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Psychological Stress and Gut Microbiota Composition: A Systematic Review of Human Studies

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Abstract

Introduction: The associations between psychological stress and gut microbiota composition are not fully understood. This study investigated associations between psychological stress and gut microbiota composition and examined the potential modifying effects of age, sex, and ethnicity on such associations. ***Methods:*** A systematic literature search was conducted using PubMed, Web of Science, PsycINFO, and Embase databases for studies published until November 2021 which examined associations between psychological stress and gut microbiota composition. ***Results:*** During the search process, 10,790 studies were identified, and after screening, 13 met the eligibility criteria and were included. The median sample size was 70, and the median age of participants was 28.0 years. Most of the included studies did not report associations between measures of alpha- and beta diversity of the gut microbiota composition and psychological stress. A few studies reported that the Shannon index, Chao 1, Simpson index, and weighted UniFrac were negatively associated with psychological stress. Significant reductions in several taxa at the phyla-, family-, and genus-levels were observed in participants with higher psychological stress. At the phylum level, the abundance of Proteobacteria and Verrucomicrobia were negatively associated with psychological stress. At the family-level, no more than two studies reported associations of the same microbiota with psychological stress. At the genus level, the following results were found in more than two studies; psychological stress was negatively associated with the abundance of *Lachnospira,* Lachnospiraceae, Phascolarctobacterium*, Sutterella,* and *Veillonella*, and positively associated with the abundance of *Methanobrevibacter,*

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Rhodococcus, and *Roseburia*. However, it was not possible to determine the influence of age, sex, or ethnicity due to the limited studies included. ***Conclusion:*** Our findings provide evidence that psychological stress is associated with changes in the abundance of the gut microbiota. Larger sample longitudinal studies are needed to determine the causal relationship between psychological stress and the gut microbiota.

Introduction

The bi-directional dialog between the gut-brain axis and the role of psychological stress has recently become the focus of intense debate. Given that many trillions of bacteria reside and have co-evolved in the human gastrointestinal (GI) tract, this has resulted in a symbiotic relationship where the GI tract offers a hospitable environment for these bacteria, which in turn perform a plethora of roles implicated in the support of human health above and beyond the fermentation of non-digestible substrates [1]. Perhaps, one of the most important of these is the modulation of the central nervous system, with mounting evidence demonstrating that psychological stress can mediate the diverse range of microorganisms residing in the human intestine [2]. However, despite this, the relationship remains poorly understood.

Psychological stressors can come in many forms, ranging from those experienced during early childhood, through adulthood, and have been shown to impact upon the composition of the gut microbiota. For example, acute stress can increase the presence of catecholamines, which can increase levels of pathogenic bacteria by up to 10,000 fold in vitro, as well as causing localized shifts in microbiota habitats [3]. Chronic stress has also been implicated in long-term modifications of the gut microbiota in animal models that can result in differences in alpha diversity, which appear to differ dependent on the characteristics of the stressors [4]. Examples are that the gut microbiota of students suffering from academic stress is composed of fewer health-promoting bacteria [5], and very recent evidence has revealed dysbiosis in the microbiota of frontline healthcare workers who experienced psychological stress while working during the COVID-19 pandemic [3, 6]. Therefore, both acute and chronic stress can cause morphological and functional changes in the human gut microbiota.

Despite these associations of acute and chronic psychological stress with gut microbiota composition, the underlying mechanisms remain elusive, with evidence suggesting that the dysregulation of tryptophan metabolism may be a contributing factor [7]. Regardless of the implicated mechanisms, it is important to note that when stressors are removed in rats, the relative microbial abundance in terms of both species and distribution appear to resolve [8]. However, interestingly, the microbial metabolic profiles remain altered, potentially suggesting that the recovery time for gut microbial metabolic functionality from stressful experiences may be slow [8].

This impaired recovery time may have important implications in terms of aging, where the composition of the gut microbiota and their metabolic outputs in the blood of older adults has been shown to deteriorate with declining health and has been proposed as a modifiable predictor of healthy trajectory [9]. In addition to this, disparities in the gut microbiota have also been observed between genders as well as across ethnicities [10, 11]. For example, a cohort study showed that age and gender were among the 69 factors which were shown to correlate significantly with overall microbiome community variation [12]. Substantial ethnic differences in the composition of the gut microbiota have also been found [13]. Although this is likely to be influenced by a plethora of extrinsic factors, psychological stress is known to be vitally important [10, 14]. Furthermore, the type of stress may be a modifier of the associations between stress and gut microbiota [15]. However, further work is required to fully understand its role in dysbiosis across different demographics.

In summary, the ability of acute and chronic psychological stress to modulate the gut microbiota composition is yet to be fully elucidated. Despite this, evidence exists which suggests that the role of psychological stress on the gut microbiota can differ across age, ethnicity, and the type of psychological stress and between gender [16]. Our systematic review will, for the first time, synthesize this literature and provide a summary of the findings on how age, gender, ethnicity, and the types of stress may moderate the associations between psychological stress and gut microbiota composition, offering insights based on the totality of the evidence.

Methods

This study was developed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [17] and other standards (e.g., Johnson and Hennessy [18], 2019). The review protocol is listed in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD: 42021284124).

Literature Search

A literature search was performed in electronic bibliographic databases: PubMed, Web of Science, PsycINFO, and Embase, from inception to November 2021. Search strategies included combinations of terms related to acute and chronic psychological stress, gut microbiota, and human study. A summary of search strategies was provided in online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000533131). Furthermore, to minimize the effect of publication bias, a snowball method, characterized by manual checking of references from retrieved studies, was applied to relevant studies that met the selection criteria outlined below.

Search results were merged into the reference management software EndNote. Two authors (Y.T.Y. and Y.L.) independently reviewed the records, in case of disagreement between the two authors, a third author (M.L.) was consulted to make the final decision.

Study Selection

Studies were included if they (a) were cross-sectional studies, case-control studies, longitudinal studies, randomized controlled trials, clinical trials with either parallel, crossover, or cohort design; (b) examined the associations between psychological stress and gut microbiota, or the associations between gut microbiota and psychological stress in humans; (c) psychological stress included at least acute laboratory stress, chronic stress, stressful life events, perceived stress, or early life stress; (d) had samples that did not overlap with other identified studies (if data or data subsets were from duplicate publications, only publications with the largest sample size was included); and (e) were published as full-text articles in peer-reviewed scientific journals. Studies were excluded if they were (a) without human subjects or (b) were qualitative studies, case reports, editorials, protocols, meta-analyses, or reviews.

