuse (see Fig. 2).

3.4.1. Literature search of microbial features

The results of the PubTator search (Table 3) revealed inflammation, as well as dysbiosis, were the most annotated MeSH terms. Our literature search results further showed that only one bacterial taxa, Clostridiales Family XI Murdochiella, was not associated with any of the annotated MESH terms.

4. Discussion

This study examined gut microbiota differences among adults to determine whether history of traumatic events conferred demonstrable impact on the microbiome. Though animal studies link traumatic stress with microbiome differences and human studies link gastrointestinal distress with traumatic stress (Park et al., 2016), this study, to our knowledge, is among the first to investigate the gut microbiome in humans and the impact of traumatic stress. Multiple types of traumatic stress were investigated as possible correlates of gut dysbiosis; history of childhood physical abuse (i.e. being slapped repeatedly, beaten, or otherwise attacked or harmed by a parent or caregiver) stood out as the only significant factor correlated with differences in microbiota composition and diversity.

Four bacterial taxa were identified as being increased in participants who reported physical childhood abuse in comparison to those who did not. Of these four taxa, three are consistently implicated in the literature as related not just to dysbiosis, but also to inflammation. Prevotellaceae Prevotella in particular appeared in over 1500 publications related to inflammation (per Pubtator, Wei et al., 2019). In fact, numerous studies have identified an association between a disproportionate abundance of

members of the Prevotella taxa and a range of infections and inflammatory conditions including rheumatoid arthritis, intestinal and vaginal dysbiosis, metabolic disorders and major depressive disorder (Aroutcheva et al., 2008; Iljazovic et al., 2021; Lin et al., 2017).

Integration of the current study’s findings into the extant literature on the relationship between stress, inflammation and gut dysbiosis allows us to postulate that childhood physical abuse, through inflammatory and HPA axis responses, triggers epigenetic changes thus contributing to ongoing dysbiosis in the gut, which can then be seen decades later. Childhood physical abuse, by definition, occurs during crucial temporal periods during which multiple physiological systems are developing and during which plasticity and malleability are at their peak (McDade et al., 2017; Merrill et al., 2019). There are considerable data that link childhood traumatic stress to dysregulated neuroendocrine-immune function and increased inflammation (Carpenter et al., 2010; Danese et al., 2007; Fagundes et al., 2013; Gouin et al., 2012; Kiecolt-Glaser et al., 2012). These changes may keep the microbiome in a chronic state of dysfunction, which continues into adulthood, marking a process through which childhood trauma contributes to persistent biological changes.

Of interest and of note for continued exploration is the variables that were not significant correlates of gut dysbiosis: overall trauma score, as well as the three higher-order trauma factors. The current study’s findings are not wholly inconsistent with literature demonstrating differential physical and psychological symptom pathways after different types of abuse (Tietjen and Peterlin, 2011; Westermair et al., 2018). Overall trauma failed to be associated with gut dysbiosis, suggesting that non-significance of other domains within overall trauma were sufficient to nullify any associations strengthened by childhood physical trauma. Further studies are needed to better understand the lack of associations in this sample and why more proximal traumatic events (e.g., those that occurred during adulthood) are less impactful than more distal childhood events. Boyce’s developmental theory of adversity may speak to this finding. It suggests that not only is the interaction between genes and environment a critical component of patterns of risk, but there are specific windows in time in which the environmental factors are most impactful (Boyce et al., 2021). This theory has not yet been thoroughly explored empirically but is increasingly understood as a comprehensive model of risk for pathology, and may help us understand why trauma is more damaging at certain points in the lifespan (Nelson et al., 2019).

Importantly, this sample consists of adult patients at an inpatient psychiatric hospital that provides treatment over a period of 4–6 weeks for severe and persistent mental illness. Gut dysbiosis has been previously associated with psychiatric illness (Rogers et al., 2016), and trauma is considered part of the etiology for almost all psychiatric illness. Even with the homogenous nature of the sample in terms of psychiatric distress and likely accompanying heightened levels of

