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Nutritional interventions to counteract the detrimental consequences of early-life stress

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Exposure to stress during sensitive developmental periods comes with long term consequences for neurobehavioral outcomes and increases vulnerability to psychopathology later in life. While we have advanced our understanding of the mechanisms underlying the programming effects of early-life stress (ES), these are not yet fully understood and often hard to target, making the development of effective interventions challenging. In recent years, we and others have suggested that nutrition might be instrumental in modulating and possibly combatting the ES-induced increased risk to psychopathologies and neurobehavioral impairments. Nutritional strategies are very promising as they might be relatively safe, cheap and easy to implement. Here, we set out to comprehensively review the existing literature on nutritional interventions aimed at counteracting the effects of ES on neurobehavioral outcomes in preclinical and clinical settings. We identified eighty six rodent and ten human studies investigating a nutritional intervention to ameliorate ES-induced impairments. The human evidence to date, is too few and heterogeneous in terms of interventions, thus not allowing hard conclusions, however the preclinical studies, despite their heterogeneity in terms of designs, interventions used, and outcomes measured, showed nutritional interventions to be promising in combatting ES-induced impairments. Furthermore, we discuss the possible mechanisms involved in the beneficial effects of nutrition on the brain after ES, including neuroinflammation, oxidative stress, hypothalamus-pituitary-adrenal axis regulation and the microbiome-gut-brain axis. Lastly, we highlight the critical gaps in our current knowledge and make recommendations for future research to move the field forward.

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INTRODUCTION

Early-life is a period of rapid central nervous system (CNS) development and of unique sensitivity, during which environmental factors, for example stress and nutrition, can profoundly influence brain structure and function long-term [1–3]. There is increasing evidence from preclinical and clinical studies that exposure to stress during this sensitive developmental period lastingly affects neurobehavioral outcomes and increases vulnerability to psychopathology later in life [4–7]. Early-life stress (ES) includes a wide range of exposures, amongst others physical stress (e.g. pain, physical abuse or malnutrition) and emotional stress (e.g. parental neglect, parental separation or emotional abuse). Despite major advances in the field concerning the neurobiological substrates underlying the ES-induced increased risks for adverse neurobehavioral outcomes and psychopathology, the underlying mechanisms remain complex, multi-faceted, not yet completely understood and often hard to target, rendering the development of effective interventions challenging [8, 9].

Given (i) that during fetal and early postnatal life, the brain is a fast growing organ, thus very high in energy and nutrient demand [10–13]; (ii) the observed similarities in neurocognitive, mental and behavioral outcomes between children exposed to perinatal malnutrition and to ES [14–17]; and (iii) the converging mechanisms and interplay between the regulation of the stress and food intake, it has been suggested that nutrition is instrumental in mediating and a potential target for combatting the ES-induced (long-term) impairments [8, 9, 18].

The aim of this paper is to comprehensively review the existing literature on nutritional interventions aimed at targeting the effects of ES on neurobehavioral outcomes in preclinical and clinical settings, discuss the possible mechanisms involved (Fig. 1) and highlight the critical gaps in our current knowledge to move the field forward. Understanding how ES influences brain development and if and how nutrition affects this process is essential for the development of effective nutritional therapies to improve long-term (mental) health in children exposed to ES.

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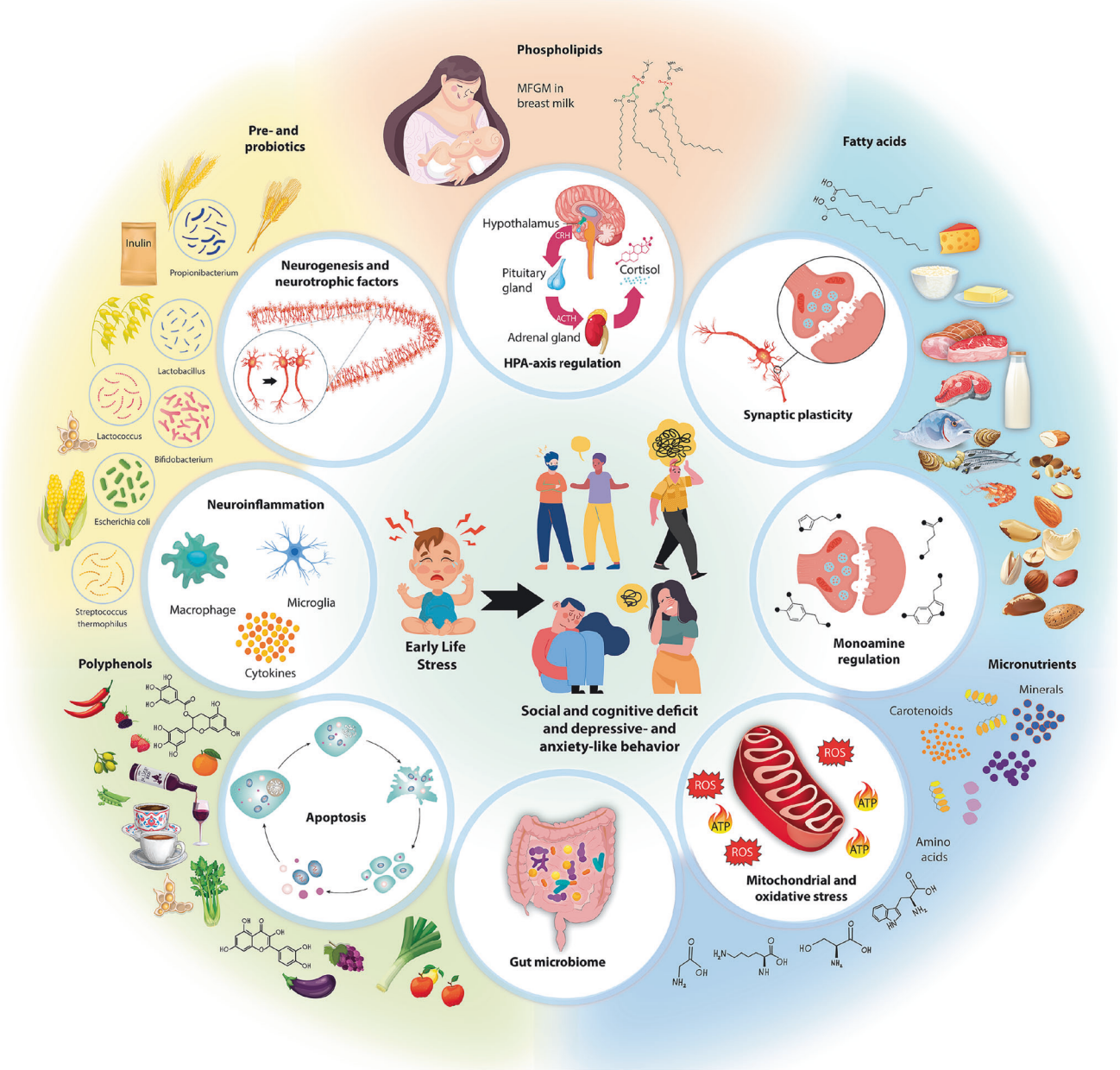

Fig. 1 Overview of the nutritional interventions tested to combat the impact of early-life stress. This figure details the various nutrient groups which have been tested in the context of early-life stress and the potential mechanisms of action and pathways via which they might work to counteract the impact of early-life stress on behavior.

Nutritional strategies hold much potential as they are relatively safe, cheap and easy to implement.

MATERIALS AND METHODS

Search strategy

A comprehensive literature search was performed in the database PubMed. The aim of the search was to identify papers on the effect of nutrition/diet on the (long-term) neurobehavioral/cognitive consequences of ES from human and rodent studies. The timeframe within the database(s) was from inception to 29th of November 2024 and the search was conducted by GLB. The search included keywords and free text terms for (synonyms of) 'diet' combined with (synonyms of) 'Early-Life Stress'. A full overview of the search strategy can be found in the Supplementary Information (see Supplementary table 1). No limitations on date or language were applied in the search.

Definitions and inclusion/exclusion criteria

Concerning ES: ES was defined as stress during early-life, from conception up to up to 18 years of age (human studies) or weaning (preclinical studies). ES exposure for human studies included stress exposure in both the (pregnant/lactating) mother or in the child (see Supplementary table 2A): (maternal) perceived stress, (maternal) anxiety, (maternal) depression and other forms of stress (e.g. bereavement, violence, a disaster, low socioeconomic status, hospital admission etc.). For the preclinical studies, papers were included that employed an early-life stressor of a physical or psychological nature (e.g. prenatal restraint, variable stress, maternal separation or the limited nesting and bedding material paradigm, see Supplementary

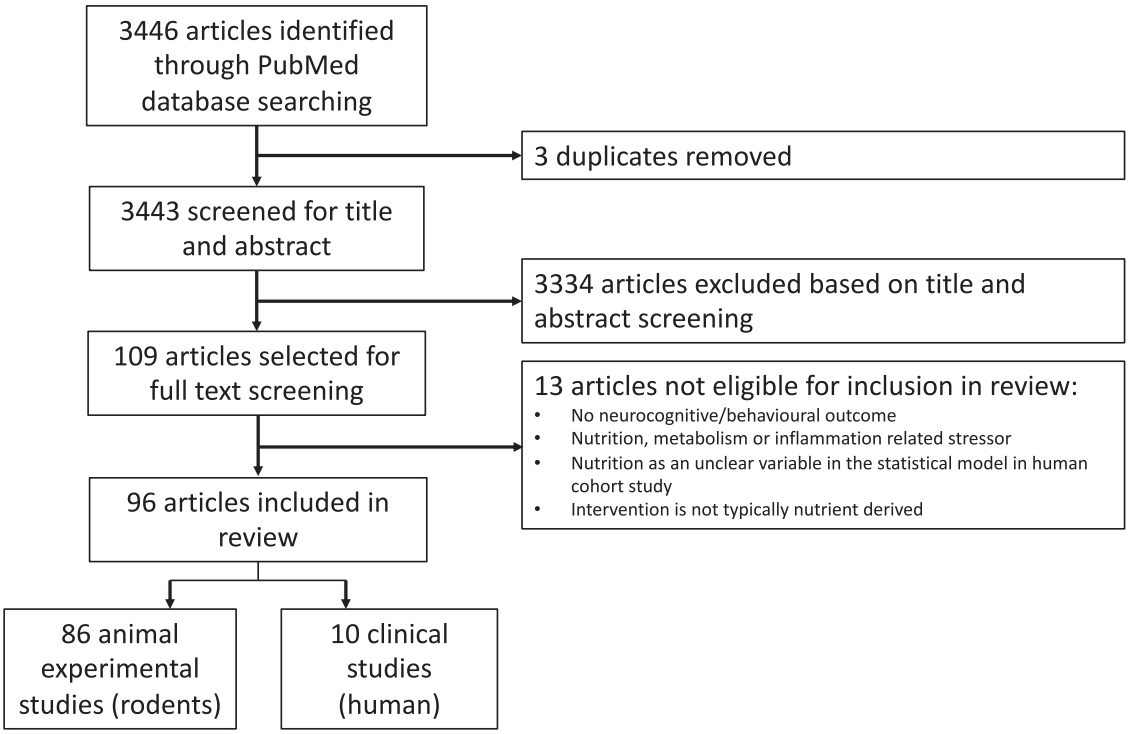

Fig. 2 Flowchart of the review process according to the PRISMA statement.

table 2B). Papers that used a nutrition-, metabolism- or inflammation-related stressor were excluded.

Concerning nutritional intervention (i.e. specific nutrients /diets and time window of intervention): Nutrition or diet was defined as the administration, consumption, supplementation or omission of a nutrient, pre-/pro-/synbiotic or diet at any point in time (before or after stressor, and before or after the manifestation of ES-related symptoms) by the infant/offspring or the pregnant/lactating mother/dam. There were no limitations on route of administration (e.g. per os (including oral gavage, tube feeding, intramuscular or intravenous).

During screening, only articles with a functional neurocognitive or behavioral outcome were included. For the preclinical studies outcomes were subdivided in the following domains: depressive-like behavior, anxiety-like behavior, cognition and social behavior. See Supplementary table 3A for outcomes in human studies and Supplementary table 3B for outcomes in preclinical studies. For human studies, all types of studies were included.

Studies addressing the effects of ES as well as nutritional interventions in both males and females were included, however the literature to date mostly fails to test whether the efficacy of the nutritional intervention is sex-specific.

Exclusion criteria were defined as follows:

- Known nutritional-, metabolism- or inflammation-related stressors
- Premature birth as a stressor
- Nutrition only described as a variable in the statistical model of a human cohort study (and not in main research question of study)
- Intervention with pharmacological extracts/molecules that are not typically nutrient-derived
- Studies that did not include non-stressed controls
- Only a structural or mechanistic outcome measure
- Reviews

Considerations for interpretation of neurobehavioral outcomes in response to ES and nutritional intervention

Throughout this review we will refrain from assigning positive or negative connotations concerning to neurobehavioral consequences of ES and nutritional interventions as these can be adaptive or maladaptive contingent on the specifics of environment and setting where these are expressed [19, 20]. In addition, it is important to acknowledge that the interpretations of the behavioral tests used in preclinical research aimed to test specific traits and phenotypes of complex and multifaceted conditions like depression, anxiety are often debated and poses some challenges. For example, the FST and TST, commonly used to test depression-like behavior, measure immobility, often interpreted as "behavioral despair". However, there is substantial debate about whether immobility truly reflects a depressive state or rather an adaptive coping strategy such as energy conservation [21, 22]. In this review, we have relied on the interpretations provided by the original authors of the referenced studies while synthesizing the results, however, we acknowledge the limitations of these paradigms and the need for caution in their interpretation.

Data collection

Figure 2 shows the flowchart of the review process according to the PRISMA-statement. Through database searching in PubMed 3446 records were identified. After removal of duplicates, 3443 records were screened for title and abstract. All studies were written in English. One-hundred-and-nine of these articles were eligible for full text screening, out of which 96 articles were included in the current review (Table 1). Snowball searching did not result in new inclusions.

RESULTS

Evidence of effect of nutritional interventions on ES-induced behavioral deficits

Of the 96 included articles (For an overview of all articles, see Table 1 and Supplementary Table. 4), ten studies included human subjects, while the other 86 studies were performed in rodents. Below, for the preclinical studies, we will first describe the effect of ES on behavioral outcomes across the various domains and thereafter describe the effect of nutrition on the ES-induced alterations divided by nutrient group. In Supplementary table 4B,

Table 1. Overview of the papers included to comprehensively review the impact of nutritional intervention on early-life stress induced behavioral outcome.

	Year of publication	Species	n	Male/ female	Type of early-life stress	Timing/ duration of stress	Specific diet/supplement	Timing/duration diet/supplement	Age outcome was measured	Outcome(s): result of supplementation	Suggested underlying mechanisms
Fatty acids											
Human											
Keenan et al.	2016	Human	64	Both	Low SES	PRS and POS	450mg of DHA/day	W16-21 of gestation until delivery	3 months	No effect on cognitive development	*No underlying mechanisms investigated*
Brunst et al.	2014	Human	255	Both	Maternal stress score (NLE score)	PRS	Lower N-6/N-3 PUFA ratio intake (FFQ)	First or second trimester of pregnancy	6 months	Improvement on temperament orienting and regulation domain No effects in other domains	*No underlying mechanisms investigated*
Rodent											
Reemst et al.	2024	Mouse	14 per group	Male	LBN	POS (P2-9)	Low (1:1) LA/ALA ratio	P2-42	P120	Stress-induced cognitive impairments: ↓(A)	**miRNA regulation:** ● ↑Different miRNA set in response to ELS.
Zhao et al.	2023	Mouse	11 per group	Male	MS	POS (P7-15)	EPA (165 mg/kg)	P22-49	P49	Stress-induced depressive like behavior: ↓(B, C, D) No effect of stress on anxiety-like behavior (E, F) No effect of stress on cognition (G, H)	*No possible underlying mechanisms investigated*
Wah et al.	2019	Rat	8 per group	Male	PSc	POS (P28-34)	Proprionic acid (500 mg/kg)	P40 and P43 and P74, P77	P40, P43, P74	No effect of stress on anxiety-like behavior (I) Stress-induced changes in pre-pulse inhibition ↓(J)	*No possible underlying mechanisms investigated*
Yam et al.	2019	Mouse	7–11 per group	Male	LBN	POS (P2-9)	Low (1:1) LA/ALA ratio	P2-42	P42 and P120-160	Stress-induced cognitive impairments: ↓(A, H, K)	**Neurogenesis:** ● ↑ Cell survival **Neuroinflammation:** ● ↓ CD68 (phagocytic marker) **FA profile**: ● Altered central profile ● Altered periphal profile
Rêus et al.[a]	2018	Rat	10–12 per group	Male	MS	POS (P1-10)	N-3 PUFAs (0.72 g/kg)	P41-61	P60-61	Stress-induced depressive-like behavior: ↓(B)	**Oxidative stress:** ● ↓ MPO ● ↓ Protein carbonylation ● ↓ Lipid peroxidation ● ↓ Nitrite/nitrate ● ↑ SOD activity ● ↑ Catalase activity
Valvassori et al.	2015	Rat	8 per group	Male	MS	POS (P1-10)	Sodium butyrate (injection, 500 mg/kg/day)	P60-67	P67	Stress-induced depressive-like behavior: ↓(B) No effect of stress on anxiety-like behavior (E)	**Mitochondrial function:** ● ↑ Complex 1, 2 (partially) and 4 activity ● ↓ SDH activity ● ↓ MDH activity
Pusceddu et al.	2015	Rat	10 per group	Female	MS	POS (P2-14)	N-3 PUFAs (80%EPA, 20% DHA)	W5-11	W11	No effect of stress on depressive-like behavior (B), anxiety-like behavior (E, F) or cognition (H)	**HPA-axis regulation:** ● ↓ Ratio activation GRs in nucleus/cytosol
Ferreira et al.	2013	Rat	13–17 per group	Female	MS	POS (P1-10)	N-3 PUFA deficiency (2.2g/kg)	P35-160	P140-160	No effect of stress on depressive-like behavior (B, C)	*No supporting underlying mechanisms found*
Jones et al.	2013	Mouse	9–35 per group	Both (pooled for behavior)	CVS	PRS (G6-G21)	High (51.3:1) N-6/N-3 ratio	Breeding until weaning	P60	No effect of stress on anxiety-like behavior (F), or social behavior (L)	*No possible underlying mechanisms investigated*