Definition of Microbial Indices Utilized in the Literature

In this study, assessments of the biodiversity and composition of microbiota were based on stool sample testing using culture-dependent methods, real-time polymerase chain reaction, fluorescence in situ hybridization, or pyrosequencing for bacterial 16s ribosomal ribonucleic acid genes. The alpha diversity and beta diversity were used to assess the biodiversity of gut microbiota. The alpha diversity provides a summary statistic of the microbial community, whereby a higher alpha diversity indicates a greater number of species, with more even representation, and/or greater biodiversity according to the ancestral dissimilarity of species. Beta diversity is an inter-individual measure that examines similarity of communities relative to the other samples analyzed. All bacterial information was reviewed and selected before the final analyses, including bacterial taxonomy, percentage, and relative abundance at different taxonomic levels. For consistency, the included studies were analyzed at the phylum-, family-, and genus-levels in the current study. We contacted the investigators of the eligible studies if we were unable to extract data on bacterial abundance from the published studies.

Data Extraction

Data were extracted by two independent authors, and disagreements were reviewed and resolved by the first author. Data extracted included the following: (a) study level (country, author, publication year, study design, type and measurement of stress, microbiota diversity assessment method and estimation, confounding variables), (b) sample level (participants' age, sex, and ethnicity), and (c) effect sizes (analyses which compared the gut microbiota between cases and controls, or assessed associations between psychological stress, and the gut microbiota).

Pearson correlation coefficient r, β coefficient, odds ratio, or standardized mean difference was used to determine the associations. They were set to be positive (greater than the null value) for associations that favored the hypotheses. When a study reported both overall effect size and subgroup effect sizes, such as by sex, the overall effect size was used in the overall analysis.

Study Quality Assessment

Two authors independently assessed the quality of the studies using the U.S. National Institutes of Health Study Quality Assessment Tools (National Heart Blood and Lung Institute, 2019). The assessment tool rates each study based on 14 criteria. For each criterion, a score of one was assigned if "yes" was the response, whereas a score of zero was assigned otherwise (i.e., an answer of "no," "not applicable," "not reported," or "cannot determine"). Overall quality was rated based on the total score of the scale: "7≤ total score" = good, "4< total score <7" = fair, "total score <4" = poor. The risk of bias of each study decreased with the increase in the total score (online suppl. Table 2).

Results

The literature search identified 13 eligible studies that investigated the associations between psychological stress and the composition of the gut microbiota as a primary outcome. The 13 studies were summarized in Table 1.

Literature Search and Study Selection Process

The study selection process that followed the literature search is summarized in Figure 1. A total of 10,790 citations were identified through four databases. After initial screening and removal of duplicates, 10,398 records remained, of which 10,205 were screened by abstract and excluded. Following the initial screening, 193 full-text studies were retrieved for detailed review and were assessed against the established selection criteria.

One hundred and eighty full-text records did not fulfill the set inclusion criteria and after their removal, 13 studies were included in the current review. All the included 13 studies had good quality according to the National Heart, Lung, and Blood Institute's Quality Assessment Tool (online suppl. Table 2).

Characteristics of the Included Studies

The characteristics of the included studies are summarized in Table 1. The studies were conducted in 7 countries including the USA (5 studies) [19, 22, 26, 27,

Table 1. Characteristics of the 13 studies examined the associations between psychological stress and gut microbiota in the systematic review

First author, publication year	Country	Study design	Participant's age (mean±SD/range) years	Participant's healthy status	Sample size (girls %)	Ethnicity	Psychological stress		Gut microbiota	
							type	measurement	diversity assessment	measurement methods
1. Coley et al. [19], 2021	USA (developed)	Cross-sectional	Low early traumatic inventory: 27.28±7.55 years High early traumatic inventory: 28.81±7.05 years	Healthy	128 (66.4%)	Not reported	1. Early life stress 2. Perceived stress	1. The Early Traumatic Inventory-Self Report (ETI-SR) 2. The Perceived Stress Scale (PSS-10)	α: Shannon and Chao 1 β: Aitchison distance metric	Liquid chromatography tandem mass spectrometry-based untargeted metabolomic profiling
2. Sobko et al. [20], 2020	Chinese (developing)	RCTs	Control group (N = 18): 2.98±0.71 years (baseline) Intervention group (N = 27): 2.98±1.02 years (baseline)	Healthy	Control group: 10 (55.56%) (Baseline) Intervention group: 13 (48.15%) (Baseline)	Not reported	Perceived stress	Perceived Stress Scale for Children (PSS-C)	α: Simpson index, Chao 1, and Shannon β: not reported	Enzyme linked immunosorbentassay (ELISA) 16S rDNA Not report
3. Naudé et al. [21], 2020	South African (developing)	Birth cohort	21.9–31.24 years	Healthy	84 (100.0%)	Not reported	Maternal prenatal stress	The self-reporting questionnaire 20-item (SRQ-20)	α: Shannon β: computed based on the "w" metric	16Sr RNA V4
4. Mackner et al. [22], 2020	USA (developed)	Longitudinal	17.00±2.75 years (baseline)	Crohn's disease (CD)	22 (64.0%)	Caucasian (67.0%) and other ethnicities (33.0%)	Perceived stress	The Perceived Stress Scale (PSS-10)	α: Shannon and Chao 1 β: UniFrac (unweighted)	16S rRNA Not reported
5. Humbel et al. [23], 2020	Switzerland (developed)	Prospective cohort	17–82 years (baseline)	Inflammatory bowel disease (IBD)	204 (56.4%)	Not reported	Perceived stress	The Perceived Stress Questionnaire (PSQ-30)	α: Shannon and Simpson indices β: Bray-Curtis dissimilarity matrix	16S rRNA V5/V6
6. Michels et al. [24], 2019	Belgium (developed)	Cross-sectional	10.8–13.6 years	Healthy	93 (48.0%)	Not reported	1. Chronic stress 2. Self-report stressful life events (or negative events) 3. Self-report negative and positive emotions (or negative emotions and happiness) 4. Emotional problems reported by the parent	1. Hair cortisol 2. The Coddington Life Events Scale for Children (CLES-C) 3. Negative and positive emotions reported by self-report 4. Strengths and Difficulties Questionnaire 5. Heart rate variability (pnn50 parameter reflecting parasympathetic activity)	α: Observed species, Simpson index, and Chao 1 β: UniFrac (weighted or unweighted)	16S rDNA V3–V4

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Table 1 (continued)