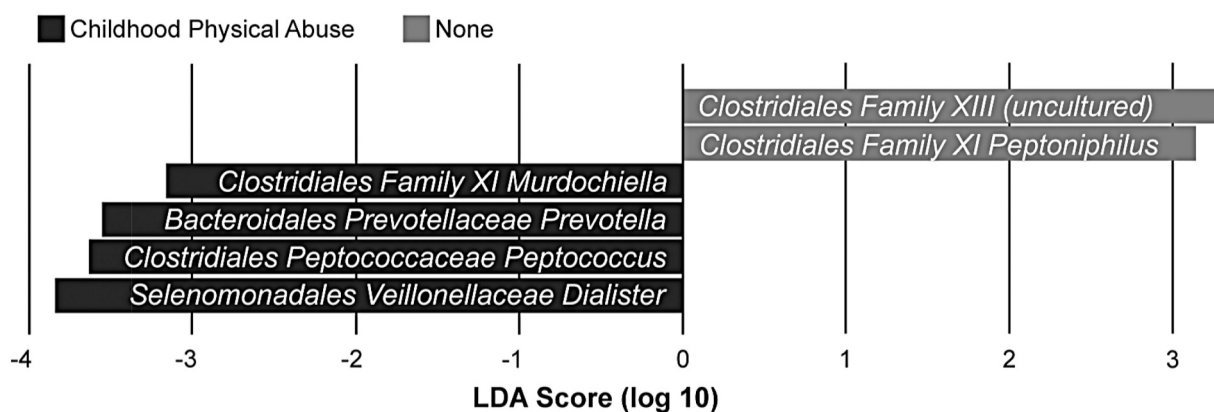


Fig. 2. Bacterial taxa associated with childhood physical abuse. Note. LefSe plot identified bacterial biomarkers associated individual genus level taxa with the presence and absence of physical abuse. Only bacteria taxa with a linear discriminant analysis (LDA) threshold of >2 are shown.

Table 3

Literature search results for bacterial taxa associated with childhood physical abuse.

Bacterial taxa	Abundance	Inflammation	Dysbiosis	Butyrate	Short chain fatty acids	Gut-brain axis	Trauma
<i>Prevotellaceae Prevotella</i>	+	650	548	222	257	45	37
<i>Dialister</i>	+	47	69	22	32	10	4
<i>Peptococcaceae Peptococcus</i>	+	22	15	12	8	1	3
<i>Clostridiales Family XI Peptoniphilus</i>	–	12	8	10	3	0	3
<i>Clostridiales Family XIII (uncultured)</i>	–	2	2	2	0	1	0
<i>Clostridiales Family XI Murdochiella</i>	+	0	0	0	0	0	0

Note. Seven MeSH terms relevant to gut-brain microbiome research were searched in PubTator on March 4th, 2022 in conjunction with the LefSe identified taxa. The numbers represent the number of manuscripts associated with the search terms. Abundance in table is describing taxa abundance within the group of individuals with childhood physical abuse when compared to group that did not have childhood physical abuse. Abundance: + = increased, – = decreased.

trauma and gut dysbiosis as compared to the general population, childhood physical trauma still emerged as a significant predictor of gut dysbiosis, underscoring its importance.

Additionally, attention to potential interventions for dysbiosis related to physical abuse suggests the importance of healthy lifestyle behaviors for gut health. Animal models have demonstrated the utility of directly addressing the condition of the gut microbiome through probiotics or other interventions (Smith et al., 2014; Sudo et al., 2004). In fact, a recent review suggested that psychobiotics, or live microorganisms that influence bacteria–brain relationships, may confer mental health benefits, such as improvement in symptoms of anxiety and depression (Smith et al., 2019). Furthermore, human subjects research suggests that the gut microbiome may be malleable to some degree, with an estimated 30–40 % of microbiota able to be altered through lifestyle changes such as diet and physical activity (Kashtanova et al., 2016).

The results of the current study should be interpreted within the context of several limitations. While a restricted menu of dietary options was available at the hospital, we did not gather data on diet prior to or during the study period; future studies should account for dietary differences. The absolute variance accounted for by the four taxa was small (4 %). Nonetheless, given the tremendous sources of variability present in the transition from childhood to adulthood, we consider these findings to be practically meaningful. Although the group who experienced childhood physical abuse were more racially diverse than the group who did not experience childhood physical abuse, the study was not powered for subgroup analysis. There are well documented cultural differences in dietary habits (e.g., Vadiveloo et al., 2020; Wang et al., 2014) and experience of traumatic events (e.g., McLaughlin et al., 2018; Tolin and Foa, 2006); future research should explore sociodemographic contributions to observed associations. Overall, this study represents the first to demonstrate differences in gut microbiome composition based on experience of childhood physical abuse, contributing an important component to an overall theory of the ways in which trauma impacts body composition and future health.