Table 1. continued

	Year of publication	Species	n	Male/ female	Type of early-life stress	Timing/ duration of stress	Specific diet/supplement	Timing/duration diet/supplement	Age outcome was measured	Outcome(s): result of supplementation	Suggested underlying mechanisms
Feng et al.	2012	Rat	9–10 per group	Both (studied separately)	RS	PRS (G14-G20)	DHA (2 doses: 100 and 300 mg/kg/day)	For two weeks before breeding	P30	Stress-induced cognitive impairments: ↓(K)	**Neurotrophic factors:** ● ↑ BDNF **Apoptosis:** ● ↓ Bcl-2 (only in females) ● ↓ BAX (only in males) ● ↓ Procaspase 9 and -3 **Mitochondrial function:** ● ↑ Complex 1-2, 5 activity and complex 5 activity (only in males) ● ↓ Complex 3-4 activity ● ↓ MFN1 and MFN2 (only in females) ● ↓ Drp1 (only in females) ● ↓ Cytochrome C **Oxidative stress:** ● ↑ iNOS and nNOS **Autophagy:** ● ↓ Atg3 ● ↓ Atg7 (only in females) ● ↓ Beclin-1 ● ↑ Phosphorylation of Akt and mTOR
Mathieu et al.	2011	Rat	11 per group	Male	MS	POS (P6-21)	Multigenerational n3 PUFA deficiency (LA 1200/ALA <0.1)	Two generations of female rats	W12	No effect of stress on anxiety-like behavior (F), or cognition (M, N, O)	*No possible underlying mechanisms investigated*
Mathieu et al.	2008	Rat	11 per group	Male	MS	POS (P6-11)	Multigenerational n3 PUFA deficiency (LA 1200/ALA <0.1)	Two generations of female rats	W12	No effect of stress on depressive-like behavior (B, C), or anxiety-like behavior (E)	**FA profile:** ● Altered central profile
Polyphenols											
Human											
Tan et al.	2020	Human	6404	Both	Adverse Childhood Experiences	POS	Flavonoid intake (FFQ)	Intake during the past year	mean 61.9 years of age	Improvement in perceived stress and depressive symptoms	*No possible underlying mechanisms investigated*
Rodent											
Shukla et al.	2024	Rat	8 per group	Male	MS	POS (P1-10)	Resveratrol (20 or 40 mg/kg)	P51-62	P62-65	Stress-induced depressive-like behavior: ↓(B, C) Stress-induced anxiety-like behavior: ↓(E, I) Stress-induced agressive behavior: ↓ (P)	**Neurogenesis:** ● ↑ Nissl bodies **Oxidative stress:** ● ↑ GSH ● ↑ SOD ● ↑ Catalase ● ↓ MDA **HPA axis:** ● ↓ Serum corticosterone **Monoamine regulation:** ● ↑ DA ● ↑ NE ● ↑ 5-HT
Karimi et al.	2024	Mouse	15 per group	Male	MS	POS (P2-14)	Umbelliprenin (12.5 and 25 mg/kg)	7 days between P51-P60	Immediately after treatment	Stress-induced anxiety-like behavior: ↓(F) Stress-induced cognitive impairment: ↓(Q) Stress-induced social impairment: ↓(L) Stress-induced repetitive behavior: ↓(R)	**Oxidative stress:** ● ↓ MDA ● ↓ Nitrite ● ↑ TAC (high dose only)
Moghaddam et al.	2023	Rat	6 per group	Male	MS	POS (P1-9)	Quercetin (10 and 40 mg/kg) or quercetin-loaded nanophytosome (10 and 40 mg/kg)	P21-P42	P39-P42	Stress-induced anxiety-like behavior: ↓(E) Stress-induced social impairment: ↓(S)(Only in Quercetin-loaded nanophytosome 40 mg/kg)	**Apoptosis:** ● ↓ BAX ● ↑ Bcl-2 ● ↓ Caspase 3 **Oxidative stress:** ● ↑ Catalase ● ↑ SOD ● ↑ GPx ● ↓ Nrf2

Table 1. continued

	Year of publication	Species	n	Male/ female	Type of early-life stress	Timing/ duration of stress	Specific diet/supplement	Timing/duration diet/supplement	Age outcome was measured	Outcome(s): result of supplementation	Suggested underlying mechanisms
Verma et al.	2022	Rat	6 per group	Unspecified	MS	POS (P1-21)	Rosmarinic acid (25 and 50 mg/kg)	P35-P55	P35, P45 and P55	Stress-induced depressive like behavior: ↓(B)(both doses - P35, P45, P55), ↓(C)(only high dose dose - P35, P45, P55)	**Neurotrophic factors:** ● ↑BDNF **Inflammation:** ● IL-10 **Oxidative stress:** ● ↑ SOD ● ↑ GSH **HPA axis:** ● ↓ Corticosterone
Sun et al.	2021	Rat	8–10 per group	Female	RS	PRS (G14-G20)	Proanthocyanidins (200 mg/kg)	P21-30	P30	Stress-induced depressive like behavior: ↓(B, C)	**Neurogenesis:** ● ↑ Nissl bodies **Apoptosis:** ● ↓ NLRP3 ● ↓ Caspase 1 **Inflammation:** ● ↓ IL-1β **Oxidative stress:** ● ↓ Cellular ROS
Arabi et al.	2021	Mouse	8 per group	Unspecified	MS	POS (P2-14)	Auraptene (5, 10, and 50 mg/kg, injection)	P45-60	P60	Stress-induced anxiety like behavior: ↓(E, F)	**Apoptosis:** ● ↓ Dark neurons **Inflammation:** ● ↓ TLR4 ● ↓ IL-1β **Oxidative stress:** ● ↑ Fe(2+) ● ↓ MDA ● ↓ Nitrite **Structure:** ● ↑ CA3 region diameter
Donoso et al.	2020	Rat	10–12 per group	Male	MS	POS (P2-12)	Three groups: Phlorotannins (0.03%), Xanthohumol (0.015%) or Quercitin (0.03%)	W8-16	W12-13	All polyphenols tested: Stress-induced depressive-like behavior: ↓(B) Stress-induced anxiety-like behavior: ↓(E), and no effect of stress (F)	**Neurotrophic factors:** ● ↑ BDNF (xanthohumol) **HPA-axis regulation:** ● ↓ Baseline corticosterone (xanthohumolor and phlorotannins) ● ↓ Corticosterone response to stress (xanthohumol) **Microbiome:** ● Normalization of gut microbiome ● ↑ Proprionate
Omotoso et al.	2020	Rat	Unspecified	Unspecified	MS	POS (P9)	Kolaviron (200 mg/kg)	P21-P35	PND 35?	Stress-induced anxiety-like behavior: ↓(E) Stress-induced cognitive impairments: ↓(G, K)	**Neuroinflammation:** ● ↓ GFAP **Oxidative stress:** ● ↑ SOD
Zheng et al.	2019	Rat	8 per group	Male	RS	PRS (G14-G20)	Ferulic acid (12.5, 25, and 50 mg/kg/day)	P60-88	P89-95	Stress-induced depressive-like behavior: ↓(B, C) Stress-induced anxiety-like behavior: ↓(E)	**Neurogenesis:** ● ↑ Nissl bodies **Neuroinflammation:** ● ↓ IL-6, IL1β, TNF-α and NFkB phosphorylation ● ↑ IL-10 **Oxidative stress:** ● ↓ nNos **HPA-axis regulation:** ● ↓ Corticosterone ● ↓ ACTH ● ↑ GR protein expression
Menezes et al.	2017	Rat	Unspecified	Male	MS	POS (P1-10)	Catechins (green tea) (0.8 mg/mL)	P21-80	P81-90	Stress-induced anxiety-like behavior: = (E, F, T) Stress-induced cognitive impairments: ↓(H)	**Oxidative stress:** ● ↓ total ROS ● ↑ FRAP

Table 1. continued

	Year of publication	Species	n	Male/ female	Type of early-life stress	Timing/ duration of stress	Specific diet/supplement	Timing/duration diet/supplement	Age outcome was measured	Outcome(s): result of supplementation	Suggested underlying mechanisms
Toumi et al.	2016	Rat	8–12 per group	Both (studied separately)	PSc	PRS (G19)	Quercetin (50 mg/kg)	G14-G19	P35-44	Stress-induced anxiety-like behavior(only in males): ↓(I, U) Stress-induced cognitive impairments(only in females): ↓(H)	**Blood:** ● ↑ Hgb ● ↑ HCT ● ↑ MCV ● ↓ MCHC ● ↓ PLT
Zheng et al.	2015	Rat	10–20 per group	Male	RS	PRS (G14-G20)	Hydroxytyrosol (10 and 50 mg/kg/day)	2 weeks before breeding	M1	Stress-induced cognitive impairments: ↓(K, V)	**Neurotrophic factors:** ● ↑ BDNF **Synaptic plasticity:** ● ↑ NMDA-R (R1, R2A, R2B) ● ↑ SYP ● ↑ GAP43 **Mitochondrial function**: ● ↑ MtDNA copy number ● ↑ Complex 1-5 activity **Oxidative stress**: ● ↓ Carbonyl protein content ● ↑ SOD2 and total SOD ● ↑ HO-1 ● ↑ FOXO1 and FOXO3 **HPA-axis regulation**: ● ↑ GR
Cao et al.	2014	Rat	10–20 per group	Both (studied separately)	RS	PRS (G14-G20)	Resveratrol (100 mg/kg/day)	G1-delivery	M1	Stress-induced cognitive impairments: ↓(K, V)	**Neurotrophic factors:** ● ↑ BDNF ● ↑ EMX2 **Synaptic plasticity:** ● ↑ GAP43 ● ↑ NMDA-R ● ↑ SCG10 ● ↑ Arc (only in male) **Mitochondrial function:** ● ↑ AmPK phosphorylation ● ↑ PGC1a ● ↑ Complex 1 and 4 (3 and 5 only in male) activity **Oxidative stress:** ● ↑ Nrf2 ● ↑ NQO1 ● ↑ HO-1 ● ↑ GCLc and GCLm ● ↑ GSH ● ↓ Carbonyl protein content
Pro- and prebiotics											
Human											
Vicariotto et al.	2023	Human	95 per group	Both	Maternal postpartum depression (EPDS)	POS	*Limosilactobacillus reuteri* PBS072 and *Bifidobacterium breve* BB077, for a final dosage of 4 × 109 CFU/day (2×10^9 CFU for each strain)	P3-93	P48 and P93	Less crying/fussing behavior in the supplementation group compared to control group at both time points	*No possible underlying mechanisms investigated*
Rodent											
Zhu et al.	2024	Mice	10–11 per group	Males	MS	POS (P3-21)	*Lactobacillus Reuteri ATCC23272 (1 × 10^8 CFU/day)*	P21-P63	P63-70	Stress-induced anxiety-like behavior: ↓ (E, F) Stress-induced social impairment: ↓(L), = (S)	Synaptic plasticity ●↑ Enrichment in Glucocortoicoid receptor signaling pathways ●↑ Glutamin, glutamate and GABA levels in mPFC ● Rescue of Glutamatergic and GABAergic transmission in mPFC
Zhu et al.	2022	Mouse	6–17 per group	Both (pooled for behavior)	MS	POS (P1-21)	*Bifidobacterium breve CCFM1025* (4×10^9 CFU/day)	G0-delivery	P49	Stress-induced depressive-like behavior (only when sexes were pooled): ↓(B)	**HPA axis:** ●↓ GR (only in males) ●↓ CRH **Gut:** ●↑ colonic c-Fos ●↑ 5-HT

Table 1. continued

	Year of publication	Species	n	Male/ female	Type of early-life stress	Timing/ duration of stress	Specific diet/supplement	Timing/duration diet/supplement	Age outcome was measured	Outcome(s): result of supplementation	Suggested underlying mechanisms
Carlessi et al.	2022	Rat	10–12 per group	Both (studied separately)	MS	POS (P1-10)	*Bifidobacterium infantis* (1×10^9)/100 mL	P11-P60	P21, P41, P61	P21: No effect of stress on depressive-like behavior (W) Stress-induced depressive-like behavior (in females): ↓(B) No effect of stress on anxiety-like behavior (E) P41: No effect of stress on depressive-like behavior (W) Stress-induced effect on depressive-like behavior (in males): = (B) No effect of stress on anxiety-like behavior (E) P61: No effect of stress on depressive-like behavior (X) Stress-induced depressive-like behavior (in females): ↓(B) No effect of stress on anxiety-like behavior (E)	**Oxidative stress:** ● ↓ TBARS ● ↓ protein carbonylation ● ↓ Nitrite/nitrate ● ↓ MPO activity ● ↑ SOD activity ● ↑ Catalase activity **BBB integrity:** ● reversed BBB breakdown
Huang et al.	2022	Rat	6 per group	Unspecified	RS	PRS (G15-G20)	*Bifidobacterium trisporus* (dose unknown)	G15 - P60	P60-70	Stress-induced anxiety-like behavior: ↓(F) Stress-induced cognitive impairments: ↓(H, X)	**Neurogenesis** ● ↑ Nissl bodies **Apoptosis** ● ↑ Bcl-2 ● ↓ BAX ● ↓ Caspase 3 **Inflammation** ● ↓TNF-α ● ↓IL-1β
Karen et al.	2021	Rat	6 per group	Unspecified	MS	POS (P5-10)	*Lactobacillus paracasei* (1×10^9 CFU/day)	P2-16	P33-34	Stress-induced depressive-like behavior: ↓(D) Stress-induced anxiety-like behavior: ↓(E)	**Apoptosis:** ● ↓ Caspase 3 **Synaptic plasticity:** ● ↓ GluR1 and GluR2 levels ● ↓ NR2A and NR2B **HPA-axis regulation:** ● ↓ Corticosterone ● ↓ ACTH ● ↓ GR **Monoamine regulation:** ● ↓ 5-HT **Gut:** ● Normalization of fecal metabolites **miRNA regulation:** ● ↑ miRNA-124 ● ↓ miRNA-132
Park et al.	2021	Mouse	3–10 per group	Both (pooled for behavior)	MS	POS (P5-14)	*Lactobacillus reuteri* (1×10^6 CFU/day)	P5-14	P5-14	Stress-induced reduction in calling behavior: ↓	**Synaptic plasticity:** ● ↓ Glutamate-related stress gene expression **(Neuro)inflammation:** ● ↑ CD200 **Monoamine regulation:** ● ↓ Epinephrine
O'Mahony et al.[a]	2020	Rat	12 per group	Male	MS	POS (P2-12)	Prebiotics: polydextrose 6.44 g/kg and galacto-oligosaccharides 20.86 g/kg	P21-W13/14	W7-13	Stress-induced cognitive impairments: ↓(K), = (H) Stress-induced increase in pain behavior: = (Y)	**Synaptic plasticity:** ● ↑ MAG **Microbiome:** ● altered microbiome composition
Daugé et al.	2020	Rat	10–12 per group	Male	MS	POS (P1-14)	*Lactobacillus helveticus, Bifidobacterium longum, Lactococcus lactis and Streptococcus thermpohilus* (1×10^9 CFU per mL)	W6-15	W8-10	No effect of stress on depressive like behavior (B) Stress-induced anxiety-like behavior: = (F, I, Z), ↓(E)	**Gut:** ● ↑ Tjp1 in ileum ● ↓ IFN-γ mRNA in ileum ● Changes in gut microbiome

