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# The relationship and interaction between stress-induced inflammation and the gut-brain (GBA) axis in the future development of post-traumatic stress disorder (PTSD) or post-traumatic stress symptoms: a systematic review

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## ABSTRACT

Post-traumatic stress disorder (PTSD) is a complex condition that often arises from exposure to traumatic events and affects a significant portion of the global population. Managing PTSD and understanding its multifaceted nature have become areas of heightened research and clinical interest. While there is uncertainty regarding the causes of PTSD, there is a growing recognition of the potential impact of stress-induced inflammation and alterations in the gut-brain (GBA) axis on the development and severity of PTSD symptoms. This systematic review protocol follows the PRISMA guidelines and aims to investigate the relationship between stress-induced inflammation and changes in the gut-brain axis, specifically how these factors contribute to the development of post-traumatic stress disorder (PTSD) or post-traumatic stress symptoms in adults. The study will conduct a systematic review of literature published in English from 2010 onwards, focusing on original evidence from various study designs including microbiota composition, immune responses, and gut microbiota-related markers. By conducting a comprehensive analysis of existing literature from various databases, including PubMed, CENTRAL, APA PsycINFO, CINAHL, Cochrane Library, Scopus, Sociological Abstracts, and Web of Science, this review seeks to provide valuable insights into the effects of stress-induced inflammation and gut microbiota dysbiosis on the development of PTSD symptoms, providing insights into potential mechanisms. The review is ongoing and expected to be completed by February 2024, sponsored by the College of Nursing at the University of Tennessee.

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# The relationship and interaction between stress-induced inflammation and the gut-brain (GBA) axis in the future development of post-traumatic stress disorder (PTSD) or post-traumatic stress symptoms.

*This protocol follows PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) -P guidelines.*

**Review Question:**
What are the connections between stress-induced exacerbated inflammation and structural changes in the gut microbiota that contribute to the future development of Post-traumatic Stress Disorder (PTSD) or post-traumatic stress symptoms in adults?

**Searches:**
The following databases will be utilized with medical subject headings, Boolean logic, and pre-established text-word searches: PubMed, CENTRAL, APA PsycINFO, CINAHL, Cochrane Library, Scopus, Sociological Abstracts, and Web of Science. The referenced literature is originally published in English. Indicated reports are exported to Endnote and duplicates will be removed. The search strategy will include only terms relating to or describing the above-stated research hypothesis. The search terms will be adjusted for utilization alongside distinct bibliographic databases along with filters specific to each database. Included studies will be those published between January 2010 to July 2023. Searches were run beginning in July 2023 and will continue to be run through the end of September 2023. These searches will be re-run and verified on the final day of the search period.

**Types of study to be included initially:**
Original evidence from case-control studies, cohort case studies, cross-sectional studies, prospective and retrospective cohort studies, intervention studies with baseline data and exploratory studies will be considered.

**Domain/Condition being studied:**
PTSD in adults, stress or trauma, gut microbiota composition and diversity, immune responses.

**Participants/Population:**
Inclusion criteria:
This review includes all published literature written in English from 2010 onward. Included literature involves stress-induced exacerbated inflammation and associates an imbalance or disruption in the composition and diversity of the

gut microbiota, in relation to the development of PTSD as defined via the DSM-V or self-reported post-traumatic stress symptoms. Individuals of interest include a general adult population (aged 18-65 years) as well as animal subjects. Both observational case studies and interventional studies will be reviewed.

Included literature must perform microbiota analysis and provide measures of inflammatory markers like cytokines, C-reactive protein, TNF-α, and NF-κB, or markers of gut permeability like zonulin, Lipopolysaccharides (LPS), and mannitol. The literature may also involve lactulose testing, fluorescein isothiocyanate-dextran (FITC-D) evaluation, endoscopy, and intestinal biopsies. Outcomes of selected literature should assess the development of Post-traumatic stress disorder (PTSD) or post-traumatic stress symptoms secondary to stress-induced exacerbated inflammation and gut microbial dysbiosis.

Exclusion:
This review excludes any studies that are irrelevant to the topic, that assess separate psychiatric diseases from PTSD, that include subjects under the age of 18 or over the age of 65, and published before 2010. Studies using participants with a history of central nervous system disease, history of recent gastrointestinal surgery, congenital anomalies, or severe medical conditions are excluded. Literature such as letters, book chapters, dissertations, and theses will also be excluded.