CRediT authorship contribution statement

All authors have approved of the final article. Article was conceptualized by AM, DT, and JP. Data collection was led by JCF and AM. Data analyses were conducted by DT, JP and AM. Writing and editing of the article was done by all authors.

Role of funding source

This work was supported by the Houston Methodist Foundation (JR, KB, AM, JCF, DT), The Menninger Clinic Foundation (AM, JCF, CF), and Baylor College of Medicine's Alkek Center for Metagenomics and Microbiome Research (DT, JP). None of these funding sources had a role in the study design, collection, analysis, or interpretation of the data, writing the article, or in the decision to submit the article for publication.

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgements

The authors are thankful to Michelle Patriquin, PhD and Humsini Viswanath, MPH, MS for their assistance with pharmacy data abstraction.

References

- Allen, J.G., Frueh, B.C., Ellis, T.E., Latini, D.M., Mahoney, J.S., Oldham, J.M., Wallin, L., 2009. Integrating outcomes assessment and research into clinical care in inpatient adult psychiatric treatment. *Bull. Menn. Clin.* 73 (4), 259–295.
- Allen, J.G., Madan, A., Fowler, J.C., 2015. Reliability and validity of the Stressful Life Events Screening Questionnaire among inpatients with severe neuropsychiatric illness. *Bull. Menn. Clin.* 79, 187–202.
- Ambrosi, E., Arciniegas, D.B., Madan, A., Curtis, K.N., Patriquin, M.A., Jorge, R.E., Salas, R., 2017. Insula and amygdala resting-state functional connectivity differentiate bipolar from unipolar depression. *Acta Psychiatr. Scand.* 136, 129–139.
- Aroucheva, A., Ling, Z., Faro, S., 2008. *Prevotella bivia* as a source of lipopolysaccharide in the vagina. *Anaerobe* 14 (5), 256–260.
- Austin, A.E., Herrick, H., 2014. The Effect of Adverse Childhood Experience on Adult Health: 2012 North Carolina Behavioral Risk Factor Surveillance System Survey. Department of Health and Human Services, State Center for Health Statistics.
- Avetisyan, M., Schill, E.M., Heuckeroth, R.O., 2015. Building a second brain in the bowel. *J. Clin. Invest.* 125 (3), 899–907.
- Bailey, M.T., Dowd, S.E., Galley, J.D., Hufnagle, A.R., Allen, R.G., Lyte, M., 2011. Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor-induced immunomodulation. *Brain Behav. Immun.* 25 (3), 397–407.
- Baldwin, J.R., Arseneault, L., Caspi, A., Fisher, H.L., Moffitt, T.E., Odgers, C.L., Kopa, A., 2018. Childhood victimization and inflammation in young adulthood: a genetically sensitive cohort study. *Brain Behav. Immun.* 67, 211–217.
- Boyce, W.T., Levitt, P., Martinez, F.D., McEwen, B.S., Shonkoff, J.P., 2021. Genes, environments, and time: the biology of adversity and resilience. *Pediatrics* 147 (2).
- Bremner, J.D., 2006. Stress and brain atrophy. *CNS Neurol. Disord. Drug Targets* 5 (5), 503–512.
- Bushnell, B., Rood, J., Singer, E., 2017. BBMerge—accurate paired shotgun read merging via overlap. *PLoS one* 12 (10), e0185056.
- Carabotti, M., Scirocco, A., Maselli, M.A., Severi, C., 2015. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Ann. Gastroenterol.* 28 (2), 203.
- Carpenter, L.L., Gawuga, C.E., Tyrka, A.R., Lee, J.K., Anderson, G.M., Price, L.H., 2010. Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. *Neuropsychopharmacology* 35 (13), 2617–2623.
- Chen, E., Miller, G., Yu, T., Brody, G.H., 2018. Unsupportive parenting moderates the effects of family psychosocial intervention on metabolic syndrome in African American youth. *Int. J. Obes.* 42 (4), 634–640.
- Danese, A., Pariante, C.M., Caspi, A., Taylor, A., Poulton, R., 2007. Childhood maltreatment predicts adult inflammation in a life-course study. *Proc. Natl. Acad. Sci.* 104 (4), 1319–1324.
- Danese, A., Tan, M., 2014. Childhood maltreatment and obesity: systematic review and meta-analysis. *Mol. Psychiatry* 19 (5), 544–554.
- Fagundes, C.P., Glaser, R., Kiecolt-Glaser, J.K., 2013. Stressful early life experiences and immune dysregulation across the lifespan. *Brain Behav. Immun.* 27, 8–12.
- First, M., Gibbon, M., Spitzer, R., Williams, J., 1997. Structured Clinical Interview for DSM-IV Axis I Personality Disorders (SCID-II). American Psychiatric Press Inc, Washington DC.
- First, M., Spitzer, R., Gibbon, M., Williams, J., 2002. Structured clinical interview for DSM-IV TR axis I disorders, research version, patient edition. In: Biometrics Research. New York State Psychiatric Institute, New York.
- Fowler, J.C., Allen, J.G., Oldham, J.M., Frueh, B.C., 2013. Exposure to interpersonal trauma, attachment insecurity, and depression severity. *J. Affect. Disord.* 149, 313–318.