Table 1. continued

	Year of publication	Species	n	Male/ female	Type of early-life stress	Timing/ duration of stress	Specific diet/supplement	Timing/duration diet/supplement	Age outcome was measured	Outcome(s): result of supplementation	Suggested underlying mechanisms
Hadizadeh et al.	2019	Rat	6 per group	Male	NoS	PRS (thrid trimester)	*Lactobacillus acidophilus, Lactobacillus fermentum and Bifidobacterium lactis* (1×10^{10} CFU per bacterium/mL)	G1-14 or P31-45	P45-46	For both supplementation time frames: Stress-induced anxiety like behavior: ↓(F) Stress-induced cognitive impairment: ↓(K)	**HPA-axis regulation:** ● ↓ Corticosterone
Peng et al.	2019	Rat	5–10 per group	Male	MS	POS (P2-14)	*Lactobacillus rhamnosus and Lactobacillus helveticus* (1×10^{9} CFU)	P2-14	P17-24	Stress-induced anxiety-like behavior: = (E), ↓(F, I) Stress-induced cognitive impairment: ↓(N)	**Neurotrophic factors:** ● ↓ BDNF **Synaptic plasticity:** ● ↓ c-Fos **HPA axis regulation:** ● ↓ ACTH ● ↓ Corticosterone
Cowan et al.	2019	Rat	Unspecified	Male	MS	POS (P2-P14)	*Lactobacillus rhamnosus and Lactobacillus helveticus* (1×10^{9} CFU)	P2-14	P17-24	Stress-induced cognitive impairment: ↓(N)	**Synaptic plasticity:** ● ↓ pMAPK
Liao et al.	2019	Mouse	6–8 per group	Male	MS	POS (P2-14)	*Lactobacillus paracasei* (strain PS23, 5×10^{9} CFU/ml)	P28-56	P54-56	Stress-induced depressive-like behavior: ↓(B) Stress-induced anxiety like behavior: = (F)	**Inflammation:** ● ↓ IL-6 ● ↑ IL-10 **HPA axis regulation:** ● ↓ Corticosterone **Monoamine regulation:** ● ↓ DOPAC ● ↓ HVA
McVey Neufeld et al.	2019	Rat	5–9 per group	Male	MS	POS (P2-12)	Prebiotics Polydextrose + Galactooligosaccharide and/ or Probiotic *Lactobacillus rhamnosus* (1×10^{8} CFU)	P21-49	W7-11	Stress-induced anxiety-like behavior: ↓(E)(both pre- and probiotics separately and together) Stress-induced cognitive impairment: ↓(K)(only pre- and probiotics together)	**Synaptic plasticity:** ● ↓ GABA A2 (combination of pre- and probiotics) **HPA axis regulation:** ● ↓ MR (probiotics alone) ● ↑ GR (probiotics alone) ● ↑ CRHR1
Moya-Pérez et al.	2017	Mouse	9 per group	Male	MS	POS (P1-20)	*Bifidobacterium pseudocatenulatum* (1×10^{8} CFU daily via oral gavage)	P2-21	P41	Stress-induced anxiety-like behavior: ↓(F)	**Monoamine regulation:** ● ↓ NE **HPA axis regulation:** ● ↓ Baseline corticosterone ● ↓ Corticosterone response to stress **Gut:** ● ↓ DA ● ↓ E ● Normalization of microbiome ● ↓ IFN-y
Cowan et al.	2016	Rat	10–14 per group	Male	MS	POS (P2-14)	*Lactobacillus rhamnosus and Lactobacillus helveticus* (1×10^{9} CFU)	P2-14	P17-24	Stress-induced anxiety-like behavior: = (F) Stress-induced cognitive impairment: ↓(N)	*No possible underlying mechanisms investigated*
Liu et al.	2016	Mouse	10–12 per group	Male	MS	POS (P2-14)	*Lactobacillus plantarum strain PS128* (strain PS128, 5×10^{9} CFU/ml)	P29-57	P57-63	Stress-induced depressive-like behavior: ↓(B, C) Stress induced anxiety-like behavior: = (F)	**HPA-axis regulation:** ● ↓ Corticosterone **Inflammation:** ● ↓ IL-6 ● ↑ IL-10 **Monoamine regulation:** ● ↑ Serotonine turnover ● ↓ 5-HIAA ● ↑ Dopamine turnover ● ↑ DA
Barrett et al.[a]	2012	Rat	15 per group	Unspecified	MS	POS (P2-12)	*Bifidobacterium breve* (CFU = 1×10^{10} cells/ml)	P28-77	P77	No effect of stress on pain behavior (Y)	**FA profile:** ● Altered central FA profile ● Altered periferal FA profile

Table 1. continued

	Year of publication	Species	n	Male/ female	Type of early-life stress	Timing/ duration of stress	Specific diet/supplement	Timing/duration diet/supplement	Age outcome was measured	Outcome(s): result of supplementation	Suggested underlying mechanisms
Desbonnet et al.	2010	Rat	7–11 per group	Male	MS	POS (P2-14)	*Bifidobacterium infantis* (1×10^8 CFU/mL)	P50-95	P90	Stress-induced depressive-like behavior: ↓(B)	*No supporting underlying mechanisms found*
Micronutrients											
Amino acids											
Rodent											
Musillo et al.	2023	Mouse	9–15 per group	Both (studied separately)	RS	PRS (G12.5-18.5)	N-acetylcysteine (1 g/kg/day)	5 weeks before mating - G16	P33-50	Stress-induced depressive-like behavior in males =(B) Stress-induced anxiety-like behavior in females= (E, F), males=(F) No effect of stress on social behavior =(S)	**HPA axis:** ● Buffer enhanced corticosterone response after acute stress **Neurotrophic factors:** ● ↓BDNF
Davis et al.[a]	2022	Mouse	9–12 per group	Both (studied separately)	RS	PRS (G12-18)	N-acetylcysteine (injection 200 mg/kg/day)	G12-delivery	W10-14	Stress-induced anxiety-like behavior: = (F), and no effects of stress (E) Stress-induced social impairment: = (L)	**NeuroInflammation:** ● ↓ Microglia ramifocation **Synaptic plasticity:** ● ↓ Cortical parvalbumin neurons (male) ● ↑ Cortical parvalbumin neurons (female)
Rêus et al.[a]	2018	Rat	10–12 per group	Male	MS	POS (P1-10)	N-acetylcysteine (20 mg/kg/day)	P41-61	P60-61	Stress-induced depressive-like behavior: ↓(B)	**Oxidative stress:** ● ↓ MPO ● ↓ Carbonyl protein content ● ↓ MDA ● ↓ Nitrite/nitrate ● ↑ SOD ● ↑ Catalase
Vitamins											
Human											
Lipton et al.[a]	2017	Human	137	Both	Maternal recent negative life events during pregnancy	PRS	Prenatal intake of vitamins A, C, and E (FFQ)	Prenatal	30 months of age	Vitamin A and C: trend towards improvement in temperament domain of negative affectivity Vitamin E: no effect	*No possible underlying mechanisms investigated*
Rodent											
Hao et al.	2023	Rat	15 per group	Male	MS	POS (P1-10)	Vitamin PP (Nicotinamide) (100 mg/kg/d)	P56-85	Unknown	Stress-induced cognitive impairment: ↓(H, X) Stress-induced changes in pre-pulse inhibition ↓(J)	**Apoptosis:** ● ↓ NeuN+TUNEL+ cells (mitochondria-related apoptosis)
Wang et al.	2023	Rat	5 per group	Male	MS	POS (P1-20)	Leucine (rich diet: 5% and deficient diet: 0.22% L-leucine)	P20-60	P60	Stress-induced anxiety-like behavior: =(E) Stress-induced cognitive impairment: ↓(K)	**Apoptosis:** ● ↑Bcl-2/BAX ratio
Lorigooini et al.[a]	2020	Mouse	8 per group	Male	MS	POS (P2-14)	Vitamin E (injection 50 mg/kg/day))	P31-45/47	P45-47	Stress-induced depressive-like behavior: ↓(B), = (W) Stress-induced anxiety-like behavior: ↓(F)	**Oxidative stress:** ● ↓ MDA ● ↓ NO stress
Rêus et al.[a]	2018	Rat	10–12 per group	Male	MS	POS (P1-10)	Folic acid (50 mg/kg/day)	P41-61	P60-61	Stress-induced depressive-like behavior: ↓(B)	**Oxidative stress:** ● ↓ MPO ● ↓ MDA ● ↓ Nitrite/nitrate ● ↓ Carbonyl protein content ● ↑ SOD

Table 1. continued

	Year of publication	Species	n	Male/ female	Type of early-life stress	Timing/ duration of stress	Specific diet/supplement	Timing/duration diet/supplement	Age outcome was measured	Outcome(s): result of supplementation	Suggested underlying mechanisms
Minerals											
Human											
Lipton et al.[a]	2017	Human	137	Both	Maternal recent negative life events during pregnancy	PRS	Prenatal intake of magnesium, zinc and selenium (FFQ)	Prenatal	30 months of age	Zinc and selenium: improvement in temperament domain of negative affectivity Magnesium: no effect	*No possible underlying mechanisms investigated*
Rodent											
Sameei et al.	2023	Rat	7–8 per group	Female	RS	PRS (G15-19)	Zinc (30 mg/kg/day)	G0-19	P25-27	Stress-induced depressive-like behavior: ↓(B) Stress-induced anxiety-like behavior: ↓(E, F)	*No possible underlying mechanisms investigated*
Carotenoids											
Human											
Lipton et al.[a]	2017	Human	137	Both	Maternal recent negative life events during pregnancy	PRS	Prenatal intake of beta-carotene (FFQ)	Prenatal	30 months of age	No effect of supplementation on infant temperament	*No possible underlying mechanisms investigated*
Rodent											
Davis et al.[a]	2022	Mouse	9–12 per group	Both (studied separately)	RS	PRS (G12-18)	Astaxanthin (injection 30 mg/kg/3x/day)	G12-delivery	W10-14	Stress-induced anxiety-like behavior: = (E, F) Stress-induced social impairment: = (L)	**Neuroinflammation**: ● ↓ Microglia ramification **Synaptic plasticity:** ● Prevented interneuron changes ● ↑ GAD67 (males)
Yajima et al.	2013	Mouse	6–8 per group	Unspecified	LS	PRS and POS (Late gestation-P22)	Lutein (0.2% in diet)	Late gestation - W9	W9	Stress-induced anxiety like behavior: ↓(F)	*No supporting underlying mechanisms found*
Other micronutrients											
Rodent											
Alhassen et al.	2021	Mouse	9–10 per group	Male	PSc	PRS (G17-21)	Acetyl-L-carnitine (0.03% in drinking water)	Two time frames: P21-56 or P49-56	W8-13	Stress-induced depressive like behavior: ↓(B) No effect of stress on anxiety-like behavior (E, F) or cognition (H, N, V)	*No possible underlying mechanisms investigated*
Moreno Gudine et al.	2017	Rat	8 per group	Male	MS	POS (P1-14)	Choline (5.0g/kg diet)	P21-60	P90	Stress-induced cognitive impairments: ↓(A, H)	*No possible underlying mechanisms investigated*
Jia et al.	2016	Rat	10 per group	Both (studied separately)	RS	PRS (G14-20)	Taurine (2000 or 200 mg/kg body weight per day)	P21-30	P31	Stress-induced cognitive impairment: ↓ (K)(only high dose)	**Mitochondrial function:** ● ↑ mRNA and protein levels of PGC1α ● ↓ ROS **Oxidative stress:** ● ↑ MMP ● ↑ ATP ● ↑ CcO ● ↑ SOD2 ● ↑ Catalase **Apoptosis:** Normalization of Bcl-2/BAX ratio and cleaved caspase 3/full-length caspase 3 ratio **Synaptic plasticity:** ● ↑ pAkt ● ↑ pCREB
Schulz et al.	2014	Rat	10–14 per group	Both (studied separately)	USP	PRS (G14-21)	Choline (5g/kg diet)	G0-P21	P79-106	Stress-induced anxiety-like behavior: = (E), ↓(F) (only females) Stress-induced social impairment: ↓(S)(only males)	*No possible underlying mechanisms investigated*

Table 1. continued

	Year of publication	Species	n	Male/ female	Type of early-life stress	Timing/ duration of stress	Specific diet/supplement	Timing/duration diet/supplement	Age outcome was measured	Outcome(s): result of supplementation	Suggested underlying mechanisms
Corriveau et al.	2012	Rat	7–8 per group	Male	RS	PRS (G15-19	Choline (5 mg/kg)	P25-50	P75	No effect of stress on anxiety-like behavior (Z)	*No possible underlying mechanisms investigated*
Tönjes et al.	1986	Rat	6 per group	Male	MS	POS (P3-14)	Choline chloride (injection) (Early: 0.3 mg on day 1–4 and 0.6 mg on day 5–14; Late: 0.6 mg on day 15–21 1.2 mg on days 22–28 (Not specified for BW)	Two time frames: P1-14 or P15-28	P80 and 180	Stress-induced cognitive impairment: ↓(M)	*No possible underlying mechanisms investigated*
Combination preparates (mix of different nutrients)											
Rodent											
Egerton et al.	2022	Rat	10–12 per group	Male	MS	POS (P2-12)	Diet containing 7% fish oil (+vitamins and minerals)	W8-16	W10-16	Stress-induced depressive-like behavior: = (B) Stress-induced anxiety-like behavior: ↓(E, F)	**FA profile:** ● Altered central FA profile **HPA axis regulation:** ● ↓ Corticosterone **Monoamine regulation:** ● ↑ Serotonin turnover **Microbiome:** ● ↑ SCFA producers
O'Mahony et al.[a]	2020	Rat	12 per group	Male	MS	POS (P2-12)	Milk fat globule membrane (15.9g/kg diet) + polydextrose 6.44 g/kg and galacto-oligosaccharides 20.86 g/kg	P21-W13-14	W7-13	Stress-induced cognitive impairments: ↓(K), = (H) Stress-induced increase in pain behavior: ↓(Y)	**HPA-axis:** ● ↑ HPA-axis feedback after stressor **Microbiome:** ● altered microbiome composition **Synaptic plasticity:** ● ↑ MAG
Provensi et al.	2019	Rat	6–8 per group	Male	RS + SIS	POS (P30-45)	0.44% EPA, 0.30% DHA, 45,000IU/kg Vit. A	P25-P76	Adolescence (P46-51) Adulthood (P70-76)	Stress-induced cognitive impairment (both adolescents and adults): ↓ (H, N)	**Neurotrophic factors:** ● ↑ BDNF **Microbiome:** ● increase alpha diversity (adolescent rats)
Bengoetxea et al.[a]	2017	Rat	8–10 per group	Both (studied separately)	USP	PRS (G14-21)	Folic acid (5.55 mg/kg of diet), vitamin B12 (0.551 mg/kg of diet) betaine (5 g/kg of diet) and choline (5.369 g/kg of diet)	G14-P21	Young (M1-M2) and Aged (M19-M20)	Stress-induced depressive-like behavior (only young males): ↓(B) Stress-induced cognitive impairments (only aged females): ↓(H) Stress-induced cognitive impairments (all aged animals): ↓(K)	*No possible underlying mechanisms investigated*
Naninck et al.	2017	Mouse	9–14 per group	Male	LBN	POS (P2-9)	Folic acid (15 µg/kg diet), vitamin B6, vitamin B12 (both 1.5 µg/kg diet), betaine (15g/kg diet), choline (15g/kg diet), methionine (7.5 µg/kg diet), zinc (150 µg/kg diet)	Lifetime	M4	No effect of stress on anxiety-like behavior (F) and cognition (V) Stress-induced cognitive impairment: ↓(H, K), = (A)	**HPA-axis regulation:** ● ↓ Corticosterone **Altered AA profile:** ● Normalisation of methionine levels (central/peripheral)
Paternain et al.	2016	Rat	8 per group	Female	MS	POS (P2-21)	Folic acid (5.55 mg/kg of diet), vitamin B12 (0.551 mg/kg of diet) betaine (5 g/kg of diet) and choline (5.369 g/kg of diet)	P60-186	P165-186	Stress-induced depressive-like behavior: ↓(B) Stress-induced cognitive impairment: = (H)	**Epigenetics:** ● ↑ total DNA methylation in hippocampus **Metabolic:** ● Normalization of total and HDL cholesterol
Barrett et al.[a]	2012	Rat	15 per group	Unspecified	MS	POS (P2-12)	*Bifidobacterium breve* (CFU = 1×10^{10} cells/ml) + linoleic acid (0.5%) and α-linolenic acid (0.5%)	P28-77	P77	No effect of stress on pain behavior (Y)	**FA profile:** ● Altered central FA profile ● Altered periferal FA profile
Borsonelo et al.	2011	Rat	9–11 per group	Male	RS	PRS (G14-20)	Diet containing 11% Fish oil coconut oil (rich in SFA)	G0-P21	P90	No negative effect of stress on depressive-like behavior (B)	**HPA-axis regulation:** ● ↓ Corticosterone

