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*Review*

# Trace Minerals and Anxiety: A Review of Zinc, Copper, Iron, and Selenium

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**Abstract:** Anxiety disorder is characterized by excessive fear or avoidance of perceived threats that can be persistent and debilitating. Diet is a modifiable risk factor that may contribute to the pathogenesis or treatment of anxiety, depending on diet quality. Although the biological mechanisms by which food, specific nutrients, and nutraceuticals impact mental health are not completely understood, implicated pathways include inflammation, oxidative stress, brain plasticity effects, mitochondrial dysfunction, and neurotransmitter metabolism. Essential dietary trace minerals such as zinc, copper, iron, and selenium are critical components for numerous biological proteins and may have a role in these proposed mechanisms related to brain health and anxiety. This narrative review examines the influence of essential trace elements zinc, copper, iron, and selenium on anxiety symptoms based on the latest peer-reviewed scientific evidence. Current research indicates that deficiencies in zinc, iron, and selenium are associated with anxiety, while copper overload may impact anxiety to a greater degree than copper deficiency. Further investigation is needed to understand the specific neurobiological mechanisms involved. Overall, the collective findings demonstrate the importance of optimizing trace mineral homeostasis for the mitigation of anxiety disorders and preservation of mental health.

**Keywords:** mineral; trace element; diet; anxiety; behavior; zinc; copper; iron; selenium; mental health

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## 1. Introduction

Anxiety disorder is characterized by excessive fear or avoidance of perceived threats that can be persistent and debilitating [1]. It involves constant anticipation of real or imagined future threat or danger. According to the World Health Organization, 301 million people were living with an anxiety disorder in 2019, including 58 million children and adolescents [2]. The National Institute of Mental Health reports an estimated 31.1% of U.S. adults will experience some type of anxiety disorder during their lifetime, with a higher prevalence for females (23.4%) than for males (14.3%). For U.S. adolescents aged 13–18, an estimated 31.9% had any anxiety disorder, with a higher prevalence for females (38.0%) than for males (26.1%) [3]. Specific types of anxiety include generalized anxiety disorder, panic disorder, agoraphobia, social anxiety disorder, specific phobia, separation anxiety, and selective mutism [1]. Worldwide, anxiety disorders account for 3.3% of the global burden of disease and are ranked the ninth most health-related cause for disability. The pathophysiology of anxiety involves dysfunction in brain circuits that respond to danger and can be influenced by genetics, the environment, and epigenetic factors. Cognitive behavioral therapy and pharmacotherapy are the most common treatment methods, although alternative strategies include exercise, mindfulness practice, and transcranial stimulation techniques [4]. Nutritional psychiatry is an emerging discipline that involves the practice of using food and nutritional supplements to improve mood disorders in conjunction with conventional treatments, showing promise for enhanced methods to treat anxiety [5–8].

Diet is a modifiable risk factor that may contribute to the pathogenesis or treatment of anxiety, depending on diet quality [9]. Epidemiological studies suggest that healthy dietary

patterns, such as the Mediterranean Diet, may reduce the risk of anxiety, while poor-quality diets that include regular consumption of fried foods, sugar, refined grains, and alcohol are associated with higher risk for anxiety disorders [10]. There is growing evidence that diet interventions based on improved dietary patterns or specific nutrients show potential for the prevention or treatment of various mental health disorders [7,9–12]. Specific nutrients play important roles in maintaining brain health and central nervous system homeostasis. For example, polyunsaturated omega-3 fatty acids, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), have known beneficial effects on brain structure and function [9]. Monounsaturated fatty acids have been shown to modulate brain activity. Quality proteins provide amino acids such as tryptophan and tyrosine for the synthesis of key neurotransmitters, including serotonin, melatonin, and dopamine. High fiber carbohydrates provide prebiotics for a healthy microbiome by stimulating the synthesis of short chain fatty acids for immune system protection and anti-inflammatory effects with a downstream effect on mood. Vitamins, minerals, and bioactive compounds have also been shown to improve brain health through improved cognition, increased antioxidant activity, and protection against neurodegeneration [9,11]. Key micronutrients regulate stress responses through their role in the production and metabolism of neurotransmitters and are involved in the synthesis of omega-3 fatty acids that are associated with a lower risk of anxiety [10]. Additionally, certain dietary nutrients have an impact on neuronal membrane structure and neurotransmitter release. Based on current evidence that food can impact mood with the influence of key nutrients on important neurobiological processes [7–12], it is imperative that diet should be considered for the preservation of mental health. Furthermore, dietary analysis with appropriate recommendations should be integrated into more treatment plans for the alleviation of anxiety symptoms.

