

## Review Article

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# Perinatal diet and offspring anxiety: A scoping review

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**Abstract:** Health behaviors during pregnancy have an impact on the developing offspring. Dietary factors play a role in the development of mental illness: however, less is known about the impact of diet factors during pre-conception, gestation, and lactation on anxiety levels in offspring. This scoping review sought to systematically map the available research involving human and animal subjects to identify nutritional interventions which may have a harmful or protective effect, as well as identify gaps. Studies investigating an association between any perinatal diet pattern or diet constituent and offspring anxiety were included. The number of studies reporting an association with increased or decreased levels of anxiety were counted and presented in figures. A total of 55,914 results were identified as part of a larger scoping review, and 120 articles met the criteria for inclusion. A greater intake of phytochemicals and vitamins were associated with decreased offspring anxiety whereas maternal caloric restriction, protein restriction, reduced omega-3 consumption, and exposure to a high fat diet were associated with higher levels of offspring anxiety. Results were limited by a very large proportion of animal studies. High quality intervention studies involving human subjects are warranted to elucidate the precise dietary factors or constituents that modulate the risk of anxiety in offspring.

**Keywords:** nutrition, perinatal, anxiety, mental health, psychiatry

## 1 Introduction

A developing offspring is extremely sensitive to their environment which can be impacted by a range of intrauterine exposures and interventions [1]. Health behaviors during pregnancy, such as alcohol consumption and smoking, have long been studied for their adverse effects on offspring development [2]. Emerging evidence shows that many components of maternal diet are critical in shaping aspects of the offspring's health including the microbiome and neonatal immune system [2]. Although most women are aware that a healthy diet is important during pregnancy, women may lack knowledge, skills, or resources needed to improve their diet [3]. Moreover, healthy eating while pregnant may be a challenge as some women experience food aversions, cravings, nausea, vomiting, or heartburn [3,4]. Evidence from animal studies suggest that maternal diet can change the development of the brain and endocrine system of the developing offspring as well as have a long-term impact on offspring behavior [5]. A balanced, nutritious diet during pregnancy is crucial to maintain the extra demands on the mother's body [6]. It is established that adequate nutrient intake is needed to support the growth of the fetus and maintain healthy birth weight [6]. There is emerging interest in a possible role of dietary factors on the risk of mental health disorders in offspring as well.

Numerous animal models have been employed to understand the intricate biological mechanisms of developmental programming in maternal exposures and its impact on offspring anxiety [7]. While data from primate studies may be more generalizable to humans, the majority of the research in this area has involved rodent models, in part due to the reduced amount of time for gestation and maturation [7]. Established methods of assessing anxiety behaviors in animal models have been validated. These models have provided insight to the brain and behavioral mechanisms that may be associated with the etiology and physiopathology of anxiety disorders; yet limitations exist with respect to understanding how these findings translate to humans and the emotional experience of anxiety symptoms [8].

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Despite limitations, animal models play an important role in understanding the mechanisms contributing to the development of offspring anxiety [9].

Anxiety disorders are common; the lifetime prevalence of any anxiety disorder was reported to be 31.2% in a national comorbidities study [10]. Established risk factors include trauma, stress, genetics, comorbidities, and the use of alcohol and drugs [10]. Anxiety disorders result in a high degree of personal distress, disability, and reduced quality of life among those affected, as well as a societal cost resulting from increased primary care and specialist healthcare service utilization [10–12]. The therapeutic approaches commonly provided include psychotherapy and psychopharmacology; [13] however, a substantial number of patients do not find these treatments tolerable, accessible, or effective in relieving anxiety symptoms [14]. To date, strategies for preventing anxiety disorders have consisted primarily of psychosocial interventions directed at children or adolescents of elevated risk of sub-syndromal presentations; however, these require availability of programs and adequate screening to identify individuals at increased risk [15]. Given the limitations in the currently available approaches to treatment and prevention, adjunctive strategies are needed.

The evidence supporting the role of dietary factors in the development and progression of mental illnesses is emerging [16]. Less is known about the impact of perinatal diet factors on anxiety levels in the offspring. A limited amount of synthesis research has identified evidence on particular nutrients or dietary patterns but a systematic effort to capture the range of research that has been undertaken on this topic has not been undertaken [17]. Given the need for additional prevention and treatment strategies, the emerging evidence about nutrition and mental health and the established relationship between perinatal exposures and other offspring health outcomes, research into perinatal diet and offspring anxiety outcomes is warranted. The objective of the present scoping review was to systematically map out the current body of literature on perinatal diet and offspring anxiety to identify nutritional interventions which may be effective for the prevention of offspring anxiety symptoms as well as identify gaps and opportunities for further research.

## 2 Methods

The framework for scoping reviews presented by Arksey and O'Malley provided the methodological approach for this review [18]. A previous, large scoping review was

undertaken to assess the relationship between dietary patterns, constituents, and foods in humans and animals, and the development and/or progression of anxiety disorders [19]. This review examined studies involving assessment or administration of a dietary factor and subsequent measurement of anxiety symptoms within subjects [19]. Studies that assessed maternal diet exposure and offspring anxiety levels were excluded from the larger scoping review and have been included in the present review for separate analysis.

The scoping review was completed using an extensive search strategy, and developed *a priori* by an experienced medical librarian (refer Supplemental File 1 in ref. [19] for the complete search strategy). The databases Ovid MEDLINE and Embase Classic + Embase were searched using controlled vocabulary and keywords. The searches were not limited by language or date, but editorials were removed. The searches were performed on March 25th, 2020. The program Abstrackr was used to facilitate title and abstract screening. Screening of abstracts was completed in duplicate, and disagreement was resolved by consensus. Abstracts were screened manually until Abstrackr's artificial intelligence predicted that all remaining studies were unlikely to be relevant. Testing of this method has found the likelihood of excluding useful studies to be very low [20–22].

The present review is an analysis of the human and animal studies related to perinatal diet exposure. Studies were eligible to be included in the present review if they assessed the relationship between perinatal diet and levels of anxiety in the offspring. The perinatal period was defined to include pre-conception, gestation, lactation, and early infancy. Studies were eligible if they assessed anxiety disorders or symptoms using a validated method such as a questionnaire, clinician assessment, or an established method of assessing anxiety severity in animals [23]. Dietary factors of relevance included dietary patterns, macronutrients, micronutrients, individual foods, and natural health products containing nutrients present in the typical North American diet. Studies were ineligible for inclusion if they assessed the use of herbal medicines (apart from those generally used for culinary purposes) or constituents not typically present in the North American diet in appreciable quantities. Review articles, opinion papers, letters, and systematic reviews were all excluded, as well as non-English language papers or inaccessible papers on occasions where the abstract contained insufficient information for data extraction. Eligible study types included observational or clinical studies involving humans or animals as well as meta-analyses. Review articles, opinions, and systematic reviews were excluded.

In addition to reviewing the results identified by the previous scoping review, a grey literature search was also undertaken. This involved the search of two databases for systematic reviews on related topics and review of the included studies within each review. Any studies that met the criteria for the present review but had not been previously identified were included. A piloted extraction template was used for data extraction, in duplicate. Studies were sorted based on similar diet interventions and whether the study increased or decreased the dietary factor of interest. Studies reporting an increase or decrease in offspring anxiety were counted and presented in figures.

### 3 Results

The larger scoping review search identified 55,914 unique results (Figure 1). Eight additional articles were identified through the grey literature search. Manual screening of the titles and abstracts was completed for 13,286 results.

The remaining results ( $n = 42,628$ ) were screened by Abstrackr's artificial intelligence feature.

After title and abstract screening for the present sub-analysis on perinatal studies, six human studies were included. Following full text screening, three met criteria for inclusion, two observational studies and one experimental study. After title and abstract screening, 169 animal studies met criteria. Following full text screening, 120 met criteria for inclusion in the analysis. Of these, one was a meta-analysis. The vast majority of the studies used rodent models ( $n = 117$ , 98%) with the remaining 3 studies involving human participants. A list of all studies included is available in Supplemental File 1.

#### 3.1 Human studies

There is a very small body of literature that exists in the form of human experimental ( $n = 1$ ) and observational ( $n = 2$ ) studies that sought to modify or observe perinatal

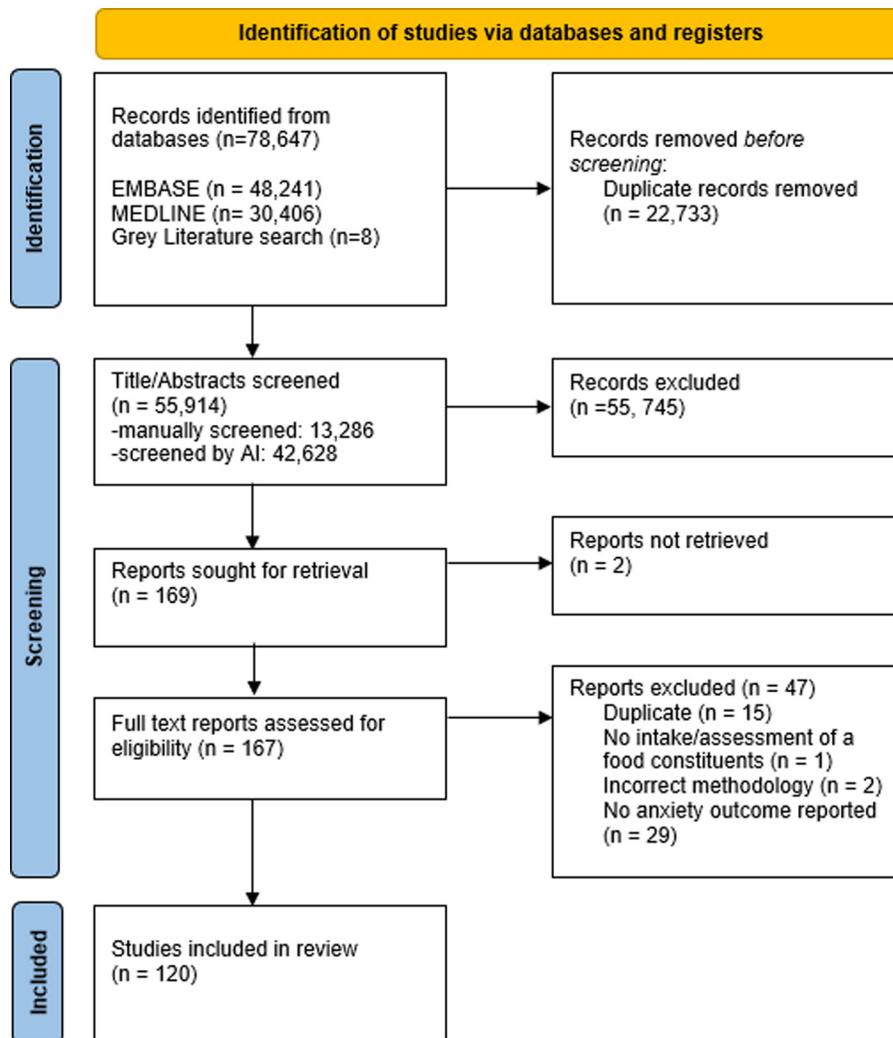


Figure 1: PRISMA flow diagram.