Table 1. continued

	Year of publication	Species	n	Male/ female	Type of early-life stress	Timing/ duration of stress	Specific diet/supplement	Timing/duration diet/supplement	Age outcome was measured	Outcome(s): result of supplementation	Suggested underlying mechanisms
Diets/nutritional programs											
Human											
Wang et al.	2023	Human	7438	Both	Maternal prenatal depression (EPDS)	PRS	Maternal empirical dietary inflammatory pattern (EDIP) score	Habitual intake over the last three months (pregnancy)	6 months of age	Lower risk of neurodevelopmental delay (Denver Developmental Screening Test-II) lower higher EDIP	**Inflammation:** ● ↓ maternal CRP during pregnancy
Fahmida et al.	2022	Human	240	Both	Disaster survivors (earthquake)	POS (Under 5y of age)	Nutritional education + supplementation of the diet with liver, fish and anchovy twice weekly	For six months	6 to 49-month-old	Improvement in cognitive and behavioral development	*No possible underlying mechanisms investigated*
Morton et al.	2021	Human	9301	Both	Adverse Childhood Experiences	POS	Plant-based dietary intake	Over the last years	Adulthood (mean 60y of age)	Improvement in later life mental health outcomes	*No possible underlying mechanisms investigated*
Arons et al.	2016	Human	327	Both	Low SES	PRS and POS	The Special Supplemental Nutrition Program for Women, Infants, and Children (Provision of nutritional education and healthy supplemental foods)	Different	12–14 months of age	No effect of supplementation program on socioemotional development	*No possible underlying mechanisms investigated*
Barker et al.	2013	Human	6979	Both	Maternal depression	PRS and POS	Maternal healthy diet (FFQ)	Habitual intake (pregnancy and lactation)	8y of age	Improvement in child cognitive function	*No possible underlying mechanisms investigated*
Rodent											
Clauss et al.	2022	Mouse	12–13 per group	Both (studied separately)	RS	PRS (G14-20)	Western-pattern diet (40 kcal % fat, 43 kcal% carbohydrates)	G14 to P80-83 or G14 to weaning	P80-83	Stress-induced anxiety like behavior: ↓(E) (only G14 to P80-83), partially in males (G14-weaning)	**Monoaminergic regulation:** ● ↑ DRD1 (Nac) ● ↓ DRD2 (Nac and VTA)
Machado et al.	2022	Rat	8–10 per group	Both (studied separately)	MS	POS (P1-10)	Olive oil-rich diet (4%)	G1-P21	P80-87	Stress-induced depressive-like behavior: = (C), ↓(B) (only in males)	**Oxidative stress:** ● ↓ DCFH oxidation
Abbink et al.	2020	Mouse	Unspecified	Male	LBN	POS (P2-9)	Early-life: Standard infant milk formula diet or Concept Nuturis® IMF diet (28.3% w/w S-IMF or N-IMF, further matched to AIN-93M). Adulthood: Western style diet (22% w/w lard, 0.1% w/w cholesterol) or standard diet (AIN-93M)	Early-life diets: P16-42 Adulthood diets: P42-230	P140-180	No effect of stress on cognition (A, H, V)	*No possible underlying mechanisms found*
Ali et al.	2018	Rats	40 in total	Male	ESE	POS (P27-29)	Palatable diet (4.7 kcal/g, 23.3% fat, 17.3% protein, 47.6% carbohydrates)	P21-P75-76	P61-P64	Stress-induced social impairment: ↓(S)	**Monoaminergic regulation:** ● ↑ DRD1 (NA) ● ↑ DRD2 (PFC, NA)
Rincel et al.	2018	Rat	8–12 per group	Male	MS	POS (P2-14)	High-fat-diet (4.7 kJ/g, energy 45% fat (lard), 20% protein, and 35% carbohydrates (sucrose 17.5%))	G0-P21	M6	Stress-induced cognitive impairments: ↓(AA)	**Synaptic plasticity:** ● ↓ Spine loss and dendritic atrophy **Gut:** ● ↓ gut leakiness (FITC-dextran)
Bengoetxea et al.[a]	2017	Rat	Unspecified	Both (studied separately)	USP	PRS (G14-21)	High-fat-diet (45 kcal% Fat)	G14-P21	Young (M1-M2) and Aged (M19-M20)	Stress-induced depressive-like behavior (only in young males): ↓(B) Stress-induced cognitive impairments (only in aged females): ↓(H), stress-induced cognitive impairments (in all aged rats): ↓(K)	*No possible underlying mechanisms investigated*

Table 1. continued

	Year of publication	Species	n	Male/ female	Type of early-life stress	Timing/ duration of stress	Specific diet/supplement	Timing/duration diet/supplement	Age outcome was measured	Outcome(s): result of supplementation	Suggested underlying mechanisms
Rincel et al.	2016	Rat	8–12 per group	Male	MS	POS (P2-14)	High-fat-diet (40% of energy from fat)	G0-P21	M4-M7	No effect of stress on depressive-like behavior (C) Stress-induced anxiety-like behavior: ↓(E) Stress-induced cognitive impairment: ↓(K) Stress-induced social impairment: ↓(S)	**HPA-axis regulation:** ● ↓ Corticosterone **Neurotrophic factors:** ● ↑ BDNF
Maniam et al.	2016	Rat	9–10 per group	Male	LBN	POS (P2-9)	High-fat-high-sugar diet (energy 43% fat, 17% protein, 40% sucrose)	P21-91	P70-77	Stress-induced anxiety-like behavior: ↓(F) No effect of stress on cognition (A, H)	**HPA-axis regulation:** ● ↑ GR
Kim et al.	2015	Rat	8 per group	Female	MS	POS (P1-14)	Highly palatable food (cookies) (energy content unspecified)	P28-65	P54-59	Stress-induced depressive-like behavior: ↓(B) Stress-induced anxiety-like behavior: ↓(E, F)	**Synaptic plasticity:** ● Normalization of ΔFosB **Neurotrophic factors:** ● ↑ BDNF
MacKay et al.	2014	Rat	40 juveniles, 56 adults	Male	ESE	POS (P27-29)	Palatable diet (4.7 Kcal/g, 23.2% fat, 17.3% protein, 47.6% carbohydrates	P21-P60 (2 hrs/day)	Juveniles P30-37, adults P60-67	Stress-induced anxiety-like behavior (adults): ↓(F) Stress-induced social impairment (adults): ↓(S)	*No possible underlying mechanisms found*
Lee et al.	2014	Rat	8–12 per group	Male	MS	POS (P1-14)	Highly palatable food (energy content unspecified)	P22-59	P54-59	Stress-induced depressive-like behavior: = (B) Stress-induced anxiety-like behavior: ↓(E), = (F)	**HPA-axis regulation** ● ↓ Baseline corticosterone ● ↑ Corticosterone reactivity to stressor
Maniam et al.	2010a	Rat	12–15 per group	Male	MS	POS (P2-14)	High-fat-diet (32 kcal% Fat)	P20-84	W10-12	Stress-induced depressive-like behavior: ↓(B) Stress-induced anxiety-like behavior: ↓(F, I)	H**PA-axis regulation:** ● ↓ Corticosterone reactivity to stressor ● ↑ GR **Monoamine regulation:** ● ↑ 5-HT1A receptor **Neurotrophic factors:** ● ↑ BDNF
Maniam et al.	2010b	Rat	Unspecified	Both, studied separately	MS	POS (P2-14)	Highly palatable food (15.3 kJ/g, energy 32% fat, 18% protein, and 50% carbohydrate)	P20-84	P34-84	Stress-induced depressive-like behavior: ↓(B)(males) Stress-induced anxiety-like behavior: ↓(I)(in females) and no effect of stress (F)	*No possible underlying mechanisms found*
Other											
Rodent											
Terreros et al.	2024	Rat	9 per group	Male	RS	POS (P46-51)	Quinoa-supplemented rat food (chow: quinoa=1:1)	P21-P52/53	P52-P53	No effect of stress on anxiety-like behavior (F, I) Stress-induced cognitive impairment: ↓ (G)	**Structure:** ● ↑ Total dendritic length of CA3 pyramidal neurons
Xu et al.	2023	Rat	10–12 per group	Male	MS	POS (P1-10)	Capsaicin (1 mg/kg/day)	P56-70	P63-70	Stress-induced anxiety-like behavior: ↓(E) Stress-induced cognitive deficit: ↓(H, X) Stress-induced changes in pre-pulse inhibition: ↓(J)	**Apoptosis:** ● ↑ Bcl2/BAX ● ↓ Caspase 3 and cleaved caspase 3 ● ↓ NeuN+TUNEL+ cells (mitochondria-related apoptosis)
Sivasangari et al.	2023	Rat	6 per group	Male	SDO	PRS (G16-18)	Bacopa monnieri (80 mg/kg) + acacia gum (0.5%) or L-Carnosine (1 mg/kg)	G10-P23	P31-33 or P84-86	Stress-induced anxiety-like behavior: ↓(I)	**Oxidative stress:** ● ↑ SOD1,2 ● ↑ catalase ● ↑ GPx3 **Cellular age:** ● ↓ TERT ● ↓ TRF1 ● ↑ RAP1 ● ↓ POT1

Table 1. continued

	Year of publication	Species	n	Male/ female	Type of early-life stress	Timing/ duration of stress	Specific diet/supplement	Timing/duration diet/supplement	Age outcome was measured	Outcome(s): result of supplementation	Suggested underlying mechanisms
Farzan et al.	2023	Rat	8 per group	Male	MS	POS (P2-14)	Vanillic acid at doses of 25, 50, and 100 mg/kg	P46-P60	P60	Stress-induced anxiety-like behavior: ↓(E, F) Stress-induced cognitive impairment: ↓(Q) Stress-induced increased repetitive behavior: ↓(R)	**Synaptic plasticity:** ● reversing electrophysiological alterations, increasing amplitude and slope of fEPSP **Oxidative stress:** ● ↑ Antioxidant capacity ● ↓MDA levels **Structure:** ● ↑ diameter of CA3 **Apoptosis:** ● ↓ Dark neurons **Neuroinflammation:** ● ↓ Il-1β, TNF-α ● ↓ NLRP3, TLR-4
Araki et al.	2023	Mouse	Unspecified	Male	EW	POS (P17)	2'- Fucosyllactose (5%)	Weaning - W7, Weaning-P24 and P24-W7	W7	Effect of stress on anxiety-like behavior: ↓(F)(only when supplementing from Weaning-W7)	**Synaptic plasticity:** ● ↓ amygdala hyperactivity (c-Fos) **Microbiome:** ● ↑ Shannon index ● altered microbiome composition
Collins et al.	2022	Rat	8–12 per group	Male	MS	POS (P2-12)	Milk fat globule membrane (15.9g/kg diet)	G19/21-P100	P70-77	No effect of stress on cognition (H, K) Stress-induced increase in pain behavior: ↓(Y)	*No possible underlying mechanisms found*
Moradi-Kor et al.	2020	Rat	10 per group	Female	RS	POS (P30-40)	*Spirulina platensis* (200 mg/kg/day)	P41-55	P60-70	Stress-induced depressive-like behavior: ↓(B) Stress-induced anxiety-like behavior: ↓(E, F)	**Neurotrophic factors:** ● ↑ BDNF **Monoamine regulation:** ● ↑ 5-HT3 **Oxidative stress:** ● ↑ FRAP ● ↓ MDA
Lorigooini et al.[a]	2020	Mouse	8 per group	Male	MS	POS (P2-14)	Trigonelline (injection: 10, 50 1000 mg/kg)	P31-45/47	P45-47	Stress-induced depressive-like behavior: ↓(B, W) Stress-induced anxiety-like behavior: ↓(F)	**Oxidative stress:** ● ↓ MDA ● ↓ NO
de Bem et al.	2020	Rat	10 per group	Male	MS	POS (P2-21)	Euterpe oleracea Mart. (açaí) seed extract (200 mg/kg/day)	P76-110	P106-108	Stress-induced depressive-like behavior: ↓(B) Stress-induced anxiety-like behavior: ↓(E)	*No possible underlying mechanisms investigated*
Sivasangari et al.	2020	Rat	6–7 per group	Male	SDO	PRS (G16-18)	Bacopa monnieri (80 mg/kg) + acacia gum (0.5%)	G10-P23 (dams) and P15-30 (pups)	P30-32	For both supplementation time frames: Stress-induced anxiety-like behavior: ↓(F) Stress-induced cognitive impairment: ↓(K)	**HPA-axis regulation:** ● ↓ Cortiosterone ● ↓ ACTH ● ↓ GR **Apoptosis:** ● ↓ Caspase 3 ● ↑ Bcl-2 **Synaptic plasticity:** ● ↑ Synaptotagmin-1 and SYP ● ↑ Phosphorylation of CaMKII ● ↑ PSD-95 **Monoamine regulation:** ● ↑ 5-HT1A ● ↓ 5-HT2C **Neurotrophic factors:** ● ↑ BDNF
O'Mahony et al.[a]	2020	Rat	12 per group	Male	MS	POS (P2-12)	Milk fat globule membrane (15.9g/kg diet)	P21-W13-14	W7-13	Stress-induced cognitive impairments: ↓(K), =(H) Stress-induced increase in pain behavior: = (Y)	**HPA-axis:** ● ↑ HPA-axis feedback after stressor **Microbiome:** ● altered microbiome composition

Table 1. continued

	Year of publication	Species	n	Male/ female	Type of early-life stress	Timing/ duration of stress	Specific diet/supplement	Timing/duration diet/supplement	Age outcome was measured	Outcome(s): result of supplementation	Suggested underlying mechanisms
Moradi-Kor et al.	2019	Rat	10 per group	Female	RS	POS (P30-40)	*Spirulina platensis* (200 mg/ kg/day)	P41-55	P60-70	Stress-induced cognitive impairment ↓(K, M)	**HPA-axis:** ● ↓ **Serum corticosterone** **Structure:** ● ↑ Apical dendritic length and branch points of CA3 pyramidal neurons
Zhang et al.	2012	Rat	11–12 per group	Unspecified	ES	PRS (G1-P0)	Herbal medicine (*Radix Rehmanniae Preparata, Fructus Corni Officinalis, Cortex Moutan Radicis, Rhizoma Dioscoreae Oppositae, Sclerotium Poriae Cocos, Rhizoma Alismatis Orientalis, Radix Aconiti Lateralis Preparata*, and *Cortex Cinnamomi Cassiae*)	G1-P0	P25	Stress-induced anxiety-like behavior: ↓(E)	**Monoamine regulation:** ● ↑ DA ● ↓ 5-HT **Metabolic:** ● ↑ Growth hormone
Feng et al.	2010	Rat	>8 per group	Both, studied separately	RS	PRS (G14-20)	Milk-based wolfberry preparation (50, 100 and 300 mg/kg/day)	For 2 weeks before breeding	P30	Stress-induced cognitive impairment (only in females): ↓(K)	*No possible underlying mechanisms investigated*

The table depicts the experimental design and main findings of the individual papers classified by nutrient group and whether the study was performed in human subjects or consisted of preclinical studies in rodents.

Abbreviations of the various stressors: *CVS* chronic variable stress, *RS* restraint stress, *USP* unpredictable stress protocol, *ES* earthquake simulation, *SDO* social defeat observation, *PSc* predator scent exposure, *LS* light stress, *NoS* noise stress, *MS* maternal separation, *LBN* limited bedding and nesting material, *EW* early weaning, *SIS* social instability stress, *ESE* episodic stressor exposure.

Abbreviations used in mechanism column: *ACTH* adrenocorticotropic hormone, *Akt* protein kinase B, *Arc* activity-regulated cytoskeleton-associated protein, *Atg* autophagy related, *ATP* adenosine triphosphate, *BAX* BCL-2 associated X, *Bcl-2* B-cell lymphoma 2, *BDNF* brain-derived neurotrophic factor, *CaMK* calcium/calmodulin-dependent protein kinase, *CcO* cytochrome c oxidase, *CD* cluster of differentiation, *CREB* cAMP response element-binding protein, *CRHR* corticotropin-releasing hormone receptor, *DA* dopamine, *DCFH* 2',7'-dichlorofluorescin, *DOPAC* 3,4-dihydroxyphenylacetic acid, *Drp* dynamin-related protein, *DRD* dopamine receptor D, *EMX* empty spiracles homeobox, *FOXO* forkhead box protein, *FRAP* ferric reducing/antioxidant power, *GABA* gamma-aminobutyric acid, *GAD* glutamate decarboxylase, *GAP* growth-associated protein, *GFAP* glial fibrillary acidic protein, *GLC* glutamate cysteine ligase, *GluR* glutamate ionotropic receptor AMPA type subunit, *GPx* glutathione peroxidase, *GSH* glutathione, *HCT* haematocrit, *HDL* high-density lipoprotein, *Hgb* hemoglobin, *HIAA* hydroxyindoleacetic acid, *HO* heme oxygenase, *HVA* homovanillate, *HT* hydroxytryptamine, *IL* interleukin, *IFN* interferon, *iNOS* inducible nitric oxide synthase, *MAG* myelin-associated glycoprotein, *MAPK* mitogen-activated protein kinase, *MDA* malondialdehyde, *MDH* malate dehydrogenase, *MCV* mean corpuscular volume, *MCHC* mean corpuscular hemoglobin concentration, *MFN* mitofusin, *MMP* matrix metalloproteinase, *MPO* myeloperoxidase, *MR* mineralocorticoid receptor, *mTOR* mammalian target of rapamycin, *(N)E* (Nor)epinephrine, *NF- κB* nuclear factor kappa-light-chain-enhancer of activated B cells, *NLRP* NOD-, LRR- and pyrin domain-containing protein, *NMDA* N-methyl-D-aspartate, *nNOS* neuronal nitric oxide synthase, *NQO* NAD(P)H quinone dehydrogenase, *Nrf* nuclear factor erythroid 2-related factor, *PGC* peroxisome proliferator-activated receptor gamma coactivator, *PLT* platelets, *POT* protection of telomeres protein, *PSD* postsynaptic density, *RAP* repressor/activator protein, *ROS* reactive oxygen species, *SCFA* short-chain fatty acid, *SDH* succinate dehydrogenase, *SCG* secretogranin, *SOD* superoxide dismutase, *SYP* synaptophysin, *TAC* total antioxidant capacity, *TBARS* thiobarbituric acid reactive substances, *TERT* telomerase reverse transcriptase, *TJP* tight junction protein, *TLR* toll-like receptor, *TNF* tumor necrosis factor, *TRF* terminal restriction fragment.