- Franzosa, E.A., McIver, L.J., Rahnnavard, G., Thompson, L.R., Schirmer, M., Weingart, G., Huttenhower, C., 2018. Species-level functional profiling of metagenomes and metatranscriptomes. *Nat. Methods* 15 (11), 962–968.
- Gensohlen, T., Iyer, S.S., Kasper, D.L., Blumberg, R.S., 2016. How colonization by microbiota in early life shapes the immune system. *Science* 352 (6285), 539–544.
- Goodman, L.A., Corcoran, C., Turner, K., Yuan, N., Green, B.L., 1998. Assessing traumatic event exposure: general issues and preliminary findings for the Stressful Life Events Screening Questionnaire. *J. Trauma. Stress.* 11 (3), 521–542.
- Gouin, J.P., Glaser, R., Malarkey, W.B., Beversdorf, D., Kiecolt-Glaser, J.K., 2012. Childhood abuse and inflammatory responses to daily stressors. *Ann. Behav. Med.* 44 (2), 287–292.
- Hughes, K., Bellis, M.A., Hardcastle, K.A., Sethi, D., Butchart, A., Mikton, C., Dunne, M. P., 2017. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. *Lancet Public Health* 2 (8), e356–e366.
- Iljazovic, A., Roy, U., Galvez, E.J., Lesker, T.R., Zhao, B., Gronow, A., Strowig, T., 2021. Perturbation of the gut microbiome by *Prevotella* spp. enhances host susceptibility to mucosal inflammation. *Mucosal Immunol.* 14 (1), 113–124.
- Jašarević, E., Bale, T.L., 2019. Prenatal and postnatal contributions of the maternal microbiome on offspring programming. *Front. Neuroendocrinol.* 55, 100797.
- Jašarević, E., Howerton, C.L., Howard, C.D., Bale, T.L., 2015. Alterations in the vaginal microbiome by maternal stress are associated with metabolic reprogramming of the offspring gut and brain. *Endocrinology* 156 (9), 3265–3276.
- Kashtanova, D.A., Popenko, A.S., Tkacheva, O.N., Tyakht, A.B., Alexeev, D.G., Boytsov, S.A., 2016. Association between the gut microbiota and diet: feal life, early childhood, and further life. *Nutrition* 32, 620–627.
- Kessler, R.C., McLaughlin, K.A., Green, J.G., Gruber, M.J., Sampson, N.A., Zaslavsky, A. M., Williams, D.R., 2010. Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *Br. J. Psychiatry* 197 (5), 378–385.
- Kiecolt-Glaser, J.K., Belury, M.A., Andridge, R., Malarkey, W.B., Hwang, B.S., Glaser, R., 2012. Omega-3 supplementation lowers inflammation in healthy middle-aged and older adults: a randomized controlled trial. *Brain Behav. Immun.* 26 (6), 988–995.
- Langmead, B., Salzberg, S.L., 2012. Fast gapped-read alignment with bowtie 2. *Nat. Methods* 9 (4), 357–359.
- Lerner, A., Neidhöfer, S., Matthias, T., 2017. The gut microbiome feelings of the brain: a perspective for non-microbiologists. *Microorganisms* 5 (4), 66.
- Lin, P., Ding, B., Feng, C., Yin, S., Zhang, T., Qi, X., Li, Q., 2017. *Prevotella* and *Klebsiella* proportions in fecal microbial communities are potential characteristic parameters for patients with major depressive disorder. *J. Affect. Disord.* 207, 300–304.
- Madan, A., Fowler, J.C., Patriquin, M.A., Salas, R., Baldwin, P.R., Velasquez, K.M., Frueh, B.C., 2017. A novel approach to identifying a neuroimaging biomarker for patients with serious mental illness. *J. Neuropsychiatry Clin. Neurosci.* 29 (3), 275–283.
- Madan, A., Thompson, D., Fowler, J.C., Ajami, N.J., Salas, R., Frueh, B.C., Petrosino, J.F., 2020. The gut microbiota is associated with psychiatric symptom severity and treatment outcome among individuals with serious mental illness. *J. Affect. Disord.* 264, 98–106.