intake of dietary constituents and study anxiety outcomes in offspring. One experimental study aimed to assess the effects of perinatal food supplementation on school-aged children's behavior [24]. Mothers from a malnourished population were recruited and given varying amounts of food supplementation (low or high) pre- and postnatally and their offspring (78 boys and 60 girls) were observed [24]. The high supplementation participants were given a mixture of vegetable protein, dry skim milk, and sugar, whereas the low supplementation participants were given a calorie-only supplement of only sugar and flavoring. One cup (180 mL) of the high supplement contained 11.5 g of protein and 163 calories. One cup of the low calorie-only supplement contained 59 calories. Both groups received supplements which contained essential vitamins and minerals [25]. Children were then put into same-sex, six-person groups and observed over a 2 day period [25]. Children took part in approximately nine different situations including both free play activities (e.g., clay construction and painting a mural) and structured situations that would mimic the type of challenges or stresses encountered routinely in everyday life [25]. Children born to highly supplemented mothers demonstrated superiority on responses to moderately stressful situations when compared to children born to mothers in the low supplementation group [24]. Moreover, when engaging with peers, children of highly supplemented mothers showed more positive affect and were less anxious [24].

Of the observational studies reporting on the relationship between dietary exposure and anxiety outcomes, one retrospective study enrolled 77 adults who experienced protein malnutrition within their first year of life followed by good health and nutrition for up to 12 years [26]. When compared to healthy controls, early-life malnourished participants experienced more anxiety and a lower sense of efficacy and competence as assessed by the NEO-PI-R, a 240 item self-report questionnaire [26]. Another retrospective observational study assessed the effects of maternal caffeine consumption, in the form of coffee and tea, between 15 and 30 weeks of gestation on offspring anxiety [27]. Women were interviewed twice during pregnancy (15–30 weeks of gestation) and twice following delivery (when the child was 6–18 months of age). Measured covariates included maternal age at birth, maternal pre-pregnancy body mass index, maternal smoking during pregnancy, maternal socioeconomic status, marital status, birth year of offspring, and sex of offspring [27]. 11 years later, data were collected in the form of the Strengths and Difficulties questionnaire by the children, parents, and their teachers. [27] High maternal caffeine consumption (more than 8 cups/day) at 15 weeks of gestations resulted in increased severity of

anxiety disorders in 11-year-old children [27]. These findings support the hypothesis that high caffeine consumption during pregnancy may affect the fetal brain and program for behavioral disorders later in life; however, confounding factors such as genetics, dietary intake and/or socioeconomic status may be accountable for the observed associations [27]. While these human studies suggest that there may be an association between perinatal diet exposure and offspring anxiety levels, the quantity of data is very limited; as such an exploration of other forms of evidence on this topic is warranted.

### 3.2 Animal studies

Numerous studies included in this review assessed the impact of exposure to different dietary patterns and constituents on offspring anxiety levels in animal models (Figure 2). In animal studies, anxiety-like behavior is assessed by measuring the subject's response to a novel and potentially threatening environment using batteries of tests. Among them, the elevated plus maze test is the most common and simple method to assess anxiety in rodents [23]. Other tests included the light–dark box, social interaction test, the open field test, and the novelty suppressed feeding test [23,28]. Figures 3 and 4 present the number of animal studies showing an association between changes in a dietary variable and anxiety outcomes.

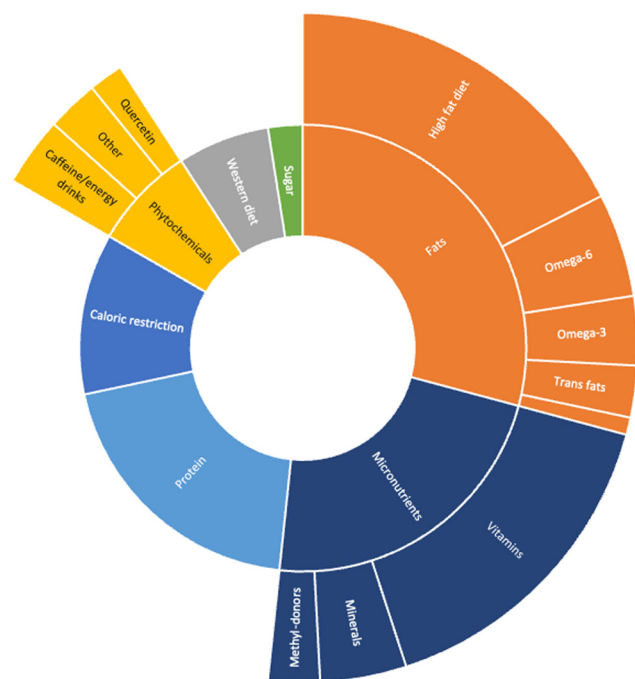


Figure 2: Distribution of included animal studies by intervention.

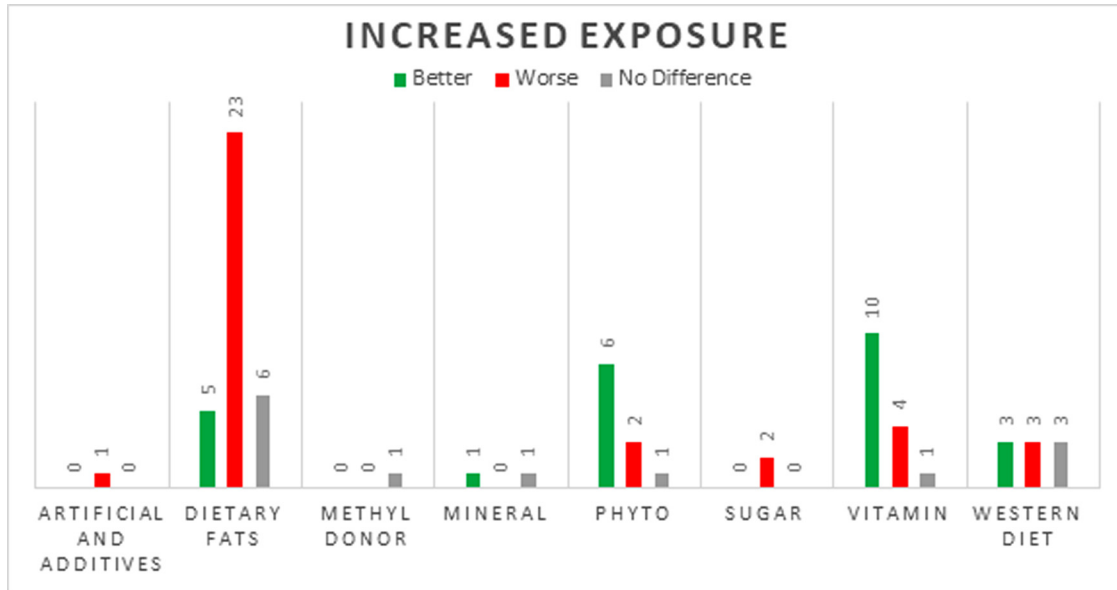


Figure 3: Change in anxiety levels in animals in response to an increase in exposure to dietary factor.

A 2016 meta-analysis included 46 animal studies that measured the effects of caloric restriction, protein restriction, and overfeeding around the period of gestation [29]. Despite the high heterogeneity among studies, the results did not indicate a difference in anxiety symptoms within offspring [29].

### 3.2.1 Dietary fats

A typical rodent diet contains about 10% fat, while diets containing 45–60% fat are considered “high-fat” [30]. Numerous animal studies have investigated the effects of increased intake of fat on rodent models of anxiety [31–47]. Many animal studies ( $n = 15, 68\%$ ) have reported

an increase in anxiety behaviors in response to consumption of a high fat diet [37–51]. Opposite effects were seen when levels of omega-3 and omega-6 fatty acids were manipulated. An increase in omega-6 primarily worsened anxiety ( $n = 5, 71\%$ ) [52–56], whereas a decreased exposure of omega-3, worsened anxiety ( $n = 3, 100\%$ ) [57–59]. A smaller number have reported a negative effect from diets high in trans-fats ( $n = 2, 67\%$ ) [47,60].