Letter coding used in behavioral outcomes column: *A* novel object location test, *B* forced swim test, *C* sucrose preference test, *D* tail suspension test, *E* open field, *F* elevated plus maze, *G* Y maze, *H* novel object recognition test, *J* light-dark box, *K* morris water maze, *L* social investigation/approach, *M* avoidance learning, *N* fear conditioning, *O* sensitivity to electrical shock, *P* resident intruder test, *Q* shuttlebox test, *R* marble burying, *S* social interaction test, *T* hot plate test, *U* novelty suppressed feeding, *V* T maze, *W* splash test, *X* barnes maze, *Y* colorectal distension, *Z* novelty seeking, *AA* conditioned odor preference.

[a]in table more than once as more than one supplement/diet was investigated.

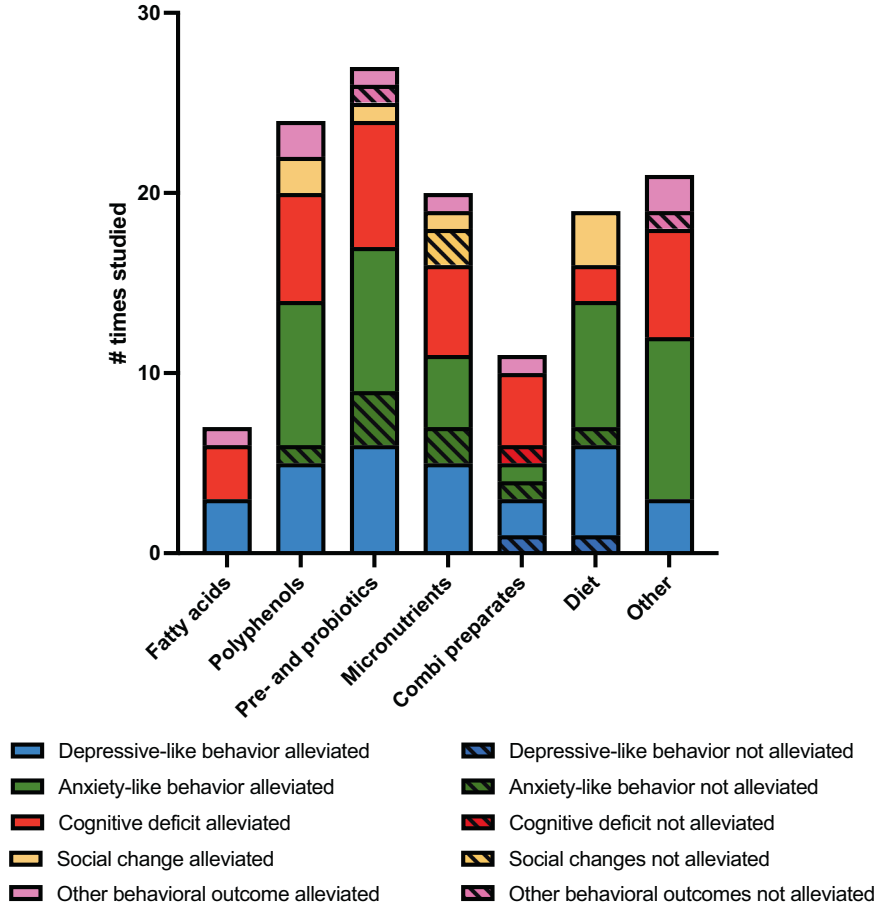

Fig. 3 Overview of the effects of nutritional interventions on ES-induced behavioral deficits, depicted per behavioral domain and nutrient group.

we calculate the percentage of effective studies per nutrient group to get a general idea of effectiveness of the specific nutrient on ES-induced outcomes.

ES affects behavior in rodent studies

Within the 86 preclinical studies that were included in the review, the effect of ES on a specific behavioral domain was investigated 150 times, as several studies investigated the effect of ES on multiple behavioral domains. Overall, the ES paradigms affected behavior in 82.00% of the cases, this was consistent across the behavioral domains assessed (depressive-like behavior 82.35%, anxiety-like behavior 78.57%, cognitive deficits 85.00% and social deficits 80.00% and other ES-induced behaviors 90.00%). This percentage reflects the expected effect of ES on rodent behavior as described in previous reviews [23]. See Supplementary table 4A for details. Some studies reported no effects of ES on any of the measured cognitive domains [24–29].

The effect of nutritional interventions on ES-induced behavioral deficits

For preclinical studies, the effect of nutrition will only be discussed for studies where an effect of ES was found on any of the behavioral domains studied as without an ES effect, the research question could not be answered. Below, the effect of a nutritional component/diet on ES-induced outcomes will be discussed per nutrient (i.e. fatty acids (FA), polyphenols, pre-and pro-biotics, micronutrients, combination preparates, diet/nutritional programs, other nutritional interventions) first in the human studies, followed by the preclinical studies. For an overview of the effects of nutritional effects on ES-induced behavioral deficits, see Supplementary table 4B, visualized in Fig. 3.

Fatty acids. Fatty acids are important macronutrients and have multiple critical functions in the (developing) brain and body [30, 31]. There are three different classes of FA (saturated FAs (SFAs), monounsaturated FAs (MUFAs) and polyunsaturated FAs (PUFAs)) [32]. PUFAs are considered essential nutrients as they cannot be produced by the body itself and can only be ingested through the diet. The most important PUFAs are the omega-6 (N-6) (linoleic acid, LA) and omega-3 (N-3) PUFAs (e.g. α-linolenic acid (ALA), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and eicosatetraenoic acid (ETA)) [33]. Rather than individual concentrations, the proportion of N-3 to N-6 PUFAs is key for the effects on health, where a lower concentration of N-6 PUFAs and a higher concentration of N-3 PUFAs is considered healthy [34]. N-3 PUFAs are well known for their critical role in development, structure and function of the brain [35] and play a critical role in supporting the healthy regulation of cellular inflammation [36]. Most of the nutritional strategies described below were with PUFAs as well as one intervention with sodium butyrate, a short chain (saturated) fatty acid. Sodium butyrate can be produced in the gut and is well known for shaping the microbiome [37] and as an important metabolite for gut-brain-axis signaling [37, 38].

Human studies: Two studies investigated the effects of PUFA supplementation/intake on child development after ES (low socioeconomic status [39] and maternal prenatal negative life

events [40] respectively). More specifically, in a randomized controlled trial in pregnant women (n = 64) with a low socio-economic status, prenatal supplementation of PUFAs (DHA (450 mg), DPA (40 mg), ETA (40 mg) and EPA (90 mg) and Vitamin E (10 mg) for six weeks had no effect on child behavioral and cognitive development at three months of age as measured by the Bayley Scales of Infant Development (BSID-III) [39]. In an observational study (n = 255) the association between maternal negative life events (NLE), infant temperament (Infant Behavior Questionnaire Revised (IBQ-r)) and PUFA intake (habitual intake ratio of N-3 and N-6 PUFAs as measured by a food frequency questionnaire) in black, white and Hispanic women was addressed. At 6 month of age there was a negative association between NLEs and Orienting and Regulation in black women only, which was attenuated by higher maternal N-3/N-6 PUFA intake ratio [40].

Rodent studies: Twelve preclinical studies investigated the effect of FA supplementation on the later-life consequences of ES, out of which seven studies found an effect of ES and will be described below.

Depressive-like behavior - In male rats, supplementation with N-3 PUFAs (postnatal day (P)41-61) [41] or sodium butyrate (P60-67) [42] mitigated the postnatal stress (POS)-induced depressive-like behavior in the forced swim test (FST) at two months of age [41] and at P67 [42]. In male mice, supplementation with EPA (P22-49) alleviated the effect of POS-induced depressive-like behavior in the FST, the sucrose preference test (SPT) and the tail-suspension test (TST) at P49 [43].

Anxiety-like behavior – In mice, supplementing the diet with a high N-6/N-3 PUFA ratio (from breeding until P14) led to increased prenatal stress (PRS)-induced anxiety-like behavior in the elevated plus maze (EPM) at two months of age [44].

Cognitive impairments – In rats, supplementation with DHA (for two weeks before breeding) ameliorated the PRS-induced cognitive impairments in the Morris water maze (MWM) at P30 [45]. In male mice, increasing the availability of N-3 PUFAs (P2-42) restored the POS-induced cognitive impairments in the novel object location test (OLT) [14, 46] novel object recognition test (ORT) [14] and MWM [14] at four months of age.

Other outcomes – In rats, supplementation with proprionic acid (at P40, P43 and P74) ameliorated the POS-induced changes in the pre-pulse inhibition test at P40, P43 and P74 [47].

In conclusion, clinical evidence on FA supplementation on behavioral outcomes after ES is scarce. However, the two studies included state that prenatal N-3 PUFA supplementation does not seem to modulate ES-induced behavioral problems, however it can be speculated that effects are different in mother-infant dyads from different ethical backgrounds. In rodents, N-3 PUFA supplementation ameliorated ES-induced depressive-like behavior and cognitive impairments. An excess of N-6 PUFAs aggravated the ES-induced anxiety-like behavior while deficiency in N-3 PUFAs did not further worsen the ES-induced depressive-like behavior.

Polyphenols. Polyphenols are naturally occurring plant metabolites available for consumption in many fruits, vegetables, coffee, tea and wine. They have shown to have a wide range of potential health benefits [48]. Chemically, polyphenols are phenolic compounds classified based on their structure and substituents [49]. The mechanisms underpinning their effects on brain functioning are not fully understood, but the general consensus attributes their benefit to antioxidant capabilities [50]. More than 8000 polyphenolic compounds have been identified in various plant species. Polyphenols may be classified into different groups as a function of the number of phenol rings that they contain and on the basis of structural elements that bind these rings [51]. Polyphenols used in the included studies belong to the main polyphenol classes of the phenolic acids (ferulic acid), flavonoids (proanthocyanidins, xanthohumol, quercetin, kolaviron, catechins), tyrosols (hydroxytyrosol), coumarins (auraptene), tannins (phlorotannins) and the stilbenes (resveratrol).

Human studies: Only one observational study investigated the effect of polyphenol supplementation on ES-induced behavior. In a longitudinal cohort study (n = 6404) the relationship between adverse childhood events (ACEs), flavonoid intake and depressive symptoms in adulthood was investigated. A higher habitual flavonoid intake as measured by a food frequency questionnaire buffered the association between perceived stress and depressive symptoms after ACEs. Depressive symptoms were lower for those that consumed more flavonoids [52].

Rodent studies: Thirteen preclinical studies investigated the effect of polyphenol supplementation on the later-life consequences of ES. All thirteen studies found an effect of ES on at least one behavioral domain and will be described below.

Depressive-like behavior – In rats, supplementation with proanthocyanidins to females (P21-P30) [53] or ferulic acid to males (P60-P88) [54], ameliorated PRS-induced depressive-like behavior as measured in the FST and SPT at one month and at three months of age respectively [53, 54]. Supplementation with resveratrol (P51-62) [55] and rosmarinic acid (P35-55) [56] improved POS-induced depressive-like behavior measured in rats in the FST and SPT at P62-65 and P39-42 respectively.

Moreover, in rats, supplementation with either phlorotannins, xanthohumol or quercetin (Week (W) 8-16), reversed POS-induced depressive like behavior in the FST at W12-13 [57].

Anxiety-like behavior – In rats, supplementation with ferulic (P60-88) [54] or quercetin (Gestational day (G)14-19) [58] improved PRS-induced anxiety-like behavior in males in the OFT at P89-95 [54] and in males, but not in females in the light-dark box (LDB) and novelty suppressed feeding (NSF) at P35-45 [58]. In rats, supplementation with either phlorotannins, xanthohumol and quercetin (W8-16) [57], kolaviron (P21-35) [59], resveratrol (P51-62) [55] or quercetin (P21-42) [60] dampened the effects of POS-induced anxiety-like behavior as measured in the open field test (OFT) at W12-13 [57], at P35 [59], at P62-65 [55], and at P39-42 [60] and in the LDB at P62-65 [55]. However, in male rats, supplementation with catechins (P21-80) did not modulate the POS-induced anxiety- like behavior in the OFT, EPM and hot plate test (HPT) at P81-90 [61]. In mice, supplementation with auraptene (P45-60) and umbelliprennin in males (for 7 days between P51-60) [62] prevented POS-induced anxiety-like behavior in OFT and EPM at two months of age [63] and in the EPM immediately after treatment [62].

Cognitive impairments – In rats, supplementation with hydroxytyrosol to males (2 weeks before breeding [64]), resveratrol (G1-P1) [65] or quercetin (G14-19) [58] ameliorated the PRS-induced cognitive impairments in MWM and the T-maze (TM) at one month [64, 65] and only in females in the ORT [58]. In rats, supplementation with catechins to males (P21-80) [61] or kolaviron (P21-35) [59] alleviated the POS-induced cognitive impairments in the HPT and ORT at P81-90 [61] and the MWM and Y-maze (YM) at a not specified age [59]. In male mice, umbelliprenin supplementation for 7 days between P51-60 alleviated POS-induced cognitive impairments in the shuttleboxtest (SBT) immediately after treatment [62].

Social impairment – In male mice and rats, umbelliprenin (for 7 days between P51-60) [62] and quercetin (P21-42) [60] supplementation lead to reductions in social impairments in POS-exposed offspring immediately after treatment in social approach (SA) [62] and at P39-42 in the social interaction (SI) test [60].

Other outcomes – In male rats, supplementing with resveratrol (P51-62) [55] led to less aggressive behavior in POS-offspring in

the resident intruder test immediately at P62-65. In male mice, supplementing umbelliprenin (for 7 days between P51-60) to POS-offspring lead to less repetitive behavior immediately after treatment [62].

In conclusion, there is not enough data to suggest a modulating role of polyphenol supplementation after ES in humans. However, in rodents, in 95.83% of the cases, supplementation with a large variety of polyphenols during and after PRS and POS mostly ameliorates ES-induced changes in behavior across the various domains. In addition, there seems to be evidence for sex-specific responses to polyphenols in the context of ES.

Pre-, pro- and synbiotics. The gut microbiome comprises of the trillions of bacteria residing in the gut, metabolizing components of the food ingested by the host and providing essential gastrointestinal ecosystem services. In the last decades both preclinical and clinical research has also pointed towards microbial regulation of brain function and behavior [66] and is incorporated as a key node within the framework of the gut-brain axis. Key initial studies showed that ES induces changes in gut microbiome composition later in life [67]. Furthermore, the seminal study by de Palma and colleagues showed that an intact microbiota is necessary to induce some effects of ES [68]. Germ-free mice (i.e. animals without a gut microbiome) exposed to maternal separation do not show changes in anxiety-like and depression-like behavior [68]. Hence, the microbiota can be a promising new target to treat the consequences of ES. The most common dietary interventions directly targeting the gut microbiome are pre- and probiotics. Prebiotics are substrates selectively utilized by host microorganisms conferring a health benefit. These can be digestible fibers that act as nutrients for the beneficial bacteria in the gut and their degradation products are short-chain fatty acids (e.g. butyrate) that are released into the circulation, affecting overall health. Fructo-oligosaccharides and galacto-oligosaccharides are the two main groups of prebiotics studied for beneficial effects on health. Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Modulation of the gut microbiome exerts health benefits via various routes including microbial metabolites [69], immune system [70], neuroendocrine system [71], the enteric nervous system, and the vagus nerve [72]. Probiotics exert their effects usually in the gastrointestinal tract, where they may influence the intestinal microbiota and exert health effects by nonspecific, species-specific, and strain-specific mechanisms [73]. The probiotics that are most frequently used for beneficial health effects are strains from the *Lactobacillus* and *Bifidobacterium* genera, which are also most frequently used in the included studies as described below.

Human studies: One clinical study investigated the effect of pro- and prebiotic supplementation on ES-induced behavior in the offspring. A randomized, double-blind, controlled trial was carried out in 190 healthy mothers divided in 2 groups (one taking a supplement containing *Limosilactobacillus reuteri PBS072* and *Bifidobacterium breve BB077* and a control group). Symptoms related to maternal depression were evaluated at day 45 and 90. At both timepoints, the score obtained from the Edinburgh Postnatal Depression Scale questionnaire was lower in the supplemented group. This led to less crying and fussing events during the treatment in the offspring [74].

Rodent studies: Eighteen preclinical studies investigated the effects of pre- and/or probiotic supplementation on ES-induced behavioral deficits. Out of these eighteen studies, seventeen found an effect of ES on at least one of the behavioral domains and will be discussed below.

Depressive-like behavior – In rats, supplementation with *L. Paracasei* (P2-16) [75], with *B. Infantis* to males (P50-P95) [76], or *B. infantis* to both sexes [77] restored the POS-induced depressive like behavior in the TST at 1 month of age [75], and in the FST at P21 (in females), 41(in males) and 61 (in females) [77] at 3 months of age [76]. In mice, prenatal supplementation with *B. breve CCFM1025* (G0-delivery) [78] or postnatal supplementation with *L. Plantarum* (P29-57) [79], *L. Paracasei* (P28-56) [80], prevented the POS-induced depressive-like behaviors in FST and TST at P57-63 [79] and in the FST at P49 [78] and P54-56 [80].