First author, publication year	Country	Study design	Participant's age (mean±SD/range) years	Participant's healthy status	Sample size (girls %)	Ethnicity	Psychological stress		Gut microbiota	
							type	measurement	diversity assessment	measurement methods
7. Hechler et al. [25], 2019	The Netherlands (developed)	Cross-sectional	31.61±3.66 years	Healthy pregnant women	70 (100.0%)	Not reported	Prenatal psychosocial stress	Questionnaires on general and pregnancy-specific stress and anxiety: general stress (EPL) and pregnancy-related stress (PES) items	α: Shannon and Chao 1 β: UniFrac (weighted or unweighted)	RT-qPCR 16S rRNA Not reported
8. Hantsoo et al. [26], 2019	USA (developed)	Case-control	18–45 Low adverse childhood experiences (*N* = 25): 29.80±5.21 years High adverse childhood experiences (*N* = 23): 25.98±4.99 years	Physically and psychiatrically healthy adult pregnant women	48 (100.0%)	Hispanic (89.6%) Non-Hispanic (10.4%)	1. Early life stress	1. The Adverse Childhood Experiences Questionnaire (ACE-Q)	α: Shannon β: UniFrac (weighted or unweighted)	16S rRNA V1–V2
9. D'Agata et al. [27], 2019	USA (developed)	Case-control	Gestational age: 26.50–29.00 days	Healthy (Exclusion criteria for entry into the parent study included birth weight >1,500 g, major congenital anomalies, moribund infants, and infants of HIV-infected mothers)	47 (55.32%)	Not reported	Daily stress experiences of infants during care in the NICU	Neonatal Infant Stressor Scale (NISS)	α: Not reported β: Not reported	PCR 16S rRNA V4
10. Chung et al. [28], 2019	Taiwan, China (developing)	Case-control	Major depressive disorder (MDD) case (*N* = 36): 45.83±14.08 years Control (*N* = 35): 41.19±12.73 years	Major depressive disorder (MDD) and healthy	Total: 71 (71.8%) MDD: 28 (2.35%) Control: 23 (62.16%)	Not reported	Perceived stress	Perceived Stress Scale (PSS-10)	α: Shannon β: UniFrac (unweighted and weighted)	16S rRNA V3–V4, V4
11. Kleiman et al. [29], 2017	USA (developed)	Cross-sectional	29.00±7.9 years	Healthy	91 (100%)	Not reported	Perceived stress	Perceived Stress Scale (PSS-10)	α: Shannon β: Not reported	PCR 16S rRNA V4
12. Hemmings et al. [30], 2017	South Africa (developing)	Case-control	Posttraumatic Stress Disorder (PTSD): 42.0±12.6 years Trauma-exposed (TE): 38.7±11.7 years	Posttraumatic Stress Disorder and trauma-exposed	Total: 30 (70.0%) PTSD: 18 (77.8%) TE: 12 (58.3%)	South African mixed ancestry (100%)	Early life stress	The Childhood Trauma Questionnaire (CTQ)	α: Chao 1, Shannon and observed species β: Bray-Curtis and UniFrac (unweighted and weighted)	16S rRNA V3/V4
13. Knowles et al. [5], 2008	Australia (developed)	Case-control	23.0±6.8 years	Healthy	23 (69.6%)	Not reported	Perceived stress	The Stress Subscale for the Depression, Anxiety and Stress Scale (DASS)	α: Not reported β: Not reported	Counting colony-forming units (CFU) on the MRS plates corresponding

RCTs, randomized controlled trials, rRNA, ribosomal ribonucleic acid.

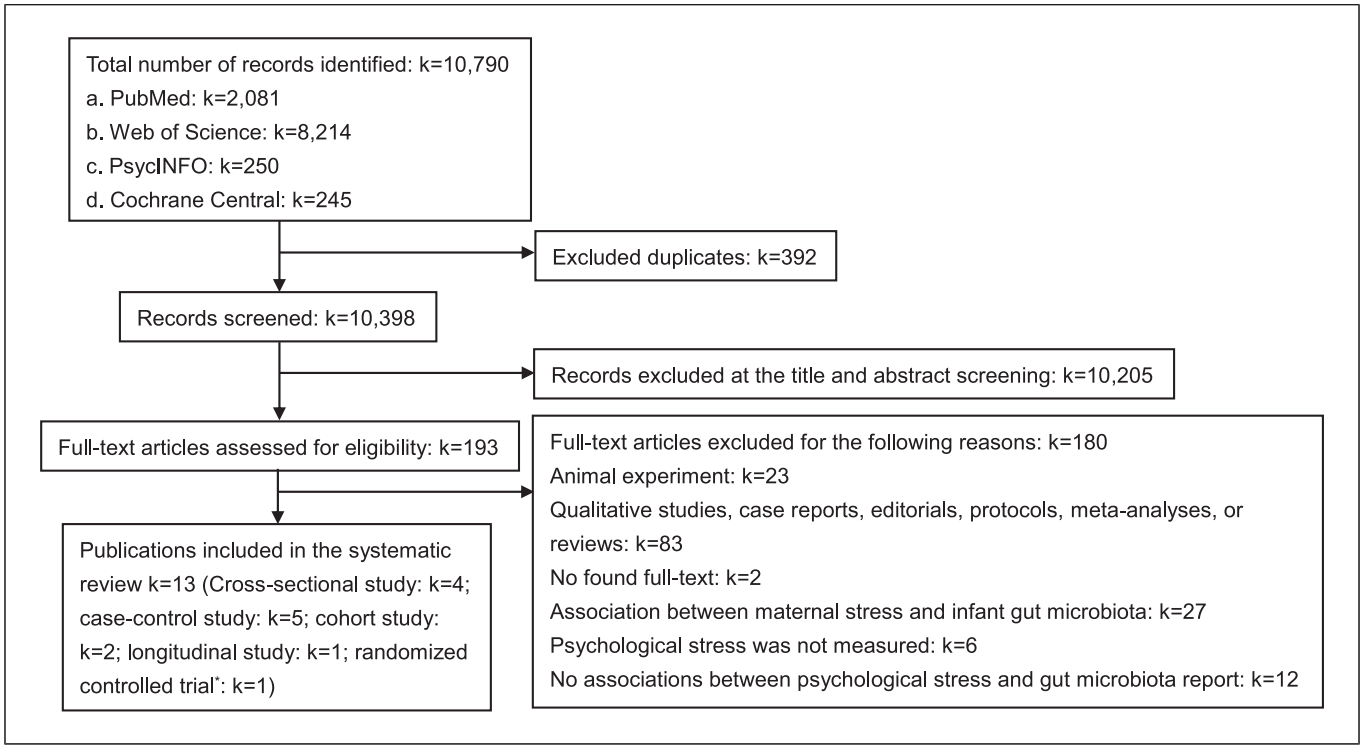

Fig. 1. Flowchart of the literature search and study selection according to the PRISMA standard. *The included randomized controlled trial was about the impact of outdoor nature-related activities on gut microbiota, fecal serotonin, and perceived stress. In this study, psychological stress and gut microbiota were not used as intervention variables, and the correlation between psychological stress and gut microbiota was analyzed using baseline and post-intervention data. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

29], China (2 studies) [20, 28], South Africa (2 studies) [21, 30], and one study each from Switzerland [23], Belgium [24], the Netherlands [25], and Australia [5]. Most of the studies were of cross-sectional ($n = 4$) [19, 24, 25, 29] and case-control design ($n = 5$) [5, 26–28, 30], which could not determine potential causal relationships between psychological stress and microbiota composition. The medium sample size of the studies was 70, ranging from 22 to 204. The medium age of participants was 28.0 years, ranging from 26.5 days to 82 years. Three studies targeted at children [20, 24, 27], and the remain ten studies targeted at adults [5, 19, 21–23, 25, 26, 28–30]. About 39.0% of the studies ($n = 5$) were conducted among participants with medical conditions such as Crohn's disease, inflammatory bowel diseases, major depressive disorder, and posttraumatic stress disorder and trauma-exposed. Except for three studies involving Caucasian [22], Hispanic [26], and South African mixed ancestry ethnic groups [30], the other studies did not report the ethnicity of participants.