### 3.2.2 Methyl-donors, minerals, and vitamins

A very small body of evidence ( $n = 3$ ) assessed the impact of dietary factors involved in methylation on anxiety with

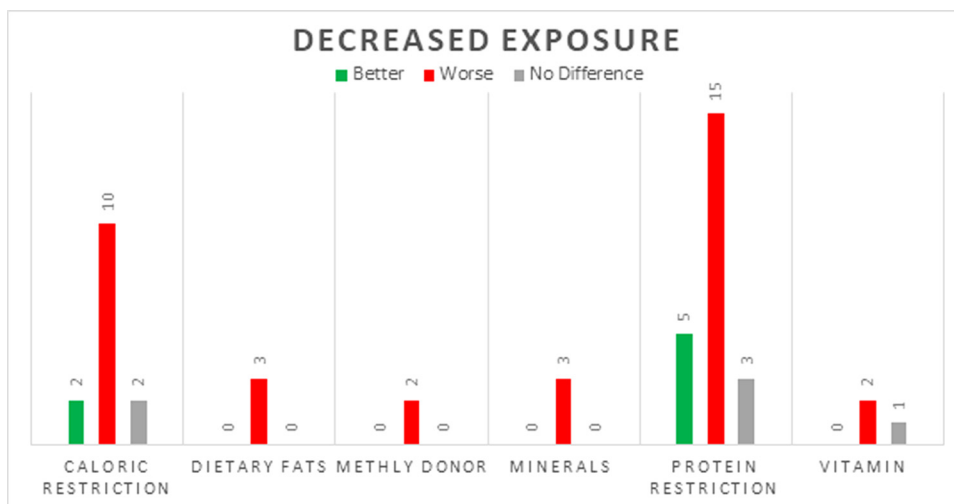


Figure 4: Change in anxiety levels in animals in response to a decrease in exposure to dietary factor.



67% showing an increase in anxiety when rodents were fed a diet depleted in methyl donors including choline, folate, and methionine [61–63]. One study that increased daily choline intake to 1 g found no difference in the anxiety symptoms [61].

The minerals that have been assessed for an impact on offspring anxiety symptoms most frequently are zinc, magnesium, iron, and selenium. Three studies (60%) suggest that when these minerals are decreased or eliminated from the maternal diet, there is an increase in offspring anxiety behavior [64–66]. A single study examining the impact of increased zinc reported no difference in the anxiety symptoms [67]. Only one study looked at the impact of selenium and suggested an anti-anxiety effect from supplementing with this nutrient [68].

A large number of animal studies have investigated the effects of vitamins B, C, D, E, choline, and folic acid with primarily beneficial effect on offspring anxiety symptoms [61,69–84]. Among the studies that increased vitamin exposure, two thirds ( $n = 10$ , 67%) of the studies were associated with less anxiety symptoms [69–76,84], while one quarter showed an increased anxiety ( $n = 4$ , 27%) [61,78–80], and only one study reported no difference [77]. Of these studies, a diverse range of animal models were used. One involved the administration of choline to a mouse model of autism and found that high choline intake ( $36 \text{ mmol kg}^{-1}$ ) notably reduced anxiety behavior [71]. Another study evaluated a wide range of perinatal vitamin D3 exposure; both deficiency and excess supplementation resulted in higher levels of anxiety during the juvenile period, when compared to adequate supplementation [75]. The remaining four studies decreased vitamin exposure and reported increased levels of anxiety [75,81–83].

### 3.3 Protein restriction

A large number of studies ( $n = 20$ ) investigated the effects of different levels of dietary protein on anxiety symptoms [79,85–103]. More than two thirds ( $n = 14$ , 70%) of animal studies assessing the impact of protein malnutrition reported a worsening of anxiety symptoms [79,85,90–101]. Five studies (23%) found that reducing protein decreased anxiety symptoms [86,87,104–106], and 2 (9%) found no difference [88,89]. One study reported mixed findings when mice were fed a low protein diet prenatally and a high fat diet postnatally; naturally conceived mice showed a modest increase in

anxiety, whereas *in vitro* fertilized C57B1/6J mice showed a decrease in anxiety behavior [103].

## 3.4 Caloric restriction

Many animal studies ( $n = 14$ ) have investigated the effects of decreased intake of calories on rodent models of anxiety [23,29,88,107–117]. Ten studies (71%) reported an increase in anxiety behaviors in response to consumption of less calories, [23,109–117] 2 (14%) showed a decrease in anxiety [107,108] and 2 (14%) showed no difference [29,88]. One meta-analysis, using different inclusion criteria compared with the present review, combined the results of 55 studies in which researchers restricted both calories and proteins and found that there was no difference in the anxiety symptoms [29]. The degree of caloric restriction varied widely with most studies restricting calories by 25–80%. Two studies that found an improvement in anxiety had a caloric reduction of 25–30%, [107,108] while all of the studies that restricted calories by more than 50% reported increased anxiety symptoms [23,109–115].

### 3.4.1 Phytochemicals

The results of the studies related to phytochemicals were largely positive. One study looked at the effect of green tea and found that administration of higher doses ( $20\text{--}50 \text{ g L}^{-1}$ ) resulted in an anxiolytic effect [118]. Anti-anxiety effects have also been reported following administration of fruit juice ( $n = 1$ ) and quercetin ( $n = 2$ ) [119–121]. A small number of studies ( $n = 3$ ) have explored the effects of caffeine on anxiety symptoms in rodents; one reported an increase in anxiety with a higher intake of maternal caffeine ( $n = 1$ , 33%) [122].

### 3.4.2 Western diet

The “Western” diet typically includes higher intake of sugar, protein, and fat, and low intake of fruit, grains, and vegetables. In many studies, the diet was compared to a chow diet, that was composed of agricultural by-products, which included ground wheat, oats, soybean, a protein source, and a vegetable oil. The results of the studies assessing the impact of a Western diet on

offspring anxiety symptoms are not consistent in their findings. Out of the eight studies that studied the effects of perinatal exposure to the Western diet, three reported benefit, [123–125] three reported a worsening in anxiety, [126–128] and two showed no difference [127,129].

### 3.4.3 Sugar

A small body of literature ( $n = 3$ , 67%) suggests a possible connection between increased sugar intake and worsened offspring anxiety symptoms [130–132]. The sugars and sweeteners that were assessed for an impact on anxiety symptoms included sucrose, fructose, and aspartame. Of the three studies, two found worsened anxiety and the remaining one reported mixed results; consumption of a high fructose diet showed an overall increase in anxiety in juvenile rats whereas it showed an overall decrease in adults [130].

### 3.4.4 Microbiome

A very small number of studies ( $n = 2$ ) have explored the impact of prebiotic and probiotic supplementation on animal models [133,134]. Both animal trials reported an improvement in anxiety symptoms when mice were supplemented with lactobacillus or a combination of short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides [133,134].

### 3.4.5 Other

There was only one study that looked at the effects of an artificial food colorings and additives (AFCAs) on anxiety outcomes [135]. Prenatal exposure to commonly used AFCA, specifically consisting of erythrosine, was associated with increased levels of offspring anxiety [135].

## 4 Discussion

The findings of the present scoping review suggest that exposure to certain dietary patterns and constituents during the perinatal period may be associated with an increased or decreased risk of the development of anxiety disorders in offspring. Predominantly, an increase in anxiety were seen following caloric restriction, protein restriction, reduced omega-3 consumption, and exposure

to a high fat diet. Conversely, increased consumption of phytochemicals and vitamins were predominantly associated with a decrease in anxiety symptoms. Human studies looked at the impact of protein restriction, maternal caffeine consumption, and undernutrition. In a population experiencing high rates of malnutrition, nutritional supplementation intervention was associated with a decreased risk of anxiety in the offspring [26]. Similarly, Barrett et al. found positive effects from nutritional supplementation on reducing offspring anxiety within an endemically malnourished population [24]. Given the limited scope of research, further human studies are needed.

## 4.1 Anxiety pathophysiology

While the exact pathophysiology of anxiety disorders is not fully understood, many mechanisms have been identified. Dysregulation of several regions of the brain have been implicated in the development of anxiety disorders, particularly structures in the amygdala, which are more active in anxious individuals compared with healthy controls [136]. The prefrontal cortex regulates anxiety through an impact on amygdala activity and has been found to be hypoactive in anxious individuals [137]. With respect to neurochemical balance, several neurotransmitters have been implicated in the pathophysiology of anxiety disorders. Dysregulation of gamma-aminobutyric acid, serotonin, endocannabinoids, and opioid peptides have been identified among anxious individuals [138]. High levels of anxiety symptoms have been associated with altered functioning of the autonomic nervous system and the hypothalamic-pituitary axis [139].

In addition to these established mechanisms, there is building evidence that inflammation may play a role in mental illness [140]. Cytokines are communication molecules released by the immune system which modulate a wide range of body systems, including the nervous system, through pro- or anti-inflammatory effects [141]. In response to chronic inflammatory challenge, this process may contribute to the development of neuropsychiatric symptoms [140]. Animal models that are designed to overexpress pro-inflammatory cytokines develop anxious behavior [142]. Higher levels of these molecules have been reported in humans with higher anxiety and experimental studies involving administration of pro-inflammatory cytokines to healthy individuals have reported an increase in anxiety [143,144]. Another recent area of study in psychiatry is the impact of the microbiome on

mental wellbeing. There is evidence that individuals with anxiety disorders have alterations to their microbiome composition and that negative changes in the microbiome alter the function of the hypothalamus [145]. These contributing pathways may help to understand the processes by which dietary exposures impact the development of psychiatric symptoms in the present data.