The biological mechanisms by which food, specific nutrients, and nutraceuticals impact mental health are not completely understood, however, implicated pathways include inflammation, oxidative stress, brain plasticity effects, mitochondrial dysfunction, and neurotransmitter metabolism [6,13]. Trace elements such as zinc, copper, iron, and selenium are cofactors for numerous biological enzymes and may have a role in these proposed mechanisms related to brain health and anxiety. Essential dietary minerals are critical for the optimization of both physical and mental health [12]. Although a healthy and varied diet that includes lean meats, vegetables, fruits, whole grains, and low-fat dairy is the preferred way to obtain essential micronutrients, dietary supplements can also be used to ensure that we are meeting our nutritional requirements [14]. Broad spectrum micronutrient interventions have shown promise for reducing symptoms associated with stress and anxiety [15–18]. Specific mineral treatments for the relief of anxiety have also been investigated [12,19–22]. In the following literature review, we focus our attention on the influence of essential trace minerals zinc, copper, iron, and selenium on anxiety treatment and prevention based on the latest peer-reviewed scientific evidence.

## 2. Methods and Search Criteria

Studies were chosen for this narrative review by searching PubMed for articles published between 1990–2022. Other databases such as Google Scholar, ProQuest, and JSTOR were used when additional information was needed to provide a balanced, comprehensive review of each mineral. Search terms and key phrases included “trace elements and anxiety”, “trace minerals and anxiety”, “microminerals and anxiety”, “micronutrients and anxiety”, “zinc and anxiety”, “copper and anxiety”, “iron and anxiety”, “selenium and anxiety”, “zinc (or other mineral) deficiency”. Additional search phrases were used replacing the term “anxiety” with “mental health”. Original research and review articles involving human and animal studies relevant to these search terms were included. All authors participated in the search process to obtain relevant, peer-reviewed research for the purpose of providing an unbiased overview of recent findings related to anxiety and trace minerals zinc, copper, iron, and selenium.

## 3. Zinc

Zinc is an essential trace mineral in the diet due to its key role in gene expression, immune function, wound healing, and cell division [23]. It also supports normal growth, sexual maturation, and our sense of taste and smell [24]. A deficiency in zinc can lead to physical health issues and mental health illnesses, including depression and anxiety [25]. The recommended dietary allowance (RDA) for zinc increases with age and ranges from 2–13 mg [24]. Adult females require 8 mg/day or 11–13 mg/day when pregnant or lactating. Adult males require approximately 11 mg/day. Consuming foods such as red meat, poultry, seafood, beans, nuts, whole grains, dairy, and fortified breakfast cereal will help to meet these dietary recommendations. Oysters are particularly high in zinc, with 74 mg per three-ounce serving, providing 673% of the daily value. Zinc is also commonly found in cold lozenges and some commercial cold remedies.

Zinc participates in several diverse roles within the body as a component of various metalloenzymes. It provides structural integrity for many proteins and is a required cofactor for numerous metabolic reactions [26]. Investigations into the molecular mechanisms involved in the development of mental health disorders suggest a role for zinc in the regulation of neurotransmitter systems, antioxidant activity, neurotrophic factors, and neuronal precursor cells [27]. Additionally, zinc may be involved in regulating neurotransmitter metabolism in the hippocampus, with a potential influence on mental health and anxiety-like behaviors [12].

There is current evidence that supports an association between dietary zinc deficiency and anxiety. For example, a cross-sectional study with female high school students found a positive correlation between dietary zinc intake and serum zinc levels and a corresponding inverse association between serum zinc and anxiety symptoms. Zinc intake was assessed using a 24 h food recall questionnaire and anxiety was evaluated using a combination of Beck's Depression Inventory and the Hospital Anxiety Depression Scale [28]. Another cross-sectional study in female university students found an inverse association between dietary zinc intake and anxiety using a 12-month food frequency questionnaire and the Beck Anxiety Inventory survey as assessment tools [29]. Furthermore, a cross-sectional study in adult Japanese workers found an inverse association between dietary zinc and anxiety symptoms. Anxiety was evaluated using the Kessler's six-item psychological distress scale, and a validated food frequency questionnaire was used to assess dietary intake [30]. In a preclinical study, male and female C3H/HenRj mice fed a prenatal zinc-deficient diet displayed higher anxiety-like behavior at the age of 15 weeks, despite being fed a postnatal zinc-sufficient diet [31].