Eleven of the 13 studies assessed alpha diversity [19–26, 28–30] and nine assessed beta diversity [19, 21–26, 28, 30] of the gut microbiome. The most frequently used measurement method was 16S ribosomal ribonucleic acid gene sequencing. Four indices were used to assess alpha diversity, including estimates of richness (observed species and Chao 1), richness/evenness (Shannon and Simpson indices). Four indices were used to assess beta diversity, including Aitchison distance metric, Bray-Curtis dissimilarity matrix, UniFrac (unweighted or weighted), and computed based on the "w" metric. Shannon and Simpson indices were the most frequently used indices to assess alpha diversity, and UniFrac was the most frequently used index to assess beta diversity. Perceived stress was the main type of stress (53.85%, $n = 7$) [5, 19, 20, 22, 23, 28, 29], and perceived stress was mainly measured by the Perceived Stress Scale-10 (30.77%, $n = 4$) in the included studies [19, 22, 28, 29].

Table 2. The main findings of the 13 studies examined associations between psychological stress and the composition of gut microbiota in the systematic review

First author, publication year	Findings on the associations between psychological stress and gut microbiota composition
1. Coley et al. [19], 2021	1. No significant difference was found for high and low early life adversity for alpha diversity: Chao 1, $p = 0.345$, Shannon, $p = 0.465$; beta diversity: Aitchison-based PCoA; perma-nova $p = 0.421$; and relative taxonomic abundance, at either phylum or genus levels (data were not reported) Age, body mass index, diet, and sex were adjusted for the association between microbial composition and life adversity
2. Sobko et al. [20], 2020	1. Correlations between perceived stress and alpha diversity of Chao 1 ($r = -0.27$, $p = 0.03$) and Shannon of Bacteroidetes ($r = -0.26$, $p = 0.03$) were significant, while correlations of perceived stress with Simpson of Bacteroidetes ($r = -0.24$, $p = 0.05$) and Shannon of Proteobacteria ($r = -0.23$, $p = 0.07$) were not significant
	2. Participants from the intervention group with decreased perceived stress exhibited a higher gut microbiota richness than those with not-decreased perceived stress Confounding variables: not reported
3. Naudé et al. [21], 2020	No significant relationships between the prenatal psychological measures and maternal fecal bacterial alpha and beta diversity indices (data were not reported) Maternal demographics (residential area, education), HIV status, smoking, mode of delivery, gestational age, birth weight and length, infant sex, antibiotic use, and household members were adjusted for the association of prenatal psychological measures with the abundance of each taxon and alpha diversity
4. Mackner et al. [22], 2020	1. Alpha (Shannon Diversity Index) and beta diversity (unweighted Unifrac) were not significantly different in Crohn's disease patients who reported higher and lower perceived stress (data were not reported)
	2. The relative abundances of Firmicutes at phylum level (t (20) = 2.45, $p < 0.05$) and *Anaerostipes* at genus level (t (20) = 4.68, $p < 0.001$, FDR $p = 0.028$) were lower in the higher perceived stress group than lower perceived stress group
	3. The relative abundance of *Parabacteroides* was significantly higher in the high perceived stress group [t (20) = 4.27, $p = 0.001$, FDR $p = 0.035$] Confounding variables: not reported
5. Humbel et al. [23], 2020	1. Alpha diversity: Shannon was lower in the higher perceived stress group than the lower perceived stress group ($p = 0.023$), no significant difference was found for Simpson ($p = 0.076$)
	2. Beta diversity differed between the higher and lower perceived stress groups (p <0.05)
	3. Perceived stress was negatively correlated with the relative abundance of *Sutterella* ($r = -0.0697$, $p = 3.54e-06$-), *Haemophilus* ($r = -0.0201$, $p = 0.000263$–), *Lachnospira* ($r = -0.016$, $p = 0.000355$–), *Parabacteroides* ($r = -0.0372$, $p = 0.000557$–), RF32 family ($r = -0.0139$, $p = 0.001$–), and *Eubacterium* ($r = -0.016$, $p = 0.00385$–) in ulcerative colitis patients
	4. No significant correlations between microbial profiles and perceived stress in Crohn's disease Age, body mass index, sex, smoking habits, medication, surgical resection, disease activity, and anatomic location were adjusted for the association between stress levels and the abundance of the microbial community
6. Michels et al. [24], 2019	1. Alpha diversity for six stress parameters (lower stress vs. higher stress): Negative events — Observed species: 325 vs. 295, $p = 0.120$ — Chao 1: 394 vs. 372, $p = 0.351$ — Simpson: 0.964 vs. 0.949, $p = 0.022$ Negative emotions self-report — Observed species: 305 vs. 336, $p = 0.103$ — Chao 1: 376 vs. 412, $p = 0.092$ — Simpson: 0.957 vs. 0.962, $p = 0.403$ Emotional problems Parental report — Observed species: 311 vs. 319, $p = 0.852$ — Chao 1: 382 vs. 392, $p = 0.814$ — Simpson: 0.955 vs. 0.966, $p = 0.116$

Table 2 (continued)