## 4.2 Dietary fats

Dietary fats play a role in important physiologic processes; however, consumption of excess amounts and certain types have been associated with harm [146]. Given the high level of dietary fat consumption and maternal obesity in developed nations, these findings have crucial implications for the mental health of future generations [2]. Overall, animal evidence shows that supplemental omega-6 fatty acids worsen anxiety symptoms. Whereas a diet containing adequate omega-3 fatty acids may have anti-anxiety effects [147]. A possible mechanism to explain this response is the role of inflammation in the development of psychiatric disorders, including anxiety [147]. Intake of omega-3 fatty acids has been shown to increase the production of anti-inflammatory cytokines thereby reducing levels of inflammation, whereas omega-6 fatty acids increase levels of inflammatory through cytokine production [140]. There is noteworthy evidence also to suggest that a diet high in total fat and trans-fat may worsen anxiety symptoms in offspring. In contrast, one study assessing the ketogenic diet, a diet that is extremely low in carbohydrates and generally high in fat content, suggested a possible protective effect with respect to offspring anxiety [31]. One possible explanation for these seemingly contradictory results may be the type of fat that was used in the interventions. Many of the studies delivering a high fat diet primarily delivered sources of saturated fat or omega-6 fatty acids with the intention of inducing obesity or metabolic dysregulation [37,42]. While the ketogenic diet study included in this review did not report the type of fat used in the diet, it is hypothesized that the type of fat or the inclusion of other constituents may differ. Similarly, variety in the type of fatty acids used to supplement the high fat diets may be responsible for the variation in the outcomes reported. Many studies failed to report the type of fat administered; more transparent reporting of the type of fat used in future animal studies is needed. Overall, the type of dietary fat may be a significant factor in addition to the quantity of fat consumed to determine impact on offspring anxiety.

## 4.3 Protein restriction

This review identified some evidence of an association between protein restriction and worse offspring anxiety symptoms. This macronutrient, made up of amino acid subunits, is crucial for the growth and production of cellular receptors, transporters, and signaling molecules like neurotransmitters [9]. Nine essential amino acids cannot be produced endogenously and are obtained from the diet. Research in animal models has shown that placental amino acid transport is decreased when protein restriction is limited due to maternal amino acid availability [148]. Given the increased attention to plant-based diets, which may be low in protein, [149] further research on the effects of protein deficiency is warranted. It is noted that a smaller number of animal studies reported an improvement in anxiety symptoms among animals exposed to perinatal protein restriction. Authors of one such study hypothesize that the decreased behavioral inhibition seen in these animal subjects may be due to higher impulsiveness; this trait is a characteristic of attention deficit disorder which is known to be more common among malnourished children [85,106]. As such, hypotheses about the benefits of protein restriction warrant caution.

## 4.4 Caloric restriction

The findings of studies modulating the energy intake of the subject suggest that the relationship between caloric restriction and anxiety may be complex. In some, but not all of the included studies, a reduction of 20–40% of calories along with all necessary nutrients was associated with decreased anxiety. Overall, caloric restriction has the potential to prevent several diseases by utilizing protective functions that increase longevity in animal models [150]. Although the exact mechanism is still unclear, it is thought that mice exposed to moderate caloric restriction have attenuated inflammation, improvement in glucose metabolism, activation of anti-inflammatory pathways, and improvement in hippocampal plasticity [151]. On the other hand, severe maternal restriction of 40% or more can cause metabolic dysfunction, resulting in an increased adiposity and altered HPA axis [43]. It is important to note that there were differences in timing of caloric restriction between the included studies which could have impacted the study outcomes. Preliminary evidence suggests that restriction at different periods of gestation can have a unique effect on offspring anxiety; however, more research is warranted to confirm this hypothesis [93].



The mechanism by which severe caloric restriction may be associated with harm may be related to the established connection between maternal diet and neurological, immunological, and central nervous system development of offspring; disruption of any of these systems due to malnutrition can play a role in the development of mental disorders and fetal development [152]. During pregnancy, maternal malnutrition hinders placentation, impacting placental size, morphology, and blood flow all of which decrease the availability of nutrients to the fetus; this vulnerable fetal nutrition status has been linked to impacts on organogenesis, physical growth, emotional development, and morbidity [153]. The findings of undernutrition are consistent with previously published literature which report early undernutrition can have negative long-lasting impact on children's development and anxiety levels [154].

#### 4.5 Methyl-donors, minerals, and vitamins

Micronutrients like vitamins and minerals play a role in a large number of physiologic processes which may impact mental health. In this review, animal data showed anxiolytic benefits of greater vitamin and mineral intake. Specifically, an increase in choline, vitamin B3, D, and E showed a reduction in anxiety whereas an increase in folic acid worsened anxiety in several studies [78,80,155]. Choline, especially important during pregnancy, has a variety of benefits and has been shown to play a role in the development and treatment of mental health disorders [156]. B vitamins and folic acid contribute to the methylation balance which is hypothesized to be relevant to the pathophysiology of psychiatric illnesses [25]. However, very high doses of folic acid were shown to be harmful to the brain development of the fetus hypothesized by the metabolism of the body. There has been a rise in research focusing on the potential role of vitamin D3 deficiency in mental health [157]. Research to date shows that maternal vitamin D3 deficiency especially in the later stages of gestation can produce behavioral changes in offspring [158]. Due to the increased demands of physiological changes in pregnancy, micronutrient deficiency can be exaggerated and as such can result in offspring complication [159].

#### 4.6 Sugar

A small but relatively consistent body of research suggests an association between higher sugar intake and

higher offspring anxiety. High sugar consumption in adults results in an increase in blood glucose levels; however, a significant compensatory insulin spike may result in reactive hypoglycemia [160]. The hypoglycemic response has been correlated with an acute rise in epinephrine which contributes to neuropsychiatric symptoms including anxiety [160]. Dysregulation of blood sugar levels may also impact offspring mental health. It has been hypothesized that high sugar intake during the perinatal period could predispose offspring to substance use disorders [161]. Research on the effects of sugar intake in the perinatal period is a significant gap and warrants further study.

#### 4.7 Microbiome

Although only a small number of studies looked at the impact of prebiotic and probiotic supplementation on animal models, preliminary evidence suggests an improvement in anxiety symptoms with supplementation of lactobacillus, short-chain Galacto-oligosaccharides, and long-chain Fructo-oligosaccharides [133,134]. Dysbiosis and inflammation of the gut have been associated with several psychiatric illnesses, whereas a modulation of the production of gut peptide involved in the gut-brain axis and neurotransmitter synthesis has been linked to a reduction in the anxiety symptoms [162].

#### 4.8 Strengths and limitations

The present review had a number of strengths. An extensive search strategy was employed. Inclusion criteria were determined *a priori* and screening occurred in duplicate. There were also limitations. The extensive search strategy resulted in a very large number of results which necessitated the use of the software program Abstrackr. While previous investigations suggest a low likelihood of relevant studies being missed, it is possible that this may have occurred, resulting in the omission of relevant studies [20–22]. The broad scope of the research question meant that studies related to a wide range of diet exposures were reviewed. Given the large volume, in depth analysis, including assessment of the quality of individual studies was not undertaken. Consequently, the results of the review may include over-simplifications. Another limitation was the heterogeneity among individual studies assessing the same dietary patterns. Studies termed “high fat” supplemented a variety of dietary fats, including

omega-3, omega-6, lard, and olive oil; however, in many studies a description of the specific fatty acids used was absent. The effect of different dietary fats on health outcomes can vary widely and thus simply describing diets as low or high in fat could result in inconsistent findings.

The most significant limitation of this review, which precludes the application of results to clinical care, is that the vast majority of the studies involved animal subjects rather than humans. Animal models have several advantages for the study of perinatal nutrition such as a short gestation period and lifespan. These trial designs allow for highly controlled manipulation of the diet which is rarely possible in human trials. Further, ethical concerns about exposing pregnant humans to potentially harmful substances or withholding essential nutrients prevent these trials from taking place. However, the applicability of these animal study findings to humans are unclear. Assessment of anxiety symptoms is challenging as animals can not directly communicate with researchers about their emotional state. Instead, several behavioral tests have been designed and validated, allowing researchers to quantify and compare the effects of different environmental exposures on anxiety symptoms in animals [163]. Many of the models measure coping mechanisms, an animal's attempt to avoid harm or distress. Many rely on assessment of exploratory behavior, social behavior, conflict tests, and avoidance tests. These tests have been validated and are considered acceptable ways to measure anxiety in animal research [163]. However, given the differences in physiology and psychology between animals and humans, the findings of animal studies may not be reproducible in humans.

#### 4.9 Implications of findings and conclusion

Overall, there is preliminary evidence that dietary exposures during the perinatal period may impact offspring anxiety levels. At this time, the research on this topic is limited to primarily preclinical research and is highly heterogeneous with respect to the interventions provided to study subjects; as such a systematic review on this topic is not currently warranted. Given the preliminary evidence of a trend toward worse offspring anxiety, there is a need for further research on the effects of maternal dietary fat intake with increased attention to and transparent reporting of the type of fat consumed by study subjects. Further study on the effects of protein and caloric restriction are also warranted with particular attention to the degree of restriction and the timing with the gestational period. Further research is warranted on the effects of

vitamin and mineral intake. Perinatal sugar intake is an understudied area that warrants further investigation.

Overall, future research should involve human subjects in order to understand how the associations observed in animal studies might translate to human health. This could include prospective observational studies of potentially harmful diet patterns or clinical trials assessing diet patterns that are hypothesized to provide benefit. The findings of these future studies could inform public health initiatives in order to play a role in the prevention of anxiety symptoms and disorders and decrease the population burden of these common conditions. While overall the evidence is preliminary and limited, the associations identified in this review are consistent with generally accepted diet recommendations. Despite the need for more research in this area, this review highlights the need to adequate nutrition during the perinatal period.

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**Author contributions:** M.A. conceived the project. Y.S.N., S.M., and M.A. completed data extractions and data analysis and contributed to the manuscript creation. All authors reviewed and approved the final manuscript.