- Maier, L., Typas, A., 2017. Systematically investigating the impact of medication on the gut microbiome. *Curr. Opin. Microbiol.* 39, 128–135.
- McDonald, D., Clemente, J.C., Kuczynski, J., Rideout, J.R., Stombaugh, J., Wendel, D., Caporaso, J.G., 2012. The Biological Observation Matrix (BIOM) format or: how I learned to stop worrying and love the ome-ome. *Gigascience* 1 (1), 2047–217X.
- McDade, T.W., Ryan, C., Jones, M.J., MacIsaac, J.L., Morin, A.M., Meyer, J.M., Kuzawa, C.W., 2017. Social and physical environments early in development predict DNA methylation of inflammatory genes in young adulthood. *Proc. Natl. Acad. Sci.* 114 (29), 7611–7616.
- McLaughlin, K.A., Alvarez, K., Fillbrunn, M., Greif Green, J., Jackson, J.S., Kessler, R.C., Alegria, M., 2018. Racial/ethnic variation in trauma-related psychopathology in the United States: a population-based study. *Psychol. Med.* 49, 2215–2226.
- McMurdie, P.J., Holmes, S., 2013. Phyloseq: an R package for reproducible interactive analysis and graphics of microbiome census data. *PLoS One* 8 (4), e61217.
- Merrill, S.M., Gladish, N., Kobor, M.S., 2019. Social environment and epigenetics. In: Binder, E., Klengel, T. (Eds.), *Behavioral Neurogenetics. Current Topics in Behavioral Neurosciences*, Vol. 42. Springer, New York, pp. 83–126.
- Miller, G.E., Chen, E., Parker, K.J., 2011. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. *Psychol. Bull.* 137 (6), 959.
- Nelson III, C.A., Zeanah, C.H., Fox, N.A., 2019. How Early Experience Shapes Human Development: The Case of Psychosocial Deprivation. *Neural Plasticity*.
- Oksanen, J., 2012. In: *Constrained Ordination: Tutorial With R And vegan. R-Package Vegan*, pp. 1–10.
- Oksanen, J., Blanchet, F.G., Kindt, R., Legendre, P., Minchin, P.R., O'hara, R.B., Wagner, H., 2013. In: *Community Ecology Package. R Package Version*, 2(0), pp. 321–326.
- O'Mahony, S.M., Clarke, G., Dinan, T., Cryan, J., 2017. Early-life adversity and brain development: is the microbiome a missing piece of the puzzle? *Neuroscience* 342, 37–54.
- Park, S.H., Videlok, E.J., Shih, W., Presson, A.P., Mayer, E.A., Chang, L., 2016. Adverse childhood experiences are associated with irritable bowel syndrome and gastrointestinal symptom severity. *Neurogastroenterol.Motil.* 28 (8), 1252–1260.
- R Core Team, 2018. *R: A Language And Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. Available online at https://www.R-project.org/.*
- Rogers, C.B., Keating, D.J., Young, R.L., Wong, M.L., Licinio, J., Wesselingh, S., 2016. From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. *Mol. Psychiatry* 21 (6), 738–748.
- Röytiö, H., Makkala, K., Vahlberg, T., Laitinen, K., 2017. Dietary intake of fat and fibre according to reference values relates to higher gut microbiota richness in overweight pregnant women. *Br. J. Nutr.* 118 (5), 343–352.
- Segata, N., Izard, J., Waldron, L., Gevers, D., Miropolsky, L., Garrett, W.S., Huttenhower, C., 2011. Metagenomic biomarker discovery and explanation. *Genome Biol.* 12 (6), 1–18.
- Sharp, C., Fowler, C., Salas, R., Nielsen, D., Allen, J.G., Oldham, J., Fonagy, P., 2016. Operationalizing NIMH Research Domain Criteria (RDoC) in naturalistic clinical settings. *Bull. Menninger Clin.* 80, 187–212.