First author, publication year	Findings on the associations between psychological stress and gut microbiota composition			
	Happy	Observed species: 329 vs. 308, $p = 0.312$	Chao 1: 416 vs. 375, $p = 0.187$	Simpson: 0.950 vs. 0.962, $p = 0.201$
	Pnn50	Observed species: 300 vs. 320, $p = 0.326$	Chao 1: 373 vs. 392, $p = 0.435$	Simpson: 0.948 vs. 0.964, $p = 0.024$
	Hair cortisol	Observed species: 323 vs. 312, $p = 0.754$	Chao 1: 394 vs. 381, $p = 0.801$	Simpson: 0.960 vs. 0.962, $p = 0.644$
	2. Beta diversity: higher vs. lower happiness: unweighted Unifrac, $p = 0.027$; weighted Unifrac, $p = 0.009$; high vs. low pnn50: unweighted Unifrac, $p = 0.066$; weighted Unifrac, $p = 0.043$			
	3. Higher stress was consistently associated with a lower abundance of Firmicutes and Verrucomicrobia at phylum level; Acidaminococcaceae, Lachnospiraceae, Ruminococcaceae, Veillonellaceae at the family level; and *Phascolarctobacterium Coprococcus 2*, *Lachnoclostridium*, Lachnospiraceae NK4A136 *group*, Lachnospiraceae UCG-004, *uncultured, Ruminococcaceae UCG002*, *Ruminococcaceae UCG003*, *uncultured*, *Veillonella*, and *Akkermansia* at the genus level (p adjusted. <0.1). Higher stress was associated with a higher abundance of Actinobacteria, Bacteroidetes, Euryarchaeota at the phylum level; Nocardiaceae, Bacteroidaceae, Porphyromonadaceae, Rikenellaceae, Methanobacteriaceae at the family level; and *Rhodococcus*, *Bacteroides*, *Barnesiella*, *Parabacteroides*, *Alistipes*, *Methanobrevibacter*, *Coprococcus 1*, *Roseburia*, *Ruminiclosteridium 5*, *Ruminococcaceae UCG004*, and *Ruminococcus 2* at the genus level			
	4. On the phylum level, higher stress was associated with lower Firmicutes among both preadolescents and adolescents. Higher stress was associated with lower Bacteroidetes among adolescents and lower Proteobacteria in preadolescents Age, sex, socio-economic status, diet, physical activity, sleep, and weight status were adjusted for the association of six continuous stress variables (negative events, negative emotions, emotional problems, happiness, pnn50, hair cortisol) with Alpha diversity/richness indices (observed species, Chao1, and Simpson diversity) and beta diversity			
7. Hechler et al. [25], 2019	1. No associations between microbiota relative abundance and general stress ($p = 1$) and pregnancy-related stress ($p = 1$) at both phylum and genus levels (regression coefficient was not reported) Confounding variables: not reported			
8. Hantsoo et al. [26], 2019	1. No differences were found between ACE groups for richness ($p = 0.82$), Shannon index ($p = 0.58$), nor UniFrac distances (p's >0.05)			
	2. High ACE participants had a higher differential abundance of *Prevotella* (FDR-adjusted p value, $q = 5.7 \times 10^{-13}$), lower abundance of *Eubacterium* ($p = 0.019$, $q = 0.15$), and *Phascolarctobacterium* ($p = 0.041$, $q = 0.22$) than lower ACE participants Gestational age at the time of stool collection, body mass index, and dietary fiber intake was adjusted for associations between microbiome composition and ACE			
9. D'Agata et al. [27], 2019	Estimates from the Beta part of the zero-inflated beta regression model with random effects (ZIBR) for relationships between the relative abundance of genera and stress 1, 2 week prior was:			
	Genus	$Stress_{t-2}$		$Stress_{t-1}$
	Klebsiella	β = 0.000	$p = 1.000$	β = −0.018 $p = 0.970$
	Escherichia	β = −0.267	$p = 0.693$	β = −0.020. $p = 0.928$
	Staphylococcus	β = −0.037	$p = 0.990$	β = 0.092 $p = 0.970$
	Enterococcus	β = −0.053	$p = 0.349$	β = −0.165 $p = 0.896$
	Bifidobacterium	β = 0.292	$p = 0.693$	β = 0.140 $p = 0.872$
	Proteus	β = −0.487	$p = 0.015$*	β = 1.380 $p = 0.000$
	Citrobacter	β = 0.066	$p = 0.990$	β = −0.075 $p = 0.928$
	Streptococcus clostridium.	β = 0.051	$p = 0.990$	β = 0.069 $p = 0.970$
	Butyricum lostridium.	β = 0.184	$p = 0.867$	β = 0.212 $p = 0.872$
	Perfringens	β = −0.286	$p = 0.532$	β = 0.940 $p = 0.052$
	Veillonella	β = 0.086	$p = 0.773$	β = 0.047 $p = 0.033$
	Baseline variables including antibiotic, infant gender, birth weight, and gestational age were adjusted for relationships between the relative abundance of genera and stress 1, 2 week prior			

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Table 2 (continued)

First author, publication year	Findings on the associations between psychological stress and gut microbiota composition
10. Chung et al. [28], 2019	1. Correlations between perceived stress scores and relative abundance of microbiota: Phylum: Actinobacteria $r = 0.26$, $p = 0.046$; Firmicutes $r = 0.13$, $p = 0.307$; Bacteroidetes $r = -0.19$, $p = 0.148$; Proteobacteria $r = -0.29$, $p = 0.024$ Family: Prevotellaceae $r = -0.27$, $p = 0.035$; Lachnospiraceae $r = 0.09$, $p = 0.492$; Bifidobacteriaceae $r = 0.23$, $p = 0.075$; Alcaligenaceae $r = -0.34$, $p = 0.007$; Streptococcaceae $r = 0.15$, $p = 0.260$; Porphyromonadaceae $r = 0.18$, $p = 0.156$; Peptostreptococcaceae $r = 0.11$, $p = 0.381$ Genus: *Prevotella* $r = -0.27$, $p = 0.035$; *Blautia* $r = 0.34$, $p = 0.007$; *Bifidobacterium* $r = 0.23$, $p = 0.075$; *Sutterella* $r = -0.34$, $p = 0.007$; *Ruminococcus* $r = 0.34$, $p = 0.007$; *Streptococcus* $r = 0.15$, $p = 0.260$; *Megamonas* $r = -0.23$, $p = 0.079$; *Parabacteroides* $r = 0.18$, $p = 0.158$; *Eggerthella* $r = 0.32$, $p = 0.011$; *Adlercreutzia* $r = 0.08$, $p = 0.536$; *Holdemania* $r = 0.38$, $p = 0.003$; *Clostridium XI* $r = 0.07$, $p = 0.615$ Confounding variables: sequencing platform (Miniseq or Miseq) and fat intake were adjusted for correlations between perceived stress scores and relative abundance of microbiota
11. Kleiman et al. [29], 2017	No significant associations were found between stress and gut composition (alpha diversity: Shannon and beta diversity: unweighted UniFrac distance) Confounding variables: not reported
12. Hemmings et al. [30], 2017	1. No differences between posttraumatic stress disorder and trauma-exposed control groups in individual taxa and alpha diversity (Chao 1: $t = 0.832$, $p = 0.41$; observed species: $t = 0.760$, $p = 0.45$; phylogenetic diversity: $t = 0.510$, $p = 0.61$; Shannon: $t = 0.386$, $p = 0.70$) and beta diversity (Bray-Curtis distance metric: test statistic = –0.033, $p = 0.70$, weighted UniFrac distance metric: test statistic = –0.016, $p = 0.56$, unweighted UniFrac distance metric: test statistic = –0.013, $p = 0.52$)
	2. Higher posttraumatic stress disorder score was associated with a decreased total abundance of phyla Actinobacteria, Lentisphaerae, and Verrucomicrobia ($r = -0.387$, $p = 0.035$) Confounding variables: not reported
13. Knowles et al. [5], 2008	The bacterial count decreased from baseline week to exam week ($F[1, 22] = 5.50$, $p < 0.05$) Changes in dietary habits, caffeine and alcohol consumption, and smoking from baseline week to exam week were adjusted for the association of stress with the GI microbiota

GI, gastrointestinal. $Stress_{t-1}$: stress 1 week before sample collection. $Stress_{t-2}$: stress 2 weeks before sample collection. $Stress_{t-1}$ and $Stress_{t-2}$ represent 7-day total NISS scores from the respective week.