**Conflict of interest:** Authors state no conflict of interest.

**Data availability statement:** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## References

- [1] Coussons-Read ME. Effects of prenatal stress on pregnancy and human development: Mechanisms and pathways. *Obstet Med.* 2013;6(2):52–7.
- [2] O'Neil A, Itsiopoulos C, Skouteris H, Opie RS, McPhie S, Hill B, et al. Preventing mental health problems in offspring by targeting dietary intake of pregnant women. *BMC Med.* 2014;12(1):208.
- [3] Forbes LE, Graham JE, Berglund C, Bell RC. Dietary change during pregnancy and women's reasons for change. *Nutrients.* 2018;10(8):1032.
- [4] Wen LM, Flood VM, Simpson JM, Rissel C, Baur LA. Dietary behaviours during pregnancy: Findings from first-time mothers in southwest Sydney, Australia. *Int J Behav Nutr Phys Act.* 2010;7:13.
- [5] Danielewicz H, Myszczyzyn G, Dębińska A, Myszał A, Boznański A, Hirnle L. Diet in pregnancy—more than food. *Eur J Pediatrics.* 2017;176(12):1573–9.

- [6] Webb R, Ayers S. Cognitive biases in processing infant emotion by women with depression, anxiety and post-traumatic stress disorder in pregnancy or after birth: A systematic review. *Cogn Emot*. 2015;29(7):1278–94.
- [7] Penfold NC, Ozanne SE. Developmental programming by maternal obesity in 2015: Outcomes, mechanisms, and potential interventions. *Horm Behav*. 2015;76:143–52.
- [8] Cryan JF, Sweeney FF. The age of anxiety: Role of animal models of anxiolytic action in drug discovery. *Br J Pharmacol*. 2011;164(4):1129–61.
- [9] DeCapo M, Thompson JR, Dunn G, Sullivan EL. Perinatal nutrition and programmed risk for neuropsychiatric disorders: A focus on animal models. *Biol Psychiatry*. 2019;85(2):122–34.
- [10] Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: Results from the National Comorbidity Survey. *Arch Gen Psychiatry*. 1994;51(1):8–19.
- [11] Pelletier L, O'Donnell S, McRae L, Grenier J. The burden of generalized anxiety disorder in Canada. *Health Promot Chronic Dis Prev Can*. 2017;37(2):54–62.
- [12] Saarni SI, Suvisaari J, Sintonen H, Pirkola S, Koskinen S, Aromaa A, et al. Impact of psychiatric disorders on health-related quality of life: General population survey. *Br J Psychiatry*. 2007;190:326–32.
- [13] Gliatto MF. Generalized anxiety disorder. *Am Fam Physician*. 2000;62(7):1591–600.
- [14] Collins KA, Westra HA, Dozois DJ, Burns DD. Gaps in accessing treatment for anxiety and depression: challenges for the delivery of care. *Clin Psychol Rev*. 2004;24(5):583–616.
- [15] Werner-Seidler A, Spanos S, Calear AL, Perry Y, Torok M, O'Dea B, et al. School-based depression and anxiety prevention programs: An updated systematic review and meta-analysis. *Clin Psychol Rev*. 2021;89:102079.
- [16] Adan RAH, van der Beek EM, Buitelaar JK, Cryan JF, Hebebrand J, Higgs S, et al. Nutritional psychiatry: Towards improving mental health by what you eat. *Eur Neuropsychopharmacol*. 2019;29(12):1321–32.
- [17] Ortiz-Valladares M, Pedraza-Medina R, Pinto-González MF, Muñiz JG, Gonzalez-Perez O, Moy-López NA. Neurobiological approaches of high-fat diet intake in early development and their impact on mood disorders in adulthood: A systematic review. *Neurosci Biobehav Rev*. 2021;129:218–30.
- [18] Arksey H, O'Malley L. Scoping studies: Towards a methodological framework. *Int J Soc Res Methodol*. 2005;8(1):19–32.
- [19] Aucoin M, LaChance L, Naidoo U, Remy D, Shekdar T, Sayar N, et al. Diet and anxiety: A scoping review. *Nutrients*. 2021;13(12):4418.
- [20] Gates A, Johnson C, Hartling L. Technology-assisted title and abstract screening for systematic reviews: A retrospective evaluation of the Abstrackr machine learning tool. *Syst Rev*. 2018;7(1):45.
- [21] Rathbone J, Hoffmann T, Glasziou P. Faster title and abstract screening? Evaluating Abstrackr, a semi-automated online screening program for systematic reviewers. *Syst Rev*. 2015;4:80.
- [22] Gates A, Gates M, Sebastianski M, Guitard S, Elliott SA, Hartling L. The semi-automation of title and abstract screening: A retrospective exploration of ways to leverage Abstrackr's relevance predictions in systematic and rapid reviews. *BMC Med Res Methodol*. 2020;20(1):139.
- [23] Levay EA, Paolini AG, Govic A, Hazi A, Penman J, Kent S. Anxiety-like behaviour in adult rats perinatally exposed to maternal calorie restriction. *Behav Brain Res*. 2008;191(2):164–72.
- [24] Barrett DE, Radke-Yarrow M. Effects of nutritional supplementation on children's responses to novel, frustrating, and competitive situations. *Am J Clin Nutr*. 1985;42(1):102–20.
- [25] Abdolmaleky HM, Smith CL, Faraone SV, Shafa R, Stone W, Glatt SJ, et al. Methyloomics in psychiatry: Modulation of gene-environment interactions may be through DNA methylation. *Am J Med Genet B Neuropsychiatr Genet*. 2004;127b(1):51–9.
- [26] Galler JR, Bryce CP, Zichlin ML, Waber DP, Exner N, Fitzmaurice GM, et al. Malnutrition in the first year of life and personality at age 40. *J Child Psychol Psychiatry*. 2013;54(8):911–9.
- [27] Hvolgaard Mikkelsen S, Obel C, Olsen J, Niclasen J, Bech BH. Maternal caffeine consumption during pregnancy and behavioral disorders in 11-Year-Old offspring: A danish national birth cohort study. *J Pediatr*. 2017;189:120–7.e1.
- [28] Soares JKB, de Melo APR, Medeiros MC, Queiroga RCRC, Bomfim MAD, Santiago ECA, et al. Anxiety behavior is reduced, and physical growth is improved in the progeny of rat dams that consumed lipids from goat milk: An elevated plus maze analysis. *Neurosci Lett*. 2013;552:25–9.
- [29] Besson AA, Lagisz M, Senior AM, Hector KL, Nakagawa S. Effect of maternal diet on offspring coping styles in rodents: a systematic review and meta-analysis. *Biol Rev Camb Philos Soc*. 2016;91(4):1065–80.
- [30] Speakman JR. Use of high-fat diets to study rodent obesity as a model of human obesity. *Int J Obes*. 2019;43(8):1491–2.
- [31] Sussman D, Germann J, Henkelman M. Gestational ketogenic diet programs brain structure and susceptibility to depression & anxiety in the adult mouse offspring. *Brain Behav*. 2015;5(2):e00300.
- [32] Gawlińska K, Gawliński D, Korostyński M, Borczyk M, Frankowska M, Piechota M, et al. Maternal dietary patterns are associated with susceptibility to a depressive-like phenotype in rat offspring. *Dev Cogn Neurosci*. 2021;47:100879.
- [33] Rincel M, Lépinay AL, Delage P, Fioramonti J, Théodorou VS, Layé S, et al. Maternal high-fat diet prevents developmental programming by early-life stress. *Transl Psychiatry*. 2016;6(11):e966.
- [34] Zieba J, Uddin GM, Youngson NA, Karl T, Morris MJ. Long-term behavioural effects of maternal obesity in C57BL/6j mice. *Physiol Behav*. 2019;199:306–13.
- [35] Fernandes C, Grayton H, Poston L, Samuelsson AM, Taylor PD, Collier DA, et al. Prenatal exposure to maternal obesity leads to hyperactivity in offspring. *Mol Psychiatry*. 2012;17(12):1159–60.
- [36] Wise LM, Hernández-Saavedra D, Boas SM, Pan YX, Juraska JM. Perinatal high-fat diet and bisphenol A: Effects on behavior and gene expression in the medial prefrontal cortex. *Dev Neurosci*. 2019;41(1–2):1–16.
- [37] Souto TDS, Nakao FSN, Giriko C, Dias CT, Cheberle A, Lambertucci RH, et al. Lard-rich and canola oil-rich high-fat diets during pregnancy promote rats' offspring neurodevelopmental delay and behavioral disorders. *Physiol Behav*. 2020;213:112722.