Anxiety-like behavior – In rats, lifetime supplementation with *B. Trisporus* [81] or with a mixture *of L. Acidophilus*, *L. Fermentum* and *B. Lactis* (G1-G14 or P31-45) [82] ameliorated PRS-induced anxiety-like behavior in the EPM at P45-46 [82] and at P60-70 [81]. In male rats, supplementation with *L. Paracasei* (P2-16) [75], a mix of *L. Helveticus*, *B. Longum, L. Lactis* and *S. Thermophilus* (W6-15) [83], a mix of Polydextrose + Galactooligosaccharide and/or *L. Rhamnosus* (P21-49) [84] or a mix of *L. Rhamnosus* and *L. Helveticus* (P2-14) [85], ameliorated the POS-induced anxiety-like behavior in the OFT 2 weeks after supplementation [75] or in the OFT [83, 84], EPM [85] and LDB [85] right after the supplementation period. However, in male rats supplementation with a mix of *L. Helveticus*, *B. Longum*, *L. Lactis* and *S. Thermophilus* (W6-15) [83], *L. Rhamnosus* and *L. Helveticus* (P2-14) [86] or a mix of *L. Rhamnosus and L. Helveticus* (P2-14) [85], reduced the POS-induced anxiety like behavior in the EPM [83, 86], LDB [83], novelty seeking (NS) [83] an OFT [85] right after the supplementation period. In male mice, supplementation with *B. pseudocatenulatum* (P2-21) and L. reuteri (P21-P63) ameliorated the POS-induced anxiety-like behavior in the EPM at P42 [87] at P63-P70 respectively and in the OFT at P63-P70 [88]. However, supplementation with *L. Paracasei* (P28-56) [80] or *L. Plantarum* (P29-57) [79] did not affect the POS-induced anxiety-like behavior in the EPM at P54-56 [80] and at P57-63 [79].

Cognitive impairments – In rats, lifetime supplementation with *B. Trisporus* [81] or supplementation with a mixture of *L. Acidophilus*, *L. Fermentum and B. Lactis* (G1-G14 or P31-45) [82] ameliorated PRS-induced cognitive impairments in the ORT and Barnes maze (BM) at P60-70 [81], and the MWM at P45-46 [82]. In male rats, supplementation with *L. Rhamnosus* and *L. Helveticus* (P2-14) [85, 86, 89], Polydextrose + Galactooligosaccharide (P21-W13/W14) [90], or a mix of Polydextrose + Galactooligosaccharide and L. Rhamnosus (P21-49) [84], ameliorated the POS-induced cognitive impairments in fear conditioning (FC) at P17-24 [85, 86, 89] and the MWM at W7-11 [84] and at W7-13 but not the ORT at W7-13 [90].

Social impairment – In male mice, supplementation with L. Reuteri (P21-P63) reversed the POS-induced social impairment in SA at P63-P70 [88].

Other outcomes – In male POS-rat offspring, prebiotic Polydextrose + Galactooligosaccharide (P21-W13) did not affect pain behavior at 7 to 13 weeks of age [90]. In mice, supplementation with *L. Reuteri* (P5-14) normalized POS-induced alterations in calling behavior [91].

In conclusion, supplementation with both pre- and/or pro- and synbiotics alleviates ES-induced depressive-like behavior and cognitive impairments in 100% of the cases. Regarding the domain of anxiety-like behavior, in rats subjected to PRS, pre- and/or probiotic supplementation demonstrates anxiolytic effects. However, results were conflicting in rats exposed to POS. This variability in results can be attributed to differences in the timing of pre- and/or probiotic supplementation relative to the stressor or the timing of outcome measurements. In mice, it is noteworthy that supplementation during the stress period modulated the POS-induced alterations in behavior, whereas supplementation after the stress period did not. Interestingly, pre- and/or probiotic supplementation during POS ameliorates the ES-induced deficits in cognition, however, supplementation after POS required supplementation with both pre- and probiotics, as a synbiotic.

Micronutrients. Micronutrients are essential dietary elements, required to orchestrate a range of physiological functions

important for development and maintenance of a healthy brain [92]. Micronutrients can be subdivided in different categories, such as vitamins and minerals. Therefore, below we will describe the effect of supplementation with amino acids, vitamins, minerals, carotenoids and other micronutrients on ES-induced behavioral deficits.

Amino Acids: Amino acids are important micronutrients and are the building blocks for proteins and critical for almost all body processes and especially for neurodevelopment [93]. In their free form, some amino acids also work as signaling molecules and some, such as tryptophan, are important precursors for the synthesis of neuroactives [93, 94]. Most amino acids, including cysteine and tyrosine, can be synthesized by the body under normal circumstances. However, nine amino acids, are not synthesized (e.g. methionine and tryptophan) or synthesized in too low concentrations (n-acetylcysteine (NAC)) by mammals and are therefore dietary essential nutrients [93]. Interestingly, the studies that we will describe next have only supplemented NAC in the contex of ES, but no other amino acids have been studied yet in this context.

Rodent studies: Three preclinical studies investigated the effects of amino acid supplementation on ES-induced behavioral deficits. All studies found an effect of ES on at least one of the behavioral domains and will be discussed below.

Depressive-like behavior – In male rats, supplementation with NAC (P41 to P61), ameliorated the POS-induced depressive like behavior in the FST at two months of age [41]. In male mice, NAC supplementation (5 weeks pre-mating until G16) did not have an effect on PRS-induced depressive-like behavior at P33-50 in the FST [95].

Anxiety-like behavior - In mice, supplementation with NAC from G12- P1 [96] or pre-mating until G16 [95] did not have an effect on PRS-induced anxiety-like behavior in the EPM at W10-14 [96] or in the OFT and EPM at P33-50 [95].

Social impairment – In mice, supplementation with NAC (G12-P1) did not ameliorate the PRS-induced social impairments in SA at two months of age [96].

Vitamins: Vitamins are essential micronutrients that are required in small quantities for a variety of physiological functions in the body, including for those in the brain [12, 92]. There are several different vitamins that are important for the brain, each of them playing unique roles in for example antioxidative mechanisms and the production of neurotransmitters [97, 98]. The studies below describe supplementation with several different vitamins. For example, folic acid is important for functioning of the nervous system at all ages and is well known for its relation with neural tube defects [99]. Vitamin A is essential for the developing CNS where it affects neurogenesis and neuronal patterning, but keeps playing an important role in the adult brain by regulating neuroplasticity in cerebral structures [100]. Vitamin C and E are, amongst having other functions, vital antioxidant molecules in the brain studies [101, 102].

Human studies: One clinical study investigated the effect of vitamin supplementation/intake on ES-induced outcomes. An observational cohort study (n = 137) found that maternal prenatal stress, measured as NLEs during pregnancy, was associated with higher scores in the infant temperament domain of negative affectivity (Early Childhood Behavior Questionnaire-Very Short form). A trend towards mitigation of this relationship by a higher maternal habitual intake of vitamin A and C, but not E, was found [103].

Rodent studies: Four preclinical studies investigated the effect of vitamin supplementation on ES-induced behavioral deficits. All studies found an effect of ES on at least one of the behavioral domains and will be discussed below.

Depressive-like behavior – In male rodents, supplementation with vitamin E (P31-45) [104] or folic acid (P41-61) [41] reversed the POS-induced depressive-like behavior measured in the FST at P60—61 [41] and at P45-47 [104], but not in the splash test (ST) at P45-47 [104].

Anxiety-like behavior – In male rats, supplementation with leucine (P20-60), did not reduce POS-induced anxiety-like behavior in the OFT at P60 [105]. In male mice, supplementations with vitamin E (P31-45) protected against POS-induced anxiety-like behavior in the EPM at P45-47 [104].

Cognitive impairments – In male POS-offspring, both vitamin PP (P56-85) [106] and Leucine (P20-60) [105] led to improvement in ES-induced cognitive impairments in the ORT and the BM at an unknown age [106] and in the MWM at 2 months of age [105].
Other outcomes - In male POS-offspring, vitamin PP (P56-85) reversed stress-induced changes in pre-pulse inhibition in adulthood [106].

Minerals: Minerals are micronutrients and inorganic substances that cannot be synthesized by organisms, but are ingested through the diet, including for example magnesium, calcium, zinc and selenium. They play key roles in oxygen transport, the synthesis of neurotransmitters and signaling between neurons. In addition, they can have antioxidant activities.

Human study: One clinical study was identified that investigated the effect of mineral supplementation on ES-induced outcomes. An observational cohort study (n = 137) found that maternal prenatal stress, measured as negative life events during pregnancy, was associated with higher scores in the infant temperament domain of negative affectivity (Early Childhood Behavior Questionnaire-Very Short form). This association was mitigated by a higher maternal habitual intake of zinc and selenium, but not magnesium [103].

Rodent studies: One rodent study was included that investigated the effect of mineral supplementation on ES-induced behavioral outcomes.

In female rat offspring of dams that have experienced PRS, zinc supplementation (G0-19) lead to reductions in stress-induced depressive like behavior measured in the FST and stress-induced anxiety-like behavior as measured in the OFT and EPM at P25-27 [107].

Carotenoids: Carotenoids are a group of micronutrients and are organic pigments naturally found in plants, algae and bacteria. Carotenoids have powerful antioxidant capacities and anti-inflammatory functions. In addition, they seem to assist the preservation of cognitive function, independent of ES [108].

Human study: One clinical study was identified that investigated the effect of carotenoid supplementation on ES-induced outcomes. An observational cohort study (n = 137) found that maternal prenatal stress, measured as negative life events during pregnancy, was associated with higher scores in the infant temperament domain of negative affectivity (Early Childhood Behavior Questionnaire-Very Short form). This association was not affected by a higher maternal habitual intake of beta-carotene [103].

Rodent study: Two rodent studies were identified that investigated the effect of carotenoid supplementation on ES-induced behavioral deficits. Both studies reported stress-induced behavioral effects.

Anxiety-like behavior - In mice, supplementation with astaxanthin (G12-P1) had no effect on the PRS-induced anxiety-like behavior as measured in the OFT and the EPM at W10-14 [96], but supplementation with lutein (late gestation-W9) led to a reduction in stress-induced anxiety-like behavior in the EPM at 9 weeks of age [109].

Other micronutrients: The studies below describe supplementation with several micronutrients that do not officially fall in the categories of the amino acids, vitamins, minerals or carotenoids.

For example, choline and carnitine are both quaternary ammonium compounds and both important for brain development [110, 111]. Where choline mostly is important for membrane structure and the production of acetylcholine and thus neurotransmission [110], carnitine is critical in fatty acid oxidation and therefore energy production [111]. Another study will describe supplementation with taurine, a derivative of the amino acid cysteine, which has been linked to development of the CNS and the immune system [112–114].

Rodent studies: Six preclinical studies were identified that investigated the effect of supplementation with these 'other' micronutrients on ES-induced behavioral deficits, out of which five found an effect of the nutrients on ES-induced behavioral deficits on at least one of the behavioral domains investigated and will be described below.

Depressive-like behavior - In male mice, supplementation with acetyl-L-carnitine (P21-56 or P49-56) reduced the PRS-induced depressive like behavior in the FST at W8-13, the effect only lasted for a week [115].

Anxiety-like behavior – In rats, supplementation with choline (G0-P21) ameliorated the PRS-induced anxiety-like behavior in the EPM in females at P79-106, but not in the OFT [116].

Cognitive impairment – In rats, supplementation with a high, but not a low, dose of taurine, (P21-30), ameliorated the PRS-induced cognitive deficits in the MWM at P31 [117]. In male rats, supplementation with choline (P21-60) [118] or choline chloride (P1-14 or P15-28) [119] reversed the POS-induced cognitive impairments in the ORT and OLT at P90 [118] and in the avoidance learning task (ALT) at P80 and P180 [119].

Social impairment – In rats, choline supplementation (G0-P21) ameliorated the PRS–induced social impairments in the SI test in males only at P79-106 [116].

Overall, the micronutrient categories, vitamin (85.71%) and mineral supplementation (100% - 1 study) seem to ameliorate the ES-induced behavioral deficits. While in both humans and rodents, carotenoids (33%) and most amino acids (25%) did not seem convincing in mitigating ES-induced deficits. Supplementation with nutrients from the 'other micronutrients' category (carnitine, choline and taurine) did reverse the ES-induced behavioral deficits (100%). However, due to the small number of studies, the different nutrients used and heterogeneity in study designs, it is impossible to draw any conclusions.

Combination Preparations. Several studies investigated the effects of the mix of multiple nutrients rather than on individual nutrient groups on the outcomes after ES. These combination preparations differ from containing a combination of two different nutrients to a combination of seven different nutrients.

Rodent studies: Eight preclinical studies investigated the effect of supplementation with a combination of different nutrients on ES-induced behavioral deficits, out of which six studies found an effect of ES on at least one of the behavioral domains investigated and those will be described below.

Depressive-like behavior - In male rats, supplementation with fish oil (G0-P21) exacerbated the PRS-induced decrease in depressive-like behavior in FST at three months of age [120]. In addition, supplementation with a combination of folic acid, vitamin B12, betaine and choline (G14-P21) improved the PRS-induced depressive-like behavior in males in the FST between one and two months of age [121]. Supplementation with a combination of fish oil containing FAs and vitamins and minerals to males (W8-16) had no effect on POS-induced depressive-like behavior in the FST at W10-16 [122], while in females supplemented with choline, betaine, folic acid and vitamin B12 (P60-P186) the POS-induced depressive-like behavior was ameliorated in the FST at P165-186 [123].

Anxiety-like behavior – In male rats, supplementation with a combination of fish oil containing FAs and vitamins and minerals (W8-16) improved the POS-induced anxiety-like behavior in the EPM and the OFT at W10-16 [122].

Cognitive impairments – In rats, supplementation with folic acid, vitamin B12, betaine and choline (G14-P21) reduced the PRS-induced cognitive impairments in the MWM and in the ORT, only in aged females, at month (M)19-20 [121]. In male rats submitted to POS, supplementation with milk fat globule membrane (MFGM) combined with polydextrose and galacto-oligosaccharides (weaning-W13/14) resulted in improvement in the MWM, but not the ORT at W7-13 [90]. A different study submitting male rats to POS, a mix of EPA, DHA and vitamin A (P25-P76) reduced the cognitive impairments in adolescence (P46-51) and adulthood (P70-P76) as measured in FC and ORT [124]. In female rats, supplementation with choline, betaine, folic acid and vitamin B12 (P60-186) had no effect on the POS-induced cognitive impairments as measured in the ORT at P165-186 [123]. In male mice, supplementation with folic acid, vitamin B6 + B12, choline, methionine and zinc (P2-P9) reversed POS-induced cognitive deficits in the MWM and the ORT, but not the OLT at four months of age [15].

Other – In rats, supplementation with a combination of the fatty acids LA and ALA and probiotic *B. Breve* (P28-77) had no effect on POS-induced changes in pain behavior at P77 [125], but MFGM combined with polydextrose and galacto-oligosaccharides (P21-W13/14) decreased pain behavior at W7-13 [90].

Although some of the above described combination preparations seemed to be effective in the context of reducing ES-induced impairments, due to the variety in nutrients, stressors and supplementation duration/period, no definite conclusions can be drawn.

Diets/Nutritional Programs. Several studies investigated the effect of a complete diet, for example a high-fat diet, or the implementation of a nutritional program (human studies) on the outcomes after ES. In these diets/programs, the exact nutrient intakes are not specified, but a certain diet is provided over a given time period.

Human studies: Five human studies investigated the effect of specific diets/nutritional programs on ES-induced outcomes.

A community-based intervention trial (n = 240) showed that an integrated nutrition rehabilitation intervention (supplementation of the diet with shredded liver, fish and anchovy twice weekly for 6 months) had benefits on the socioemotional development (BSID-III) in ≥24-month-old Earthquake survivors. There were no effects of the intervention on the other BSID-III outcome domains [126].

Moreover, a large longitudinal cohort (n = 6979) provided evidence that maternal depression symptoms during pregnancy were associated with both more unhealthy and less healthy diets as measured by a food frequency questionnaire during pregnancy and postpartum. This was in turn prospectively associated with reduced child cognitive function at eight years of age. This suggests that maternal depression symptoms in pregnancy can affect child development via a less healthy nutritional environment [127]. A longitudinal cohort study (n = 1503), including women-infant dyads with low socioeconomic status, found no positive effect of The Special Supplemental Nutrition Program for Women, Infants, and Children (a program in which nutritional education and healthy supplemental foods are provided [128]) on child competence or problem behaviors between 12 and 24-months of age as measured by the Brief Infant Toddler Social Emotional Assessment (BITSEA) [129]. Lastly, a longitudinal cohort study (n = 6404) showed that plant-based dietary intake frequency measured by a questionnaire, was related to a reduction in the association of more than four ACEs with later-life mental health outcomes at any age [130]. Finally, a prospective cohort study including 7438 mother-child pairs, investigated whether a maternal anti-inflammatory diet reduced the risk of prenatal

environmental adversity (PEA)-induced neurodevelopmental delay. Diets with a low inflammatory score were protective for an increased risk of PEA-related neurodevelopmental delay [131].