Overall and Stress Type Stratified Associations between Alpha Diversity and Beta Diversity with Psychological Stress

Summaries of the associations of alpha diversity and beta diversity of gut microbiota with psychological stress are shown in Table 2; Figure 2, and online supplementary Figure 1. Of the 11 studies reporting the alpha diversity and beta diversity [19–26, 28–30], more than half of them did not report associations of alpha diversity and beta diversity of gut microbiota composition with psychological stress [19–26, 28–30]. Among the studies reporting such associations, two studies reported psychological stress to be associated with smaller alpha diversity measures of Shannon index, Chao 1, and Simpson index [23, 24]; no significant associations were observed between observed species and psychological stress. Only one study reported that beta diversity assessed by UniFrac (weighted) was negatively associated with psychological stress [24]. However, other studies found that psychological stress was not significantly associated with indicators of beta diversity [19, 21, 22, 25, 26, 30]. When stratified by the type of psychological stress, only perceived stress and self-reported stressful life events were significantly associated with alpha diversity and beta diversity of gut microbiota. One study showed that perceived stress was associated with the lower Shannon index, Chao 1, and Simpson index [20, 23]. One study reported that self-reported stressful life events were associated with the lower Simpson index [24]. Six of the 13 studies controlled for confounding variables to examine the associations of psychological stress with the alpha diversity and beta diversity of gut microbiota.

Overall and Stress Type Stratified Associations between the Abundance of Phylum-, Family-, and Genus-Level of Gut Microbiota with Psychological Stress

All 13 included studies assessed associations between psychological stress and the relative abundance of gut microbial taxa at phylum-, family-, and genus-levels (Table 2; Figure 3; online suppl. Fig. 2).

1. At the phylum-level, relative abundance of seven phyla were identified associated with psychological stress, including: Actinobacteria, Bacteroidetes, Euryarchaeota, Firmicutes, Proteobacteria, Tenericutes, and Verrucomicrobia. The following results were found in at least two studies. Psychological stress was consistently associated with increased abundance of Euryarchaeota in two studies [24, 25], and decreased abundance of Proteobacteria [20, 23, 28] and Verrucomicrobia in three studies [24, 25, 30]. Findings for psychological stress and other microbiota at phylum-level were not consistent.
2. At the family-level, relative abundance of 17 taxa was identified in 13 studies that were significantly associated with psychological stress. Only Alcaligenaceae was found to be consistently and negatively associated with psychological stress from two studies [23, 28]. The results for other microbiota at family level were only reported in individual studies, and most of these found that microbiota at family-level, such as Erysipelotrichaceae and Veillonellaceae were negatively associated with psychological stress.
3. At the genus level, relative abundance of 41 genera was found to be associated with psychological stress. The following results were found in at least two studies: the relative abundance of *Lachnospira* [22, 23], Lachnospiraceae NK4A136 [24, 25], *Phascolarctobacterium* [24–26], *Sutterella* [23, 28], and *Veillonella* [24, 27] were decreased while *Methanobrevibacter* [24, 25], *Rhodococcus* [24, 25], *and Roseburia* [24, 25] were increased in the higher psychological stress group compared to the lower stress group.

When stratified by the type of psychological stress, at the phylum-level, maternal prenatal stress and negative emotions were consistently associated with the increased abundance of Euryarchaeota [25]; early life stress and maternal prenatal stress were consistently associated with the decreased abundance of Verrucomicrobia [25, 30]. At the genus-level, self-report stressful life events and negative emotions were consistently associated with the reduced abundance of *Bacteroides* [24]; maternal prenatal stress and negative emotions were associated with the reduced abundance of *Methanobrevibacter, Rhodococcus,* and *Roseburia* [24, 25]. Maternal prenatal stress and negative emotions were associated with the increased abundance of Lachnospiraceae NK4A136 [24, 25]; early life stress, maternal prenatal stress, and negative emotions were associated with the increased abundance of *Phascolarctobacterium* [24–26]; daily stress experiences of infants during care in the NICU and negative emotions were associated with the increased abundance of *Veillonella* [24, 27].

Discussion

This study synthesized the literature to determine associations between psychological stress and the gut microbiota from human studies. Our findings show, based on data from limited studies targeted at children and adults, that there is an overall negative association between psychological stress and alpha diversity measures including Shannon, Chao 1, and Simpson index.

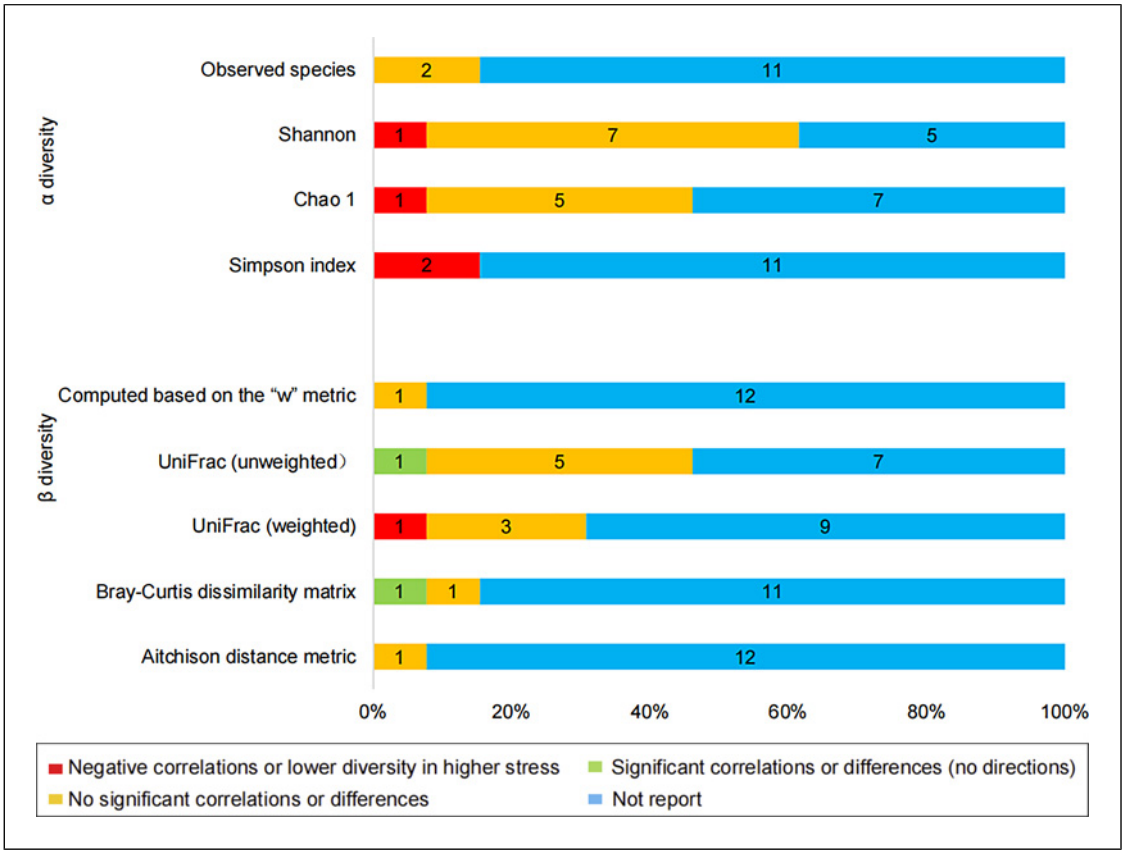

Fig. 2. Summary of the associations of α and β diversity of gut microbiota analysis with the psychological stress of the 13 studies. Not reported: associations of α and β diversity of gut microbiota and psychological stress were not reported; no significant correlations or differences: No significant correlations between psychological stress and α and β diversity of gut microbiota, or no significant differences in the α and β diversity of gut microbiota between higher and lower psychological stress groups; significant correlations or differences (no directions): significant correlations between psychological stress and the α and β diversity of gut microbiota, or significant differences in the α and β diversity of gut microbiota between higher and lower psychological stress groups, however, the directions of the correlations or differences were not reported; negative correlations or lower α and β diversity in the higher psychological stress group compared to the lower stress group. The diversity of gut microbiota was lower in the higher psychological stress group than the lower psychological stress group or negative correlations between psychological stress and the diversity of gut microbiota.