- [38] Glendining KA, Fisher LC, Jasoni CL. Maternal high fat diet alters offspring epigenetic regulators, amygdala glutamatergic profile and anxiety. *Psychoneuroendocrinology*. 2018;96:132–41.
- [39] Johnson SA, Javurek AB, Painter MS, Murphy CR, Conard CM, Gant KL, et al. Effects of a maternal high-fat diet on offspring behavioral and metabolic parameters in a rodent model. *J Dev Orig Health Dis*. 2017;8(1):75–88.
- [40] Peleg-Raibstein D, Luca E, Wolfrum C. Maternal high-fat diet in mice programs emotional behavior in adulthood. *Behav Brain Res*. 2012;233(2):398–404.
- [41] Rodríguez JS, Rodríguez-González GL, Reyes-Castro LA, Ibáñez C, Ramírez A, Chavira R, et al. Maternal obesity in the rat programs male offspring exploratory, learning and motivation behavior: Prevention by dietary intervention pre-gestation or in gestation. *Int J Dev Neurosci*. 2012;30(2):75–81.
- [42] Winther G, Elfving B, Müller HK, Lund S, Wegener G. Maternal high-fat diet programs offspring emotional behavior in adulthood. *Neuroscience*. 2018;388:87–101.
- [43] Abuaish S, Spinieli RL, McGowan PO. Perinatal high fat diet induces early activation of endocrine stress responsivity and anxiety-like behavior in neonates. *Psychoneuroendocrinol*. 2018;98:11–21.
- [44] Thompson JR, Valteau JC, Barling AN, Franco JG, DeCapo M, Bagley JL, et al. Exposure to a high-fat diet during early development programs behavior and impairs the central serotonergic system in juvenile non-human primates. *Front Endocrinol (Lausanne)*. 2017;8:164.
- [45] Eshra MA, Rashed LA, Eltelbany RFA, Omar H, ShamsEldeen AM. Omega-3 modulates anxiety and improves autistic like features induced by high fat diet but not valproate. *Neurol Psychiatry Brain Res*. 2019;33:11–21.
- [46] Bayandor P, Farajdokht F, Mohaddes G, Diba R, Hosseindoost M, Mehri K, et al. The effect of troxerutin on anxiety- and depressive-like behaviours in the offspring of high-fat diet fed dams. *Arch Physiol Biochem*. 2019;125(2):156–62.
- [47] Bilbo SD, Tsang V. Enduring consequences of maternal obesity for brain inflammation and behavior of offspring. *FASEB J*. 2010;24(6):2104–15.
- [48] Kang SS, Kurti A, Fair DA, Fryer JD. Dietary intervention rescues maternal obesity induced behavior deficits and neuroinflammation in offspring. *J Neuroinflamm*. 2014;11:156.
- [49] Sasaki A, de Vega WC, St-Cyr S, Pan P, McGowan PO. Perinatal high fat diet alters glucocorticoid signaling and anxiety behavior in adulthood. *Neuroscience*. 2013;240:1–12.
- [50] Sullivan EL, Riper KM, Lockard R, Valteau JC. Maternal high-fat diet programming of the neuroendocrine system and behavior. *Horm Behav*. 2015;76:153–61.
- [51] Winther G, Eskelund A, Bay-Richter C, Elfving B, Müller HK, Lund S, et al. Grandmaternal high-fat diet primed anxiety-like behaviour in the second-generation female offspring. *Behav Brain Res*. 2019;359:47–55.
- [52] Morgese MG, Tucci P, Mhillaj E, Bove M, Schiavone S, Trabace L, et al. Lifelong nutritional Omega-3 deficiency evokes depressive-like state through soluble beta amyloid. *Mol Neurobiol*. 2017;54(3):2079–89.
- [53] Palsdottir V, Månsson JE, Blomqvist M, Egecioglu E, Olsson B. Long-term effects of perinatal essential fatty acid deficiency on anxiety-related behavior in mice. *Behav Neurosci*. 2012;126(2):361–9.
- [54] Cinquina V, Calvigioni D, Farlik M, Halbritter F, Fife-Gernedl V, Shirran SL, et al. Life-long epigenetic programming of cortical architecture by maternal ‘Western’ diet during pregnancy. *Mol Psychiatry*. 2020;25(1):22–36.
- [55] Sakayori N, Kikkawa T, Tokuda H, Kiryu E, Yoshizaki K, Kawashima H, et al. Maternal dietary imbalance between omega-6 and omega-3 polyunsaturated fatty acids impairs neocortical development via epoxy metabolites. *Stem Cell*. 2016;34(2):470–82.
- [56] Jones KL, Will MJ, Hecht PM, Parker CL, Beversdorf DQ. Maternal diet rich in omega-6 polyunsaturated fatty acids during gestation and lactation produces autistic-like sociability deficits in adult offspring. *Behav Brain Res*. 2013;238:193–9.
- [57] Chen HF, Su HM. Exposure to a maternal n-3 fatty acid-deficient diet during brain development provokes excessive hypothalamic-pituitary-adrenal axis responses to stress and behavioral indices of depression and anxiety in male rat offspring later in life. *J Nutr Biochem*. 2013;24(1):70–80.
- [58] Auguste S, Sharma S, Fiset A, Fernandes MF, Daneault C, Des Rosiers C, et al. Perinatal deficiency in dietary omega-3 fatty acids potentiates sucrose reward and diet-induced obesity in mice. *Int J Dev Neurosci*. 2018;64:8–13.
- [59] Bhatia HS, Agrawal R, Sharma S, Huo YX, Ying Z, Gomez-Pinilla F. Omega-3 fatty acid deficiency during brain maturation reduces neuronal and behavioral plasticity in adulthood. *PLoS One*. 2011;6(12):e28451.
- [60] Pase CS, Roversi K, Trevizol F, Roversi K, Kuhn FT, Schuster AJ, et al. Influence of perinatal trans fat on behavioral responses and brain oxidative status of adolescent rats acutely exposed to stress. *Neuroscience*. 2013;247:242–52.
- [61] Plusnina IZ, Os’kina IN, Shchepina OA, Prasolova LA, Trut LN. Maternal methyl-containing dietary supplementation alters the ability to learn in adult rats in swimming Morris test. *Zh Vyssh Nerv Deiat Im I P Pavlova*. 2006;56(3):293–7.
- [62] McCoy CR, Jackson NL, Brewer RL, Moughnyeh MM, Smith DL Jr, Clinton SM. A paternal methyl donor depleted diet leads to increased anxiety- and depression-like behavior in adult rat offspring. *Biosci Rep*. 2018;38(4):1–8.
- [63] Konycheva G, Dziadek MA, Ferguson LR, Krägeloh CU, Coolen MW, Davison M, et al. Dietary methyl donor deficiency during pregnancy in rats shapes learning and anxiety in offspring. *Nutr Res*. 2011;31(10):790–804.
- [64] Fiset C, Rioux FM, Surette ME, Fiset S. Prenatal iron deficiency in guinea pigs increases locomotor activity but does not influence learning and memory. *PLoS One*. 2015;10(7):e0133168.
- [65] Eseh R, Zimmerberg B. Age-dependent effects of gestational and lactational iron deficiency on anxiety behavior in rats. *Behav Brain Res*. 2005;164(2):214–21.
- [66] Schlegel RN, Spiers JG, Moritz KM, Cullen CL, Björkman ST, Paravicini TM. Maternal hypomagnesemia alters hippocampal NMDAR subunit expression and programs anxiety-like behaviour in adult offspring. *Behav Brain Res*. 2017;328:39–47.



- [67] Summers BL, Henry CM, Rofe AM, Coyle P. Dietary zinc supplementation during pregnancy prevents spatial and object recognition memory impairments caused by early prenatal ethanol exposure. *Behav Brain Res.* 2008;186(2):230–8.
- [68] Laureano-Melo R, Império GE, da Silva-Almeida C, Kluck GE, Cruz Seara Fde A, da Rocha FF, et al. Sodium selenite supplementation during pregnancy and lactation promotes anxiolysis and improves mnemonic performance in wistar rats' offspring. *Pharmacol Biochem Behav.* 2015;138:123–32.
- [69] Schulz KM, Pearson JN, Gasparrini ME, Brooks KF, Drake-Frazier C, Zajkowski ME, et al. Dietary choline supplementation to dams during pregnancy and lactation mitigates the effects of in utero stress exposure on adult anxiety-related behaviors. *Behav Brain Res.* 2014;268:104–10.
- [70] Glenn MJ, Adams RS, McClurg L. Supplemental dietary choline during development exerts antidepressant-like effects in adult female rats. *Brain Res.* 2012;1443:52–63.
- [71] Langley EA, Krykbaeva M, Blusztajn JK, Mellott TJ. High maternal choline consumption during pregnancy and nursing alleviates deficits in social interaction and improves anxiety-like behaviors in the BTBR T + Itpr3tf/J mouse model of autism. *Behav Brain Res.* 2015;278:210–20.
- [72] Vuillermot S, Luan W, Meyer U, Eyles D. Vitamin D treatment during pregnancy prevents autism-related phenotypes in a mouse model of maternal immune activation. *Mol Autism.* 2017;8(1):1–3.
- [73] Desrumaux CM, Mansuy M, Lemaire S, Przybilski J, Le Guern N, Givalois L, et al. Brain Vitamin E deficiency during development is associated with increased glutamate levels and anxiety in adult mice. *Front Behav Neurosci.* 2018;12:310.
- [74] Yan Z, Jiao F, Yan X, Ou H. Maternal chronic folate supplementation ameliorates behavior disorders induced by prenatal high-fat diet through methylation alteration of BDNF and Grin2b in offspring hippocampus. *Mol Nutr Food Res.* 2017;61(12):1700461.
- [75] Pan P, Jin DH, Chatterjee-Chakraborty M, Halievski K, Lawson D, Remedios D, et al. The effects of vitamin D<sub>3</sub> during pregnancy and lactation on offspring physiology and behavior in sprague-dawley rats. *Dev Psychobiol.* 2014;56(1):12–22.
- [76] Wu YC, Wang Y, Tseng GF. Ascorbic acid and  $\alpha$ -tocopherol supplement starting prenatally enhances the resistance of nucleus tractus solitarius neurons to hypobaric hypoxic challenge. *Brain Struct Funct.* 2011;216(2):105–22.
- [77] Ambrogini P, Ciuffoli S, Lattanzi D, Minelli A, Bucherelli C, Baldi E, et al. Maternal dietary loads of  $\alpha$ -tocopherol differentially influence fear conditioning and spatial learning in adult offspring. *Physiol Behav.* 2011;104(5):809–15.
- [78] Barua S, Chadman KK, Kuizon S, Buenaventura D, Stapley NW, Ruocco F, et al. Increasing maternal or post-weaning folic acid alters gene expression and moderately changes behavior in the offspring. *PLoS One.* 2014;9(7):e101674.
- [79] Furuse T, Miyake K, Kohda T, Kaneda H, Hirasawa T, Yamada I, et al. Protein-restricted diet during pregnancy after insemination alters behavioral phenotypes of the progeny. *Genes Nutr.* 2017;12:1.
- [80] Chu D, Li L, Jiang Y, Tan J, Ji J, Zhang Y, et al. Excess folic acid supplementation before and during pregnancy and lactation activates fos gene expression and alters behaviors in male mouse offspring. *Front Neurosci.* 2019;13:313.
- [81] Harms LR, Eyles DW, McGrath JJ, Mackay-Sim A, Burne TH. Developmental vitamin D deficiency alters adult behaviour in 129/SvJ and C57BL/6J mice. *Behav Brain Res.* 2008;187(2):343–50.
- [82] Sahara Y, Matsuzawa D, Ishii D, Fuchida T, Goto T, Sutoh C, et al. Paternal methyl donor deficient diets during development affect male offspring behavior and memory-related gene expression in mice. *Dev Psychobiol.* 2019;61(1):17–28.
- [83] Ferguson SA, Berry KJ, Hansen DK, Wall KS, White G, Antony AC. Behavioral effects of prenatal folate deficiency in mice. *Birth Defects Res A Clin Mol Teratol.* 2005;73(4):249–52.
- [84] Ear PH, Chadda A, Gumusoglu SB, Schmidt MS, Vogeler S, Malicoat J, et al. Maternal nicotinamide riboside enhances postpartum weight loss, juvenile offspring development, and neurogenesis of adult offspring. *Cell Rep.* 2019;26(4):969–83.e4.
- [85] Almeida SS, Garcia RA, de Oliveira LM. Effects of early protein malnutrition and repeated testing upon locomotor and exploratory behaviors in the elevated plus-maze. *Physiol Behav.* 1993;54(4):749–52.
- [86] Pereira-da-Silva MS, Cabral-Filho JE, de-Oliveira LM. Effect of early malnutrition and environmental stimulation in the performance of rats in the elevated plus maze. *Behav Brain Res.* 2009;205(1):286–9.
- [87] da Silva Hernandez A, Françolin-Silva AL, Valadares CT, Fukuda MT, Almeida SS. Effects of different malnutrition techniques on the behavior of rats tested in the elevated T-maze. *Behav Brain Res.* 2005;162(2):240–5.
- [88] Rotta LN, Schmidt AP, Nogueira CW, Souza KB, Izquierdo IA, Perry ML, et al. Effects of undernutrition on glutamatergic parameters in rat brain. *Neurochem Res.* 2003;28(8):1181–6.
- [89] Lotufo BM, Tenório F, Barradas PC, Guedes PL, Lima SS, Rocha MLM, et al. Maternal protein-free diet during lactation programs male Wistar rat offspring for increased novelty-seeking, locomotor activity, and visuospatial performance. *Behav Neurosci.* 2018;132(2):114–27.
- [90] Batista TH, Veronesi VB, Ribeiro ACAF, Giusti-Paiva A, Vilela FC. Protein malnutrition during pregnancy alters maternal behavior and anxiety-like behavior in offspring. *Nutr Neurosci.* 2017;20(8):437–42.
- [91] Torres DB, Lopes A, Rodrigues AJ, Cerqueira JJ, Sousa N, Gontijo JAR, et al. Anxiety-like behavior and structural changes of the bed nucleus of the stria terminalis (BNST) in gestational protein-restricted male offspring. *J Dev Orig Health Dis.* 2018;9(5):536–43.
- [92] Belluscio LM, Berardino BG, Ferroni NM, Ceruti JM, Cánepa ET. Early protein malnutrition negatively impacts physical growth and neurological reflexes and evokes anxiety and depressive-like behaviors. *Physiol Behav.* 2014;129:237–54.
- [93] Crossland RF, Balasa A, Ramakrishnan R, Mahadevan SK, Fiorotto ML, Van den Veyver IB. Chronic maternal low-protein diet in mice affects anxiety, night-time energy expenditure and sleep patterns, but not circadian rhythm in male offspring. *PLoS One.* 2017;12(1):e0170127.
- [94] Naik AA, Patro IK, Patro N. Slow physical growth, delayed reflex ontogeny, and permanent behavioral as well as