- Smith, C.J., Emge, J.R., Berzins, K., Lung, L., Khamishon, R., Shah, P., Sherman, P.M., 2014. Probiotics normalize the gut-brain-microbiota axis in immunodeficient mice. *Am. J. Physiol. Gastrointest. Liver Physiol.* 307 (8), G793–G802.
- Smith, K.S., Greene, M.W., Babu, J.R., Frugé, A.D., 2019. Psychobiotics as treatment for anxiety, depression, and related symptoms: a systematic review. *Nutr. Neurosci.* 1–15.
- Sudo, N., Chida, Y., Aiba, Y., Sonoda, J., Oyama, N., Yu, X.N., Koga, Y., 2004. Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice. *J. Physiol.* 558 (1), 263–275.
- The Human Microbiome Project Consortium, 2012a. A framework for human microbiome research. *Nature* 486, 215–221. <https://doi.org/10.1038/nature11209>.**
- The Human Microbiome Project Consortium, 2012b. Structure, function and diversity of the healthy human microbiome. *Nature* 486, 207–214. <https://doi.org/10.1038/nature11234>.**
- Thompson, D.S., Fowler, J.C., Bradshaw, M.R., Frueh, B.C., Weinstein, B.L., Petrosino, J., Madan, A., 2021. Is the gut microbiota associated with suicidality? Non-significant finding among a large cohort of psychiatrically hospitalized individuals with serious mental illness. *J.Affect.Disord.Rep.* 6, 1–7.
- Thompson, D.S., Fu, C., Gandhi, T., Fowler, J.C., Frueh, B.C., Weinstein, B.L., Madan, A., 2023. Differential co-expression networks of the gut microbiota are associated with depression and anxiety treatment resistance among psychiatric inpatients. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 120, 110638.
- Tietjen, G.E., Peterlin, B.L., 2011. Childhood abuse and migraine: epidemiology, sex differences, and potential mechanisms. *Headache* 51 (6), 869–879.
- Tolin, D.F., Foa, E.B., 2006. Sex differences in trauma and posttraumatic stress disorder: a quantitative review of 25 years of research. *Psychol. Bull.* 132 (6), 959–992.
- Truong, D.T., Franzosa, E.A., Tickle, T.L., Scholz, M., Weingart, G., Pasolli, E., Segata, N., 2015. MetaPhlan2 for enhanced metagenomic taxonomic profiling. *Nat. Methods* 12 (10), 902–903.
- Vadiveloo, M.K., Parker, H.W., Juul, F., Parekh, N., 2020. Sociodemographic differences in the dietary quality of food-at-home acquisitions and purchases among participants in the U.S. Nationally Representative Food Acquisition and Purchase Survey (FoodAPS). *Nutrients* 12, 2354–2372.
- van Reedt Dortland, A.K., Giltay, E.J., Van Veen, T., Zitman, F.G., Penninx, B.W., 2012. Personality traits and childhood trauma as correlates of metabolic risk factors: the Netherlands Study of Depression and Anxiety (NESDA). *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 36 (1), 85–91.
- Wang, D.D., Leung, C.W., Li, Y., Ding, E.L., Chiuev, S., Hu, F.B., Willett, W.C., 2014. Trends in dietary quality among adults in the United States, 1999 through 2010. *JAMA Intern. Med.* 174 (10), 1587–1595.
- Wei, C.H., Allot, A., Leaman, R., Lu, Z., 2019. PubTator central: automated concept annotation for biomedical full text articles. *Nucleic Acids Res.* 47 (W1), W587–W593.
- Westermair, A.L., Stoll, A.M., Greggersen, W., Kahl, K.G., Hüppe, M., Schweiger, U., 2018. All unhappy childhoods are unhappy in their own way—differential impact of dimensions of adverse childhood experiences on adult mental health and health behavior. *Front.Psychiatry* 9, 198.