Most of the studies reported that psychological stress was not significantly associated with indicators of beta diversity. We also reveal more nuanced changes which occurred in the composition of the microbiota at phylum-, family-, and genus-levels, and such changes were modified by the type of psychological stress. We highlighted the challenges in determining the impact of psychological stress on the gut microbiota across gender, age, and ethnicity given the current available literature.

Although previous studies have demonstrated a negative association between psychological stress and the alpha diversity of the gut microbiota in children [24] and adults [25], ours is the first to show this using aggregated data. Furthermore, it should also be noted that whereas more than half of the studies did not report such relationships, those who found significant associations reported negative ones. These declines in microbial integrity occurring in tandem with increased psychological stress are also in line with previous research conducted in both animal models [31] and human participants [3, 6]. Although the exact mechanisms which underpin this remain unclear, it is known that the gut microbiota can respond to mammalian hormones and neurotransmitters, as well as other aspects of GI physiology, which may result in a microbial milieu characterized by a maladaptive immune response to stressors, and ultimately lead to a compromised ability to survive in an ever-changing environment [31].

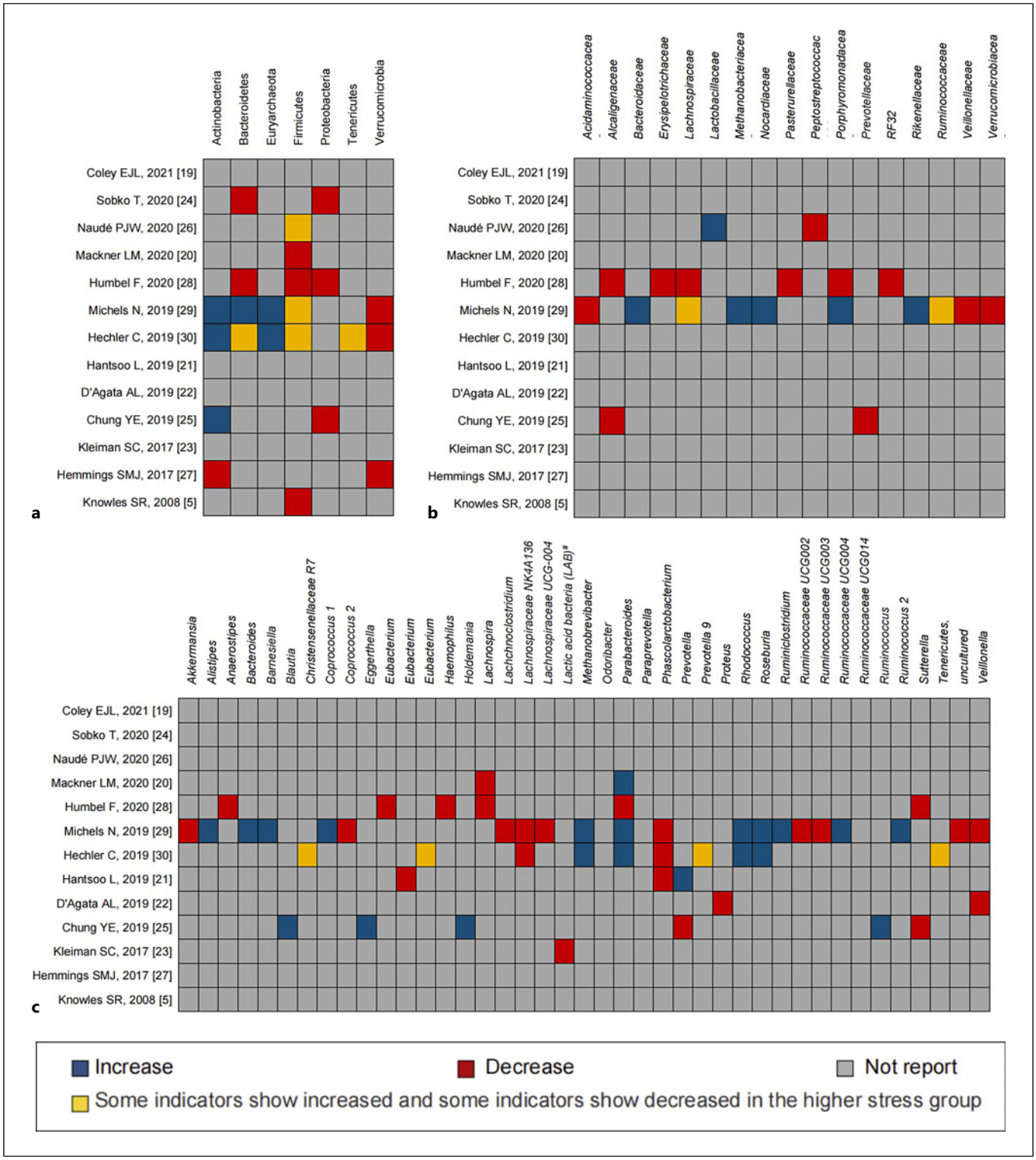

Fig. 3. Changes in the relative abundance of gut microbial taxa reported by the included 13 studies. **a** Level: phylum. **b** Level: family. **c** Level: genus. #: total lactic acid bacteria were quantified by counting colony-forming units (CFU) on the MRS (Lactobacillus broth according to deMan, Rogosa, and Sharpe) plates, not shown by the relative abundance of microbial taxa.

Moreover, we found that there were nuanced changes to the phylum-, family-, and genus- of the microbiota. Most studies which reported results were concerned with the decreased abundance of Proteobacteria and Verrucomicrobia, and increased abundance of Euryarchaeota. Proteobacteria, one of the most abundant phyla in the human gut microbiota, was shown to be negatively associated with psychological stress in children and adults [32]. This is an unexpected finding since expansions in Proteobacteria have been previously observed in mouse models of chronic stress [33]. Especially when considering that previous studies have also demonstrated that a proliferation of pro-inflammatory Proteobacteria can disrupt gut-brain communication, causing activation of microglia cells as well as contributing to increased adiposity [34]; both of which have been associated with psychological stress [35, 36]. However, previous results were based on animal models, whereas our findings were summarized from human studies, therefore the findings were inconsistent. More studies are needed to clarify the associations between psychological stress and the abundance of Proteobacteria.