- cognitive impairments in rats following intra-generational protein malnutrition. *Front Neurosci.* 2015;9:446.
- [95] Watkins AJ, Ursell E, Panton R, Papenbrock T, Hollis L, Cunningham C, et al. Adaptive responses by mouse early embryos to maternal diet protect fetal growth but predispose to adult onset disease. *Biol Reprod.* 2008;78(2):299–306.
- [96] Watkins AJ, Wilkins A, Cunningham C, Perry VH, Seet MJ, Osmond C, et al. Low protein diet fed exclusively during mouse oocyte maturation leads to behavioural and cardiovascular abnormalities in offspring. *J Physiol.* 2008;586(8):2231–44.
- [97] Ware S, Voigt JP, Langley-Evans SC. Body composition and behaviour in adult rats are influenced by maternal diet, maternal age and high-fat feeding. *J Nutr Sci.* 2015;4:e3.
- [98] Reyes-Castro LA, Rodriguez JS, Charco R, Bautista CJ, Larrea F, Nathanielsz PW, et al. Maternal protein restriction in the rat during pregnancy and/or lactation alters cognitive and anxiety behaviors of female offspring. *Int J Dev Neurosci.* 2012;30(1):39–45.
- [99] Nätt D, Barchiesi R, Murad J, Feng J, Nestler EJ, Champagne FA, et al. Perinatal malnutrition leads to sexually dimorphic behavioral responses with associated epigenetic changes in the mouse brain. *Sci Rep.* 2017;7(1):11082.
- [100] Pillay N, Rimbach R, Rymer T. Pre- and postnatal dietary protein deficiency influences anxiety, memory and social behaviour in the African striped mouse *Rhabdomys dilectus* chakae. *Physiol Behav.* 2016;161:38–46.
- [101] Zhang L, Guadarrama L, Corona-Morales AA, Vega-Gonzalez A, Rocha L, Escobar A. Rats subjected to extended L-Tryptophan restriction during early postnatal stage exhibit anxious-depressive features and structural changes. *J Neuropathol Exp Neurol.* 2006;65(6):562–70.
- [102] Nagamachi S, Nishigawa T, Takakura M, Ikeda H, Kodaira M, Yamaguchi T, et al. Dietary L-serine modifies free amino acid composition of maternal milk and lowers the body weight of the offspring in mice. *J Vet Med Sci.* 2018;80(2):235–41.
- [103] Strata F, Giritharan G, Sebastiano FD, Piane LD, Kao C-N, Donjacour A, et al. Behavior and brain gene expression changes in mice exposed to preimplantation and prenatal stress. *Reprod Sci.* 2015;22(1):23–30.
- [104] Françolin-Silva AL, da Silva Hernandez A, Fukuda MT, Valadares CT, Almeida SS. Anxiolytic-like effects of short-term postnatal protein malnutrition in the elevated plus-maze test. *Behav Brain Res.* 2006;173(2):310–4.
- [105] Hernandez AS, Almeida SS. Postnatal protein malnutrition affects inhibitory avoidance and risk assessment behaviors in two models of anxiety in rats. *Nutr Neurosci.* 2003;6(4):213–9.
- [106] Almeida SS, Tonkiss J, Galler JR. Prenatal protein malnutrition affects exploratory behavior of female rats in the elevated plus-maze test. *Physiol Behav.* 1996;60(2):675–80.
- [107] Govic A, Penman J, Tammer AH, Paolini AG. Paternal calorie restriction prior to conception alters anxiety-like behavior of the adult rat progeny. *Psychoneuroendocrinol.* 2016;64:1–11.
- [108] Fisch J, Feistauer V, de Moura AC, Silva AO, Bollis V, Porawski M, et al. Maternal feeding associated to post-weaning diet affects metabolic and behavioral parameters in female offspring. *Physiol Behav.* 2019;204:162–7.
- [109] Jaiswal AK, Upadhyay SN, Satyan KS, Bhattacharya SK. Behavioural effects of prenatal and postnatal undernutrition in rats. *Indian J Exp Biol.* 1996;34(12):1216–9.
- [110] Jaiswal AK, Upadhyay SN, Satyan KS, Bhattacharya SK. Comparative effects of prenatal and postnatal undernutrition on learning and memory in rats. *Indian J Exp Biol.* 1999;37(1):17–22.
- [111] Fernandez S, Gonzalez C, Patterson AM. Oil enriched diets and behavioral parameters in rats' recovery from early undernutrition. *Physiol Behav.* 1997;62(1):113–9.
- [112] Ramírez-López MT, Vázquez M, Bindila L, Lomazzo E, Hofmann C, Blanco RN, et al. Maternal caloric restriction implemented during the preconceptional and pregnancy period alters hypothalamic and hippocampal endocannabinoid levels at birth and induces overweight and increased adiposity at adulthood in male rat offspring. *Front Behav Neurosci.* 2016;10:208.
- [113] He B, Xu D, Zhang C, Zhang L, Wang H. Prenatal food restriction induces neurobehavioral abnormalities in adult female offspring rats and alters intrauterine programming. *Toxicol Res (Camb).* 2018;7(2):293–306.
- [114] Kumon M, Yamamoto K, Takahashi A, Wada K, Wada E. Maternal dietary restriction during lactation influences postnatal growth and behavior in the offspring of mice. *Neurochem Int.* 2010;57(1):43–50.
- [115] Govic A, Bell V, Samuel A, Penman J, Paolini AG. Calorie restriction and corticosterone elevation during lactation can each modulate adult male fear and anxiety-like behaviour. *Horm Behav.* 2014;66(4):591–601.
- [116] Akitake Y, Katsuragi S, Hosokawa M, Mishima K, Ikeda T, Miyazato M, et al. Moderate maternal food restriction in mice impairs physical growth, behavior, and neurodevelopment of offspring. *Nutr Res.* 2015;35(1):76–87.
- [117] Spencer SJ, Tilbrook A. Neonatal overfeeding alters adult anxiety and stress responsiveness. *Psychoneuroendocrinology.* 2009;34(8):1133–43.
- [118] Ajarem J, Rashedi GA, Mohany M, Allam A. Neurobehavioral changes in mice offspring exposed to green tea during fetal and early postnatal development. *Behav Brain Funct.* 2017;13(1):10.
- [119] Ward-Flanagan R, Scavuzzo C, Mandhane PJ, Bolduc FV, Dickson CT. Prenatal fruit juice exposure enhances memory consolidation in male post-weanling Sprague-Dawley rats. *PLoS One.* 2020;15(1):e0227938.
- [120] Toumi ML, Merzoug S, Baudin B, Tahraoui A. Quercetin alleviates predator stress-induced anxiety-like and brain oxidative signs in pregnant rats and immune count disturbance in their offspring. *Pharmacol Biochem Behav.* 2013;107:1–10.
- [121] Toumi ML, Merzoug S, Tahraoui A. Effects of quercetin on predator stress-related hematological and behavioral alterations in pregnant rats and their offspring. *J Biosci.* 2016;41(2):237–49.
- [122] Laureano-Melo R, da Silveira AL, de Azevedo Cruz Seara F, da Conceição RR, da Silva-Almeida C, Marinho BG, et al. Behavioral profile assessment in offspring of Swiss mice treated during pregnancy and lactation with caffeine. *Metab Brain Dis.* 2016;31(5):1071–80.
- [123] Wright T, Langley-Evans SC, Voigt JP. The impact of maternal cafeteria diet on anxiety-related behaviour and exploration in the offspring. *Physiol Behav.* 2011;103(2):164–72.