Rodent studies: Thirteen preclinical studies investigated the effect of supplementation with a complete diet on ES-induced behavioral deficits, out of which twelve studies found an effect of the diet on at least one of the behavioral domains investigated and those will be described below.

Depressive-like behavior – In rats, supplementation with a high fat diet (HFD)(G14-P21) aggravated the PRS-induced depressive-like behavior in old males in the FST at M19-20 [121]. Supplementation with an olive oil rich diet (G1-P21) [132], a highly palatable food diet in females (P28-65) [133], a highly palatable food diet in both sexes (P20-84) [134] or a HFD in males (P20-84) [135] reversed the POS-induced depressive-like behavior in the FST in males at P80-87 [132] and at W10-12 [134] and in females at P54-59 [133], and in the SPT in males at P34-84 [135]. In contrast, supplementation with a highly palatable food diet in males (P22-59) [136] and an olive oil rich diet (G1-P21) [132] did not have an effect on POS-induced depressive like behavior as measured in the FST at P54-59 [136] and in the SPT at P80-87 [132].

Anxiety-like behavior – In rats, supplementation with HFD (G0-P21 [137] and P20-84 [134], a high-fat-high-sugar diet (P21-91) [138], palatable diet (P21-P60) [139] or highly palatable food diet (P28-56 [133] and P22-59 [136] and P20-84 [135]) reversed the POS-induced anxiety-like behavior as measured in the OFT at M4-7 [137] and P54-59 [133, 136], in the EPM between W10-12 [134, 138], P60-P67 [139] and at P54-59 [133] and in the LDB at W10-12 [134] and at P34-84 in females [135]. Supplementation with highly palatable food diet (P22-59) did not have an effect on POS-induced anxiety like behavior in the EPM at P54-59 [136].

In male mice, supplementation with Western-pattern diet (G14-weaning and G14-P80/83) after PRS improved anxiety-like behavior as measured in the OFT, but in females only the time window of G14-P80/83 accomplished this effect [140].

Cognitive impairments – In rats, a HFD (G14-P21) did not have an effect on the PRS-induced cognitive impairments as measured in the MWM at M19-20 and the ORT at both M1-2 and M19-20 [121]. In male rats, a HFD (G0-P21) reduced POS-induced cognitive impairments as measured in the MWM at M4-7 [137] and the conditioned odor preference (COP) at M6 [141].

Social behavior – In male rats, a high-fat-diet (G0-P21) or a palatable diet (P21-P75/76) reduced POS-induced social impairments as measured in SI at M4-7 [137], at P61-P64 [142] and at P30-P37 and P60-P67 [139].

In conclusion, a HFD and a highly palatable diet seemed to be effective in reducing ES-induced depressive and anxiety like behaviors. However, for the cognitive domain there is too little evidence that points in the same direction to draw firm conclusions.

Other nutritional interventions. Several studies researched supplementation interventions with nutrients that do not fall into the categories as described above. Most of these are herb-, plant- or berry-derived and sometimes used in alternative medicine, for example bacopa monnieri, acacia gum, acai seed extract and wolfberry preparation, but also for example the alkaloid trigonelline.

Rodent studies: Fourteen preclinical studies investigated the effect of supplementation with one of these 'other' nutrients on ES-induced behavioral deficits. All of these studies found an effect of the diet on at least one of the behavioral domains investigated and will be described below.

Depressive-like behavior – In male rats, supplementation with *Euterpe oleracea Mart*. (açaí) seed extract (P76-110) ameliorated the POS-induced depressive like behavior in the FST at P106-108 [143]. In female rats, supplementation with spirulina platensis (P41-P55) reversed the POS-induced depressive-like behavior in the FST at P60-P70 [144]. In male mice, supplementation with Trigonelline (P31-45/47) ameliorated the POS-induced depressive like behavior in the FST and the ST at P45-47 [104].

Anxiety-like behavior – In male rats, supplementation with *Bacopa monnieri* and acacia gum (G10-P23 and P15-30) [145] or *Bacopa monnieri* and acacia gum or L-carnosine (G10-P23) [146] or herbal medicine (G1-P0) [147] ameliorated the PRS-induced anxiety-like behavior in the EPM at P30-32 [145], the LDB at P31-33 and P84-86 [146], and the OFT at P25 [147]. In male rats, supplementation with *Euterpe oleracea Mart*. (açaí) seed extract (P76-110) [143], capsaicin (P56-70) [148] and vanillic acid (VA) (P46-60) [149], reduced POS-induced anxiety-like behavior in the OFT at P106-108 [143], P63-70 [148] and P60 [149] and in the EPM at P60 [149]. In female rats, supplementation with spirulina platensis (P41-P55) reversed the POS-induced anxiety-like behavior measured in the OFT and the EPM at P60-P70 [144]. In mice, supplementation with Trigonelline in males (P31-45/47) and 2'Fucosyllactose (Weaning-W7) [150] reversed the POS-induced anxiety-like behavior as measured in the EPM at P45-47 [104] and at W7 [150].

Cognitive impairments – In rats, supplementation with *Bacopa monnieri* and acacia gum (G10-P23 and P15-30) [145] to males and with milk-based wolfberry preparation (2 weeks before breeding) [151] to females ameliorated PRS-induced cognitive impairments in the YM at P30-32 [145] and in the MWM at P30 [151]. In male rat POS-offspring, supplementation with capsaicin (P56-70) [148], VA(P46-60) [149], MFGM (P21-W13/14) [90] or quinoa supplemented food (P21-P52/53) [152] improved ES-induced cognitive impairment at P63-70 in the ORT and BM [148] and in the SBT at P60 [149], the MWM, but not the ORT at W7-13 [90] and in the YM at P52-53 [152]. In female rats, supplementing the diet with spirulina platensis (P41-P55) reversed the POS-induced cognitive impairments measured in AL and the MWM at P60-P70 [153].

Other – In male rats, supplementations with MFGM G19/21-P100 [154] and from P21-W13/14 [90] reduced the POS-induced alterations in pain behavior at P70-77 [154], but not at W7-13 [90]. In addition, in male rats, supplementations with capsaicin (P56-70) [148] and VA (P46-60) [149] reduced ES-induced changes in prepulse inhibition (PPI) at P63-70 [148] and repetitive behavior at P60 [149].

In general, the above described studies show that supplementation with *Bacopa monnieri*, acacia gum, acai seed extract, wolfberry preparation, milk fat globule and trigonelline was able to mitigate the ES-induced alterations in behavior. Due to the diversity of nutrients and the relative scarcity of studies pertinent to each, it remains impossible to draw any conclusions at this point.

POTENTIAL MECHANISMS UNDERLYING THE MODULATORY EFFECTS OF NUTRITION

In the previous section, we described the effect of nutritional interventions and their effectiveness in modulating the effect of ES on various behavioral domains. It remains of importance to understand not only if, but also how they modulate the ES-induced effects and which are the specific neurobiological processes mediating the effects of nutrients on the brain in the context of ES. This poses a significant challenge considering that most of the nutrients will have a broad impact on the brain as they are essential building blocks as well as signaling molecules, acting often as co-factors in biochemical processes in the various cell types in our brain [12, 155] rather than targeting a specific brain region, or cell type. In addition, to add an even further layer of complexity, several of them act on converging pathways and there is ample cross talk between the various mechanisms that are

modulated by specific nutrients. In the next section, we will discuss key processes and their potential crosstalk that have been implicated in the long-term effect of ES and how the above-described nutrients might contribute to or modulate these processes. This section is based on the literature identified resulting from primary search in our review, which addressed the impact of early-life stress and nutritional interventions but takes into consideration all papers independent on whether behavioral outcomes were addressed.

Neurogenesis and neurotrophic factors

Adult hippocampal neurogenesis is the process in which new neurons are generated in the hippocampus, a brain region critical for cognitive functioning, anxiety and depression-related behavior [156, 157]. Several preclinical studies have investigated immediate and lasting effects of adverse early-life experience on hippocampal neurogenesis and the associated behavioral alterations using different models for ES [158]. Both PRS as well as POS lead to learning deficits associated with a decrease in neurogenesis [159–162]. Interestingly, Increasing the bio-availability of N-3 PUFAs [14], but not enriching the diet with a combination of micronutrients [15] early in life protected against the ES-induced reduction in neuronal survival. How N-3 PUFAs specifically affected neuronal survival, how key the specific time window is within which nutrients are supplemented and whether other nutrients or the combination thereof might also modulate adult hippocampal neurogenesis in the context of ES remains to be determined.

Neurotrophic factors (e.g. brain derived neurotrophic factor (BDNF)) are a family of molecules that support the growth, survival and differentiation of both developing and mature neurons. Several studies point to the importance of BDNF in pathways of adult neurogenesis [163], suggesting it might contribute to the effect of nutrients on among others the adult neurogenic process. For example, that stress inhibits the pathway that leads to production of BDNF [164] and that following dietary restriction upregulation of BDNF is required for the antidepressant treatment-induced increase in survival of newborn granule cells [165]. Hydroxytyrosol [64], resveratrol [65], as well as DHA [45] supplementation increased BDNF expression in the brain of the ES-exposed offspring, potentially contributing to the beneficial effects on the ES-induced cognitive decline observed. Similar increases in BDNF levels were observed in the plasma of ES-exposed mice after supplementing with other polyphenols [57]. The specific mechanism via which these nutrients modulate BDNF and to what extents the role of BDNF is key for their effect on neurogenesis remain to be determined.

Furthermore, neurogenesis can be influenced by various other biological pathways, such as for example the gut microbiome [166] and neuroinflammation [9], later discussed in this review. Therefore, it is most likely that dietary factors may also indirectly affect neurogenesis not only via BDNF, but rather via a synergistic action through modulation of various pathways.

Apoptosis

Apoptosis is a tightly regulated process of programmed cell death and plays a crucial role in shaping the developing CNS. Notably, neurons are particularly vulnerable to programmed cell death, as a significant proportion of newly generated neurons are eliminated in specific brain regions during development [167]. A slight perturbation in this developmental trajectory by, for example ES, tipping the balance towards increased apoptosis, might be detrimental. Indeed, there is evidence that ES affects apoptotic pathways in the rodent brain. For example, POS leads to an immediate increase in hippocampal apoptosis [168, 169] associated with later-life cognitive deficits [168].

Nutrients could modulate apoptosis for example by inhibiting pro-apoptotic BAX and (pro-)caspases and stimulating anti-apoptotic Bcl-2 [75, 81, 117, 145]. Supplementation with DHA [45], *B. trisporus* [81], *L. paracasei* [75] and *Bacopa monnieri* [145] reversed the ES-induced increase of apoptotic markers BAX [45, 81, 117], caspase 3 [75, 81, 117, 145], pro-caspase 3 [45] and pro-caspase 9 [45] and decrease in anti-apoptotic marker Bcl-2 [81, 117].

There is evidence that neuroinflammation, oxidative stress and mitochondrial functioning might also be involved in the modulation of apoptosis and its modulation by nutrients and stress. For example, dysregulation of the NLRP3-Caspase 1 signaling pathway caused by ES, was reversed by nutritional interventions wit proanthocyanidins [53]. This signaling pathways is associated with an inflammatory-programmed cell death [170].

Synaptic plasticity

Synaptic plasticity refers to activity-dependent modification of the strength or efficacy of synaptic transmission at pre-existing synapses in response to experiences [171]. There is ample evidence that ES leads to long-lasting changes in synaptic plasticity influencing both the pre- and post-synapse [172, 173]. For example, ES reduced synaptophysin (SYP) and post-synaptic density (PSD)-95 expression, important in the formation and maintenance of synapses and their transmission [174, 175]. Nutritional interventions could increase synapse maintenance and stability by enhancing these neural proteins. Indeed, supplementation with polyphenols [64] or a diet enriched with *Bacopa monnieri* [145] and a diet rich in olive oil [132] were able to reverse the ES-induced decrease in SYP and PSD-95.

The plastic cellular process underlying learning and memory, long-term potentiation (LTP), and the herein essential glutamate ionotropic receptor (GLuR) and N-methyl-D-aspartate (NMDA) receptors (glutamatergic), are affected by ES [173]. There is evidence that nutrients might be able to modulate LTP via modulation of these receptors. For example, resveratrol supplementation [65] was able to reverse the ES-induced increase of NMDA receptors and supplementation with *L. paracasei* [75] reversed the ES-induced increase in GluR1, GluR2 and NMDA receptors.

Similarly, inhibitory Gamma-aminobutyric acid (GABA)-ergic synapses have been implicated in ES [176] and a combination of pre- and probiotics supplemented after POS [84] was able to reverse the increased number of GABA-A2 receptors [177].

Synaptic plasticity, closely linked to neurogenesis, plays a pivotal role in integrating newly formed neurons into existing neural circuits. Nutritional interventions that promote synaptic plasticity may enhance neurogenesis. Additionally, chronic neuroinflammation can impair synaptic plasticity, while nutritional interventions with anti-inflammatory properties may alleviate neuroinflammation and facilitate synaptic plasticity, that might mediate beneficial effects on cognition. Pro-inflammatory circumstances might also lead to aberrant mitochondrial functioning, thereby leading to oxidative stress, detrimental to synaptic plasticity.

Neuroinflammation

Neuroinflammation is defined as an inflammatory response within the CNS, in which the key players are microglia and astrocytes, endothelial cells and peripherally derived immune cells. This inflammation is mediated by induction of cyto- and chemokines, reactive oxygen species (ROS), and secondary messengers [178]. In addition, peripheral inflammation can lead to the release of inflammatory molecules that can cross the blood-brain barrier (BBB) and contribute to neuroinflammation [178]. ES can have a lasting impact on both peripheral and central immune systems. For instance, there is both clinical [179] and pre-clinical [180] evidence that ES leads to increased circulating levels of pro-inflammatory cytokines and pre-clinical evidence for a similar increase also in the brain later in life [181]. In addition, ES has been

shown to modulate microglia directly after the stress paradigm [182], as well as lastingly into adulthood [9, 23], possibly exerting effects on key developmental processes like synaptic pruning [183].

There are several pathways via which nutrients can influence neuroinflammation: a more direct impact, with nutrient-derived messengers crossing the BBB and thereby exerting their effects directly in the CNS or a more indirect pathway, with nutrients modulating peripheral inflammation, that can in turn exert its effect on the central immune system.

One group of interventions that has shown to be effective in reducing ES-induced (neuro)inflammation, are the probiotics. *Bifidobacteria* [83] were potent in reducing ES-induced peripheral [83], neuro- [81] and gut inflammation [87] potentially contributing to the modulatory effects on some of the behavioral domains. Supplementation with *Lactobacilli* led to a reverse in the ES-induced increase in pro-inflammatory cytokines and decrease in anti-inflammatory cytokines [80]. Interestingly, strains from these genera often converge at the functional level in terms of production of short-chain fatty acids (SCFAs), such as propionate, acetate and butyrate that may exert anti-inflammatory effects [184]. Peripherally, SCFAs influence systemic inflammation via inhibiting histone deacetylases, thereby inhibiting Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation [185]. Importantly, SCFAs can cross the BBB via monocarboxylate transporters located on endothelial cells and influence BBB integrity by upregulating the expression of tight junction proteins [186] and thereby potentially exert direct effects on microglia.

Anti-inflammatory capacities are also reported after supplementing with N-3 PUFAs. Indeed, N-3 PUFA derivatives (e.g. oxylipins) are able to directly influence microglia, by modulating their phagocytic capacity, motility and their capacity to produce inflammatory factors [23, 187].

For example, increasing N-3 PUFAs bioavailability which was protective against the ES-induced cognitive decline, also reduced the ES-induced increase in cluster of differentiation (CD)68 expression (a marker for activated microglia) [14]. Interestingly, there is evidence that ES modulates the brain lipidome and oxylipin profile long lastingly and that these profiles depend on early life N-3 PUFA availability in the diet [188]. Another study reported an increased bioavailability of N-3 PUFAs in the frontal cortex after supplementation with fish oil [120, 122]. This increase in bioavailability of N-3 PUFAs could lead to a more anti-inflammatory environment [189] in these brain regions, potentially modulating microglia. Finally, nutritional supplements can exert anti-inflammatory effects via inhibition of NF-κB. For example, supplementing with ferulic acid suppresses hippocampal NF-κB, potentially contributing to a decrease in cytokine expression in the ES-exposed offspring [54].

While it becomes thus clear that several nutrients exert modulatory effects on (neuro)inflammatory processes, the specific pathway via which they exert these effects remains to be understood and are most likely a combination of direct and indirect processes potentially involving for example the gut microbiome [166] and the hypothalamus-pituitary-adrenal (HPA)-axis [190].