**Intervention(s)/Exposure(s):**
None.

**Comparator(s)/Control(s):**
Not applicable.

**Primary Outcome(s):**
The primary outcome is to review and summarize the effects of stress-induced exacerbated inflammation and structural changes in the gut microbiota on the future development of PTSD or post-traumatic stress symptoms. The co-primary outcome is to comprehensively report differences in microbiota composition between (Stress-resilient/susceptible; Immune response/no response) subjects and classify them appropriately.

**Secondary outcomes:**
None.

**Measures of Effect:**
None.

**Data extraction:**
Peer-reviewed articles reporting the effects of stress-induced exacerbated inflammation and structural changes in the gut microbiota on the future development of Post-traumatic stress disorder (PTSD) or post-traumatic stress symptoms will be included. The following information will be extracted from the included literature:

Author
Publication Year
Title and aim of the study

Digital Object Identifier (DOI/PMID/URL/Accession number)
Diagnostic criteria and methods of diagnosis
Number of cases
Number of controls

A plural review of all titles will take place. Three reviewers will independently screen titles and abstracts to identify indicated literature and remove irrelevant studies. Interrater agreement will be standardized using Covidence.

Standardized reporting of study selection will make use of the PRISMA guidelines and flow-diagram.

**Risk of bias (quality assessment):**
Each included study will be evaluated for risk of bias along with quality assessment according to the Newcastle-Ottawa Scale. The included studies will each be assessed and given a score between 0-9 based on factors of selection, comparability, and exposure in accordance with the Newcastle-Ottawa Scale.

**Strategy of data synthesis:**
Collected data will be divided and analyzed based upon markers of inflammation and gut permeability, psychiatric diagnosis/symptoms, and the condition of the enteric microbiome. A systematic review will be conducted to summarize the studies relating to the enteric microbiota of the population of interest compared with the control population. In addition, a discussion of potential mechanisms explaining the data will be included. Conclusions are drawn in regard to gaps in the research and factors underlying the need for continued study.

**Analysis of subgroups or subsets:**
Sex, BMI, age, and education level are all subgroups that may be analyzed in the review.

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**Type and Method of Review:**
Systematic Review

**Health Area of Review:**
Blood and immune system, Digestive system, Mental health and behavioral conditions, Public health

**Anticipated or actual start date:**
5 July 2023

**Anticipated Completion Date:**
01 February 2024

**Funding sources/ Sponsors:**
College of Nursing, University of Tennessee

**Conflicts of Interest:**
No conflicts of interest.

**Collaborators:**
None.

**Stage of Review:**
Ongoing

| | Started | Completed |
|---|---|---|
| Preliminary searches | X | X |
| Piloting of the study selection process | X | |
| Formal screening of search results against eligibility criteria | | |
| Data extraction | | |
| Risk of bias (quality) assessment | | |
| Data analysis | | |

**Subject Index Terms status:**

We will use the following search string when searching PubMed, APA PsycINFO, CINAHL, Scopus, Sociological

Abstracts, and Web of Science:

(((((("Immune System"[Mesh] OR "Immune System Phenomena"[Mesh]) OR "Inflammation"[Mesh]) OR (immun* OR "natural resistance" OR "natural defense*" OR inflam* OR "innate inflam*")) AND (("Stress, Psychological"[Mesh]) OR (stress-induced OR exacerbate* OR stress*))) AND (("Gastrointestinal Microbiome"[Mesh]) OR (microbi* OR flora OR microflora OR dysbiosis OR perturb* OR alter* OR "enteric bacteria" OR enterobacteriaceae OR "human microbi*" OR "microbiota-immune axis" OR "microbiome-gut-brain axis" OR "MGBA" OR "gut inflam*" OR "enteric nervous system" OR "gut permeab*"))) AND (("Stress Disorders, Post-Traumatic"[Mesh]) OR ("post traumatic stress" OR "posttraumatic stress" OR "post-traumatic stress" OR "PTSD"))

We will use the following search string when searching CENTRAL:

((((immun* OR "natural resistance" OR "natural defense*" OR inflam* OR "innate inflam*") AND (stress-induced OR exacerbate* OR stress*)) AND (gut OR gastro* OR gastric OR intestinal)) AND (microbi* OR flora OR microflora OR dysbiosis OR perturb* OR alter* OR "enteric bacteria" OR enterobacteriaceae OR "human microbi*" OR "microbiota-immune axis" OR "microbiome-gut-brain axis" OR "MGBA" OR "gut inflam*" OR "enteric nervous system" OR "gut permeab*")) AND ("post traumatic stress" OR "posttraumatic stress" OR "post-traumatic stress" OR "PTSD")