- [124] Speight A, Davey WG, McKenna E, Voigt JW. Exposure to a maternal cafeteria diet changes open-field behaviour in the developing offspring. *Int J Dev Neurosci*. 2017;57:34–40.
- [125] Marcolin Mde L, Benitz Ade N, Arcego DM, Noschang C, Krolow R, Dalmaz C. Effects of early life interventions and palatable diet on anxiety and on oxidative stress in young rats. *Physiol Behav*. 2012;106(4):491–8.
- [126] Thompson JR, Gustafsson HC, DeCapo M, Takahashi DL, Bagley JL, Dean TA, et al. Maternal diet, metabolic state, and inflammatory response exert unique and long-lasting influences on offspring behavior in non-human primates. *Front Endocrinol (Lausanne)*. 2018;9:161.
- [127] Hiramatsu L, Kay JC, Thompson Z, Singleton JM, Claghorn GC, Albuquerque RL, et al. Maternal exposure to Western diet affects adult body composition and voluntary wheel running in a genotype-specific manner in mice. *Physiol Behav*. 2017;179:235–45.
- [128] Guedine CRC, Pordeus LCM, Riul TR, Jordão AA, Almeida SS. Cafeteria diet during lactation and/or post-lactation altered lipid profile/lipid peroxidation and increased anxiety-like behavior in male rat offspring. *Nutr Neurosci*. 2020;23(7):526–36.
- [129] Shalev U, Tylor A, Schuster K, Frate C, Tobin S, Woodside B. Long-term physiological and behavioral effects of exposure to a highly palatable diet during the perinatal and post-weaning periods. *Physiol Behav*. 2010;101(4):494–502.
- [130] Bukhari SHF, Clark OE, Williamson LL. Maternal high fructose diet and neonatal immune challenge alter offspring anxiety-like behavior and inflammation across the lifespan. *Life Sci*. 2018;197:114–21.
- [131] Le Q, Li Y, Hou W, Yan B, Yu X, Song H, et al. Binge-like sucrose self-administration experience inhibits cocaine and sucrose seeking behavior in offspring. *Front Behav Neurosci*. 2017;11:184.
- [132] Collison KS, Inglis A, Shiban S, Andres B, Ubungen R, Thiam J, et al. Differential effects of early-life NMDA receptor antagonism on aspartame-impaired insulin tolerance and behavior. *Physiol Behav*. 2016;167:209–21.
- [133] Szklany K, Wopereis H, de Waard C, van Wageningen T, An R, Van Limpt K, et al. Supplementation of dietary non-digestible oligosaccharides from birth onwards improve social and reduce anxiety-like behaviour in male BALB/c mice. *Nutr Neurosci*. 2020;23(11):896–910.
- [134] Laureano-Melo R, Caldeira RF, Guerra AF, Conceição RRD, Souza JSD, Giannocco G, et al. Maternal supplementation with *Lactobacillus paracasei* DTA 83 alters emotional behavior in Swiss mice offspring. *Pharma Nutr*. 2019;8:100148.
- [135] Doguc DK, Aylak F, Ilhan I, Kulac E, Gultekin F. Are there any remarkable effects of prenatal exposure to food colorings on neurobehaviour and learning process in rat offspring? *Nutr Neurosci*. 2015;18(1):12–21.
- [136] Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage*. 2002;16(2):331–48.
- [137] Etkin A, Wager TD. Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am J Psychiatry*. 2007;164(10):1476–88.
- [138] Nuss P. Anxiety disorders and GABA neurotransmission: a disturbance of modulation. *Neuropsychiatr Dis Treat*. 2015;11:165–75.
- [139] Dieleman GC, Huizink AC, Tulen JH, Utens EM, Creemers HE, van der Ende J, et al. Alterations in HPA-axis and autonomic nervous system functioning in childhood anxiety disorders point to a chronic stress hypothesis. *Psychoneuroendocrinology*. 2015;51:135–50.
- [140] Salim S, Chugh G, Asghar M. Inflammation in anxiety. *Adv Protein Chem Struct Biol*. 2012;88:1–25.
- [141] Viviani B, Gardoni F, Marinovich M. Cytokines and neuronal ion channels in health and disease. *Int Rev Neurobiol*. 2007;82:247–63.
- [142] Schrott LM, Crnic LS. Increased anxiety behaviors in autoimmune mice. *Behav Neurosci*. 1996;110(3):492–502.
- [143] Arranz L, Guayerbas N, De, la Fuente M. Impairment of several immune functions in anxious women. *J Psychosom Res*. 2007;62(1):1–8.
- [144] Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, Morag A, et al. Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry*. 2001;58(5):445–52.
- [145] Frankiensztajn LM, Elliott E, Koren O. The microbiota and the hypothalamus-pituitary-adrenocortical (HPA) axis, implications for anxiety and stress disorders. *Curr Opin Neurobiol*. 2020;62:76–82.
- [146] Lichtenstein AH, Kennedy E, Barrier P, Danford D, Ernst ND, Grundy SM, et al. Dietary fat consumption and health. *Nutr Rev*. 1998;56(5 Pt 2):S3–19. discussion S-28.
- [147] Firth J, Veronese N, Cotter J, Shivappa N, Hebert JR, Ee C, et al. What is the role of dietary inflammation in severe mental illness? A review of observational and experimental findings. *Front Psychiatry*. 2019;10:1–9.
- [148] Rosario FJ, Jansson N, Kanai Y, Prasad PD, Powell TL, Jansson T. Maternal protein restriction in the rat inhibits placental insulin, mTOR, and STAT3 signaling and down-regulates placental amino acid transporters. *Endocrinology*. 2011;152(3):1119–29.
- [149] Pilis W, Stec K, Zych M, Pilis A. Health benefits and risk associated with adopting a vegetarian diet. *Rocz Panstw Zakl Hig*. 2014;65(1):9–14.
- [150] Hwangbo D-S, Lee H-Y, Abozaid LS, Min K-J. Mechanisms of lifespan regulation by calorie restriction and intermittent fasting in model organisms. *Nutrients*. 2020;12(4):1194.
- [151] de Oliveira TQ, de Moura AC, Feistauer V, Damiani R, Braga MF, Almeida S, et al. Caloric restriction in mice improves short-term recognition memory and modifies the neuroinflammatory response in the hippocampus of male adult offspring. *Behav Brain Res*. 2022;425:113838.
- [152] Kim DR, Bale TL, Epperson CN. Prenatal programming of mental illness: current understanding of relationship and mechanisms. *Curr Psychiatry Rep*. 2015;17(2):5.
- [153] Marques A, O'Connor T, Roth C, Susser E, Børke-Monsen A-L. The influence of maternal prenatal and early childhood nutrition and maternal prenatal stress on offspring immune system development and neurodevelopmental disorders. *Front Neurosci*. 2013;7:120.
- [154] Martins VJB, Toledo Florêncio TMM, Grillo LP, Do Carmo P, Franco M, Martins PA, Clemente APG, et al. Long-lasting

- effects of undernutrition. *Int J Environ Res Public Health*. 2011;8(6):1817–46.
- [155] Furuse T, Miyake K, Kohda T, Kaneda H, Hirasawa T, Yamada I, et al. Protein-restricted diet during pregnancy after insemination alters behavioral phenotypes of the progeny. *Genes Nutr*. 2017;12(1):1.
- [156] Bjelland I, Tell GS, Vollset SE, Konstantinova S, Ueland PM. Choline in anxiety and depression: The hordaland health study. *Am J Clin Nutr*. 2009;90(4):1056–60.
- [157] Guzek D, Kołota A, Lachowicz K, Skolmowska D, Stachoń M, Głąbska D. Association between Vitamin D supplementation and mental health in healthy adults: A systematic review. *J Clin Med*. 2021;10(21):5156.
- [158] Pet MA, Brouwer-Brolsma EM. The impact of maternal Vitamin D status on offspring brain development and function: A systematic review. *Adv Nutr*. 2016;7(4):665–78.
- [159] Khayat S, Fanaei H, Ghanbarzahi A. Minerals in pregnancy and lactation: A review article. *J Clin Diagn Res*. 2017;11(9):Qe01–5.
- [160] Aucoin M, Bhardwaj S. Generalized anxiety disorder and hypoglycemia symptoms improved with diet modification. *Case Rep Psychiatry*. 2016;2016:7165425.
- [161] Witek K, Wydra K, Filip M. A high-sugar diet consumption, metabolism and health impacts with a focus on the development of substance use disorder: A narrative review. *Nutrients*. 2022;14(14):2940.
- [162] Clapp M, Aurora N, Herrera L, Bhatia M, Wilen E, Wakefield S. Gut microbiota's effect on mental health: The gut-brain axis. *Clin Pract*. 2017;7(4):987.
- [163] Steimer T. Animal models of anxiety disorders in rats and mice: Some conceptual issues. *Dialogues Clin Neurosci*. 2011;13(4):495–506.