Mitochondrial & Oxidative stress

Mitochondria have been receiving increasing attention for their involvement in the stress response [191]. Energy demands increase during stress due to the "fight or flight" response and allostatic biological systems, both of which rely on adenosine triphosphate (ATP) as an energy source. Mitochondria play a crucial role in meeting this energy demand by increasing cellular energy production, promoting cellular adaptation through signal generation, and undergoing biogenesis [191, 192]. During the production of ATP, ROS and reactive nitrogen species (RNS) are formed. When the production of ROS and RNS exceeds the antioxidant defenses, oxidative stress occurs, leading to damage to cellular components including lipids, proteins and deoxyribonucleic acid (DNA). Clinical studies have addressed the potential involvement of mitochondria in the context of ES. For example, individuals exposed to ES exhibit an increased mitochondrial DNA copy number content in leukocytes [193] and in saliva [194] indicating that this effect might be widespread throughout the body and have its origin in childhood. In addition, there is evidence from preclinical studies that ES (POS in particular) affects mitochondria in the brain. For example, ES-exposed offspring exhibited increased ROS [195], decreased ATP production [195, 196], higher oxidative stress [197] and decreased antioxidant levels [196] and altered mitochondrial gene expression [198] in the hippocampus when compared to controls.

Some of the nutritional interventions might exert their beneficial effects in the context of ES via modulating mitochondria. For example, hydroxytyrosol (a polyphenol) [64], DHA [45] and taurine [117] supplementation in ES offspring all led to an increased mitochondrial metabolism that potentially contributed to cognitive improvement. Polyphenols have the capacity to modulate mitochondria via various pathways. For example, polyphenols have multiple hydroxyl groups within their structure [199] rendering them exceptional in buffering excess ROS in the CNS. Indeed, supplementation of hydroxytyrosol increased mitochondrial function and decreased oxidative stress [64]. Such buffering could for example be mediated by activation of the Nrf2-Keap1-ARE pathway, which has been shown to be increased after polyphenol supplementation which in turn induces the expression of phase II detoxifying enzymes, responsible for reducing endogenous toxic metabolites [65].

In addition to having a direct impact on mitochondria, nutrients might also influence ROS levels via decreasing production of ROS, increasing its breakdown or by mitigating downstream effects of ROS.

For example, supplementing with proanthocyanidins (a polyphenolic compound) [53] reduced ROS in ES offspring. Playing a crucial role in breakdown of ROS are superoxide dismutases (SOD), which inhibit superoxide radicals; and catalase, which inhibit free diffusion of hydrogen peroxide among cells. SOD and catalase were found to be increased after the supplementation of amino acids (specifically: NAC [41] and taurine [117] and diets rich in fatty acids [132] (specifically N-3 PUFAs and MUFAs) in ES rat offspring, related in turn to increased cognitive performance and a reduction in depressive-like symptoms.

Additionally, taurine supplementation has been shown to increase mitochondrial membrane potential, which in turn could lead to increased respiratory chain enzymatic activity. This increases ATP, which supplies for the increased energy demand during stress. This could in turn increase the production of ROS that might be mitigated by the increase that is seen in SOD1 [117].

N-3 PUFAs-induced beneficial effects [41, 45] might modulate production of micelles with scavenger-free radicals, thus reducing the production of ROS [200]. (Semi)vitamins, amino acids and FAs had strong effects in mitigating the downstream effects of ROS. For instance, protein carbonylation (a post-translational modification in proteins exposed to oxidative stress) was found to be reduced in ES-exposed offspring supplemented with folic acid [41]. Another downstream effect of ROS is lipid peroxidation, which leads to an increase in malondialdehyde (MDA), which can react with DNA and proteins. The supplementation with Vitamin E [104], Folic acid [41] and Auraptene [63] successfully inhibited the increased lipid peroxidation and thereby the expression of MDA caused by ES. N-3 PUFAs were only partially inhibiting this increase, potentially because N-3 PUFA supplementation could lead to exaggerated sensitivity to lipid peroxidation [201].

The involvement of mitochondrial functioning in the efficacy of nutritional interventions could be dependent on cross-talking pathways. For example, in response to acute stress exposure,

mitochondria respond dynamically to cues from stress-signaling pathways enacted by glucocorticoids [192], to meet increased energy demands [202]. In addition, Myeloperoxidase (MPO) can affect mitochondrial function by oxidizing mitochondrial proteins and lipids [203], which can lead to mitochondrial damage and dysfunction. MPO has been found to be expressed in microglia and has been found to be reduced by PRS [41]. Thus, the decrease found in the study could be potentially related to changes in neuroinflammation which have been reported by other studies after ES exposure.

Finally, pro-caspase 9 has been shown to get activated by mitochondrial cytochrome c (which has been shown to be increased in ES) [204] also linking oxidative stress and mitochondrial functioning to apoptosis.

The intricate interaction between the HPA axis, neuroinflammation, mitochondrial functioning and oxidative stress might be crucial in mechanisms underlying the beneficial effects of the nutritional interventions in the context of ES.

HPA-axis regulation

The HPA axis is the neuroendocrine stress axis orchestrating the release of the stress hormones such as glucocorticoids. Upon stress, corticotropin-releasing factor is released from the hypothalamus, which leads to adrenocorticotropic hormone release from the pituitary which stimulates the production of glucocorticoids (cortisol in human and corticosterone in rodents) in the adrenal gland. Under basal levels of glucocorticoids, negative feedback is mediated mainly through the mineralocorticoid receptors (MR) in the hippocampus. The less sensitive glucocorticoid receptor (GR) comes into play in the hippocampus, hypothalamus, and pituitary gland under stress and therefore high glucocorticoid concentrations. The balance in these MR- and GR-mediated effects on the stress system is of crucial importance to the functioning the of HPA axis. Evidence from clinical and preclinical studies suggests that disruption of the HPA axis and changes in GR and MR balance are involved in the ES-induced behavioral alterations and the increased risk to develop psychopathologies later in life [162, 205–208].

HPA-axis regulation is one of the most addressed as a potential mechanism through which nutritional intervention could work. Nutritional supplementations with ferulic acid [54] hydroxytyrosol [64], *Lactobacilli* and *Bifidobacteria* [75, 79, 80, 82, 84, 85], micronutrients [15] and "comfort foods" (e.g. HFD [137], a high fat high sugar diet [134], or highly palatable food [136]) have all been proposed to ameliorate the ES-induced effects at least partly via modulation of the HPA axis (i.e. reduction of ES-induced corticosterone and modulation of GR expression).

Additionally, as already discussed above, none of the discussed mechanisms is acting in solo but rather through well-orchestrated interactions. There are indications that the HPA axis can be activated by the microbiome as a result of increased permeability of the intestinal barrier and a microbiota-driven proinflammatory state [209]. Moreover, glucocorticoids act on almost all types of immune cells and perform salient immunosuppressive and anti-inflammatory functions through genomic and non-genomic mechanisms [190].

Monoamine regulation

Monoamines are neurotransmitters that are derived from aromatic amino acids and include for example serotonin, dopamine (DA), and norepinephrine (NE) [210]. The serotonergic system has an important role in development, functioning in regulation of neurogenesis, synaptogenesis, neural connectivity, myelination and synaptic remodeling [211]. There are four major dopaminergic pathways, the mesolimbic and the mesocortical (important for reward-related cognition and executive functions [212]), the nigrostriatal (known for its role in motor function [213]) and the tuberoinfundibular pathway (for the regulation of prolactin secretion [214]). The dopaminergic system undergoes essential remodeling and maturation early in life. Perturbation in its signaling early in life has been associated with several neuropsychiatric disorders [215, 216]. For example, ES has been shown to lead to an enhanced adult 5-HT2-mediated function [217, 218] and elevated dopaminergic function [219]. Lastly, NE is a neurotransmitter that plays an important role in the body's "fight or flight" response to stress. There is evidence that NE is affected by ES [75, 87, 91].

5-HT, DA and NE are considered key neurotransmitters that participate in the brain-gut axis. Indeed, supplementing with the probiotics consisting of *Lactobacilli* [75, 79] modulated the ES-induced alterations in the serotonergic system. SCFA-producing bacteria in the gut influence the expression of tryptophan hydroxylase and thereby 5-HT synthesis and release [220], potentially affecting 5-HT levels in the brain [75, 79].

Similarly, supplementation with *Lactobacillus* [79] and *Bifidobacterium* [87] modulated DA in the prefrontal cortex [79] and in the gut [87] as well as NA [87].

Several authors found a beneficial effect of supplementing "comfort foods" on behavioral deficits found in ES [133–136, 138]. It could be that these comfort foods have influence via the ventral tegmental area-nucleus accumbens reward network, emphasizing the monoaminergic system to be involved as well [221].

Gut Microbiome

The gut and the brain are in constant bidirectional communication. With the emergence of the gut microbiome in modulating host behavior via various routes (metabolites, neuronal, endocrine, immune system), the microbiota-gut-brain axis has become a key player in the research of different psychopathologies. Furthermore, the gut microbiome has a functional role in the development of the brain and can determine host behavior. Illustrated by the use of germ-free mice, it was shown that the microbiome is necessary to induce at least some of the neuropsychiatric effects observed after maternal separation [68]. There is also a bidirectional relationship between stress and the gut microbiome, and stress exposures often leaves an impact on the gut microbiome. Multiple studies have thus shown a link between ES and subsequent changes in gut microbiota compositional configurations that persist into adulthood [67, 83]. However, the time of initial arise and the trajectory of microbiota perturbations are unclear. Furthermore, how these changes contribute to neurodevelopmental changes leading to psychiatric disorders remains to be elucidated, but there are substantial overlaps between the assembly of the gut microbiome postnatally and important neurodevelopmental time windows [222, 223]. A growing body of research has shown that nutritional interventions including PUFAs, polyphenols, and HFDs modulate both the microbiome and brain. However, it is unclear how much diet-induced changes in microbiota contributes to the effects on the brain per se [224]. Indeed, there are a number of important pathways by which the gut microbiota can modulate behavior.

The most classical way of interaction between the gut microbiota and the host is via the metabolites the bacteria produce. The most commonly investigated metabolites are SCFA, the product of host-indigestible dietary fibers fermented by bacteria.

SCFA have been shown to have anti-inflammatory effects [225], epigenetic modulation capabilities and affect hormone secretion via G-protein coupled receptor binding [16]. It was shown that ES can affect the production of SCFA measured directly [122] or predicted based on the relative abundance of SCFA-producing bacteria [57]. Diet plays a major role in sculpting the composition and function of the gut microbiota such that these processes might be modifiable by the interventions under consideration here. For example, supplementation with polyphenols [57], increased propionate, while a diet containing 7% of fish oil [122]

increased SCFA producers in ES-exposed animals. This shows that the effects induced by the intervention could either be due to the direct effects of the polyphenols or indirectly by modifying the configuration of the gut microbiota.

Importantly, in the last decade, a paradigm shift occurred in the field of the microbiota-gut-brain axis highlighting the need to move towards functional approaches for the assessment of gut microbes that goes beyond just compositional alterations [226]. In addition to the direct assessment of microbial metabolites discussed above, the genomic content of microbes can be analyzed and used to predict their metabolic capabilities of the gut microbiota in health and disease, as well as for specific bacterial strains. This concept evolved the field beyond compositional analysis into a functional analysis of the metabolic output of the gut population [227] with alterations in microbial metabolic pathways identified in stress-related disorders [228, 229]. These microbial metabolites include SCFA, but also monoamines and neurotransmitters including serotonin, DA, GABA and glutamate [228].

As discussed above, one of the key microbial pathways affecting host behavior is via bacteria-produced metabolites. One of the types of metabolites produced by the gut microbiome are monoamines and other neurotransmitters, most notably serotonin. The majority of serotonin in the body is produced and used in the gut from its precursor tryptophan. The concentration of serotonin can be modulated by the gut microbiome in multiple ways [230], most notably shown by altered concentration of serotonin and its metabolites in the hippocampus of germ-free animals [231]. This is most likely mediated via a humoral route based on increased availability of its precursor tryptophan in the plasma [231]. ES has been shown to affect central serotonin levels, which can be alleviated by the use of probiotics [75, 79]. The gut has multiple interactions with other involved pathways as mentioned before. An example is the influence of the gut on neurotransmitters and vice versa is the abovementioned monoaminergic system [76, 87, 232], where reduced DA and adrenaline in the gut, which led to a decrease in anxiety-like behavior, indicating probably a link of these neurotransmitters with behavior. Another important neurotransmitter produced by a wide range of *Bifidobacterium* and *Lactobacillus* strains, is GABA, the major inhibitory neurotransmitter of the CNS. Modulation of GABAergic neurotransmission, including receptor expression, by probiotics following ES-induced depression has been shown [72, 84]. While many studies provide evidence that the gut microbiota is engaged with in reciprocal crosstalk with the HPA-axis, the mechanism behind this interaction remains to be elucidated [71].

It has been proposed that levels of GABA and its receptors are one of the mechanisms by which the microbiome might modify HPA axis function by inhibiting the activation of CRH-neurons [233]. Changes in gut microbiota due to insults such as stress can affect the gut barrier integrity. This can have secondary implication on the host immune system due to potential increased translocation of bacteria and their metabolites [234]. This has been clearly demonstrated in multiple studies discussed here showing an increased immune activation in ES animals which is reversible by probiotics [80, 81, 87, 91]. Studies using similar probiotic cocktails [82, 235, 236] as discussed in this review link these changes to recovery of gut-barrier function, thus preventing inflammation via translocation across the barrier [237]. Beyond that, the precise mechanism resulting in a reduction of inflammation remains to be described.

CONCLUSION

In this comprehensive review, we set out to unravel the efficacy of nutritional strategies in mitigating effects of ES on later-life behavioral outcomes across clinical- and preclinical literature. From the included human studies, five studies were observational and only three studies were clinical trials. Out of these three clinical trials, only one study demonstrates an effect of a combined diet and behavioral program, making it impossible to disentangle the effects. The low number of clinical studies and the heterogeneous study designs significantly constrain our ability to draw conclusions regarding the effects of dietary interventions to modulate the detrimental effects of ES in human subjects and stresses the need to perform randomized clinical trials in humans.

However, in the included rodent studies, in 112 out of the 123 cases the ES induced later-life behavior could be mitigated by nutritional supplementations, underscoring the potential for such nutritional strategies. Indeed, despite large heterogeneity in the studies (i.e. the differences in timing and nature of the stressors, interventions and outcome measures), most of the interventions were able to modulate the ES-induced behaviors. However, an effect of (publication) bias cannot be ruled out and was not further assessed by this review. Notably, even though we included all the literature addressing the effects of ES and nutritional interventions in both males and females, the included studies mostly failed to test whether the efficacy of the nutritional supplementation might be sex-specific. The lack of addressing the impact of sex is not specific to the studies included in this review. In fact, even though sex and gender influence the prevalence, manifestation and progression of, as well as the treatment response to various diseases, progress in biomedical research remains slow in this domain. Indeed, most studies do not incorporate sex as a discovery variable, and thus, in only a small proportion of studies, sex is used as a predictor variable or a between-subject variable to analyse for main and interaction effects rather than as a covariate [238, 239]. Because of the key sex differences in the effect of ES [240–243] and nutrition [244] and general metabolisms [245] and disease prevalence and presentation [238, 239], it is key for future studies to consider both sexes when assessing efficacy of nutritional interventions in ES research and to include sex as a discovery variable.

Although mainly based on preclinical evidence and observational studies in humans, this review highlights the great potential of nutritional strategies for mental health of vulnerable population exposed to ES. Thus, nutrition is a very attractive element to target and to unlock its true potential and to develop an evidence-based tool for the prevention and treatment there are several barriers that we need to still overcome. In rodent studies, currently, the heterogeneity in the measured outcomes (different tasks), outcome age, and the stress models employed poses challenges to drawing strong conclusions and to pinpoint the specifics of the nutritional strategy. More studies are needed to determine which nutrients should be used in nutrition-based interventions (which exact nutrients/combinations/diets, dosages) and considering that vulnerability varies across the lifespan and between individuals, the optimal time window of opportunity (i.e. when we can best apply specific nutritional strategies for either prevention or intervention) remains to be addressed. Next to the points mentioned above, considering the very limited number of human studies, it will be key to increase clinical research in this area using randomized controlled trials and focusing on collecting prospective longitudinal data, including all appropriate control groups.

Finally, it will be key to further our insights into the biological mechanisms mediating the beneficial effect of nutrition on the brain. Through this review, the incredible complexity of these mechanisms becomes evident. While the studies presented in this review have made use of preclinical in vivo studies to explore the mechanisms underlying the biological mechanisms, an interesting avenue potentially aiding to gain further insight into the processes involved the effects of nutritional strategies in the context of ES and their relevance in the context of human biology, are humanised in vitro models. There are indeed first attempts to use cerebral organoids for exploring the effects of glucocorticoids on early human brain development, mimicking early-life stress

exposures [246] as well as the use of human hippocampal progenitor cells to test the effects of specific nutrients [247, 248] and of how fatty acid exposure interacts with glucocorticoids [249] on the neurogenic process. There is a wide plethora of various nutrients, each with their broad impact on the brain, their dual nature of building blocks, energy source and signalling molecules, the intricate crosstalk between the biochemical cycles they are involved in and the often converging pathways they act upon rendering the unravelling of this complexity the next challenge to move the field forward.

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AUTHOR CONTRIBUTIONS

AK, conceptualized and supervised this study and reviewed and edited the manuscript. Literature search was performed and screened by JG and HGJ with support from GLB. LW contributed to the mechanisms related to microbiome. JG and HGJ analyzed the included papers, prepared Figs 2 and 3 and the tables and wrote the manuscript. KJOR prepared Fig. 1. AK, JG, HGJ, LW, SRdR, JBvG, GC, and JFC contributed to critically read and edit the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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