Despite this, some of our findings were better aligned with the literature. For example, we determined that Verrucomicrobia was negatively related to psychological stress. Verrucomicrobia is a phylum of gram-negative bacteria and encompasses genera such as *Akkermansia*, which is a mucus-degrading bacterium and has been shown to infer beneficial properties in humans [30, 37], such as anti-inflammatory effects and the ability to induce regulatory T cells in adults [30]. From the studies included in the current review, Michels et al. [24] also found that the abundance of *Akkermansia* was negatively associated with chronic stress [38], which supports the findings on Verrucomicrobia phylum. Furthermore, it also supports the hypothesis that posits that a decreased exposure to anti-inflammatory bacteria can lead to an increased vulnerability to stress in mice [38]. The negative relationship between Verrucomicrobia and psychological stress as demonstrated by our findings is therefore in agreement with the wider literature and provides further evidence for a bi-directional relationship which governs the gut-brain axis [39].

In addition to this, we also found an increase in the abundance of Euryarchacota in those experiencing high levels of psychological stress. Euryarchacota is a phylum of archaea which consist of only a handful of organisms, and make up a small proportion of the gut microbiome [40]. Despite this Euyarchacota has been shown to infer pathogenic effects which are possibly thought to result from their ability to facilitate interspecies hydrogen transfer [41]. The interspecies hydrogen transfer in humans might support the growth of fermenting bacteria, which themselves could be either true pathogens or at least opportunistic pathogens [41]. The second mechanism of the negative impacts of Euyarchacota on health may be via the transformation of heavy metals to toxic derivatives, which are known to be more toxic than the original compounds. Our findings highlight how Euryarchacota is positively associated with psychological stress and given the pathological nature of these organisms this is perhaps a cause for concern since these archaea may be a contributing factor toward some of the poor health outcomes often attributed to psychological stress in adults [42].

At genus-level, we found that psychological stress was associated with change in the relative abundance of specific gut microbiota. For example, psychological stress was associated with a lower abundance of Lachnospiraceae NK4A136 in two studies [24, 25]. Some studies also reported that other mental health problems, such as depression in adults [43], were associated with a decreased abundance of Lachnospiraceae NK4A136, which is a butyrate-producing bacterium. Therefore, our findings provide further evidence that mental health problems may have detrimental effects on the abundance of Lachnospiraceae in children [44]. In addition to this, the abundance of *Roseburia* was found to be positively associated with psychological stress in the current study. This is an unexpected finding since *Roseburia* also belongs to the family of Lachnospiraceae. The associations of psychological stress with Lachnospiraceae NK4A136 and *Roseburia* were opposite in the current study. This may be related to the different measures of psychological stress. In the included studies, psychological stress measures of negative emotions and low happiness were positively associated with the abundance of *Roseburia*. However, psychological stress measures of happiness and parasympathetic activity were negatively associated with the abundance of Lachnospiraceae NK4A136. Further, some studies have indicated that *Roseburia* is an important butyrate-producing bacterium, which has beneficial effects on energy metabolism and intestinal barrier integrity in adults [45]. Therefore, more studies are warranted to determine the associations between different measures of psychological stress and the genera of Lachnospiraceae NK4A136 and *Roseburia*.

As well as aiming to determine the association between psychological stress and the gut microbiota, we also aimed to investigate the influence of age, gender, and ethnicity on such associations. Our findings show that existing studies generally recruited humans from a

diverse range of ages, spanning from 26.5 days to 82 years. This is particularly important since previous research illustrates how the diversity of the gut microbiota declines in later life [9]. That said, many studies did not stratify by age and therefore it is challenging to determine whether the negative relationship between psychological stress and the microbiota is exacerbated over an individual's lifespan and is an area which warrants further future research. Similarly, although many of the available studies were well-represented by both males and females, there was a lack of stratification making it difficult to determine the impact gender may have upon the relationship between psychological stress and the gut microbiota. As such, this is an area of research which also warrants future attention, especially since previous evidence suggests that gender may indeed have an impact [10]. In terms of ethnicity, many of the studies used in our analysis did not report this and those which did investigated predominantly Caucasian or Hispanic populations [11]. Therefore, further future research to determine the impact of ethnicity upon the relationship between stress and the gut microbiota is required in order to supports or refute existing evidence which suggests a link.

Strengths and Limitations

The primary strength of our review is that it, for the first time, provides a systematic synthesis of the existing available literature and offers unique insights into the totality of the evidence concerning the associations between psychological stress and the gut microbiota composition. Despite this, our review has several limitations. These being that there is currently a lack of evidence to enable stratification by age, gender, or ethnicity in a meaningful way. As previously mentioned, these are areas of future research which should warrant attention. Similarly, other factors such as diet and medication use were not considered. Aspects such as these are important since it is well known that dietary factors can strongly modulate the gut microbiota in complex and intricate ways which offer their own challenges in terms of measurement and interpretation which were beyond the scope of this review [46]. Furthermore, various pharmacological agents such as proton pump inhibitors, metformin, and laxatives have also been shown to influence the composition and function of the microbiome and were not considered in this study [47]. Moreover, the available data were largely derived from observational studies as few randomized controlled trials have been conducted in this area. Of the studies which have been conducted only a minority investigate the recovery time of the microbiota. This is important since some bacterial elements, such as the ratio of Fermicutes to Bactereoidetes, may have a relatively good degree of plasticity yet their associated metabolism may not, leading to potentially slower recuperations times from stress-related insults in animals as well as adults [8, 48]. Finally, from the available evidence it is also impossible to determine the direction of the relationship between stress and the microbiota or to infer causality. These are all areas which should be considered for future research and addressing these aspects would further strengthen our understanding of the relationship between psychological stress and the composition of the gut microbiota.

In conclusion, our review of the literature shows for the first time that there is an overall negative association between psychological stress and measures of alpha- and beta diversity of gut microbiota. Psychological stress was associated with a decreased abundance of Proteobacteria and Verrucomicrobia, and increased Euryarchaeota at the phylum level and was also associated with a change in the abundance of microbiota at the genus-level. There is currently a lack of evidence regarding the impact of gender, age, and ethnicity upon these factors and this should be addressed in future research. Larger sample longitudinal studies are needed to provide the causal relationship between psychological stress and gut microbiota.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

L.M., M.M., and Y.W. designed the research; Y.Y., Y.L., and L.M. conducted the literature search, data screening, and extraction; L.M., R.J.W., Y.Y., and S.M. drafted and revised

the manuscript; B.X. and X.S. help revised the manuscript; L.M., M.M., and Y.W. provided administrative support for the project and had primary responsibility for the final manuscript; all authors read and approved the final manuscript.

Data Availability Statement

Data are not publicly available due to ethical reasons. Further inquiries can be directed to the corresponding author.

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