Related studies that did not include a diet analysis found a similar relationship between zinc deficiency and anxiety. In children and adolescents with attention-deficit/hyperactivity disorder, low serum zinc was correlated with higher anxiety and conduct issues [32]. In male Chinese participants, cerebrospinal fluid zinc concentrations were negatively correlated with anxiety symptoms [33]. A study conducted in Bangladesh found that there was an imbalance of minerals in a cohort of patients with generalized anxiety disorder. Specifically, the participants who suffered from anxiety had low blood serum concentrations of zinc and high serum concentrations of copper, manganese, and iron [34]. Taken together, these clinical and preclinical studies, with or without a diet analysis, demonstrate a strong connection between zinc deficiency and anxiety.

Zinc therapy is a treatment option that has been investigated for the alleviation of anxiety symptoms in both humans and animals. A randomized controlled trial in patients with type 2 diabetes mellitus and coronary heart disease found that a combination of zinc sulfate and magnesium oxide supplementation for 12 weeks significantly reduced anxiety symptoms [35]. A recent 24-week intervention using zinc supplementation to treat symptoms of premenstrual syndrome (PMS) was also successful at reducing anxiety and other symptoms related to PMS in Iranian females [36]. A six-month randomized controlled clinical trial examined the effect of zinc oxide supplementation on the mental health of school-age children in Guatemala. Although there was no significant difference in overall mental health outcomes between the control and treatment groups after six months, the

treatment group did have higher serum zinc concentrations, and increased serum zinc was associated with reduced anxiety symptoms [22]. Zinc interventions may also be used to improve recovery rates for anorexia nervosa patients by reducing anxiety. This is based on a compilation of positive results from clinical randomized controlled trials and low incidence of side effects [37]. It is hypothesized that the anxiolytic impact of zinc may be due to its influence on the transmission of glutamate and gamma-aminobutyric acid in the brain [25]. More research is needed to clarify these neurobiological mechanisms and the role that zinc plays in the mitigation of anxiety.

The impact of zinc supplementation combined with antioxidant therapy on anxiety and serum zinc has also been evaluated. In one study, patients with anxiety were found to have lower serum zinc compared to the control group before the treatment was administered. After the zinc/antioxidant treatment, anxiety symptoms were reduced, and serum zinc was restored to normal levels [38]. A similar investigation in patients with a combination of anxiety and depression found comparable results using the zinc/antioxidant therapy to effectively reduce anxiety and normalize serum zinc [39]. A third related study discovered that participants with anxiety had lower levels of serum hepatocyte growth factor (HGF) and zinc compared to the control group. After a zinc/antioxidant treatment for eight weeks, both serum HGF and zinc significantly increased in the supplemented group [40]. HGF has a protective anti-inflammatory and regenerative effect on many tissue types and organs, including the brain [41]. It promotes the survival and maturation of neurons in the hippocampus [42] and dopaminergic neurons in the substantia nigra [41], revealing a potential link between zinc, HGF, and anxiety. There is growing evidence indicating that anxiety is associated with increased neuronal excitability in the hippocampus, and that anxiety may be treated by altering the excitability and plasticity of hippocampal neurons [43]. Therefore, it is possible that suboptimal zinc or HGF levels in the hippocampus could manifest as anxiety symptoms, with zinc supplementation as a potential treatment.

Several preclinical studies have also demonstrated that various zinc treatments may have an anxiolytic effect. In one study, adult male Wistar rats induced with Type 1 Diabetes Mellitus were treated with either zinc gluconate or zinc sulfate for four weeks. The zinc sulfate group alone showed decreased anxiety-like behavior after the treatment. Although zinc gluconate did not have the same anxiolytic outcome, it did have an antidepressant effect and neuroprotective effect by reducing alterations in the cerebral cortex [44]. These results suggest that the specific anion used in combination with the zinc cation for the purpose of zinc supplementation as an anxiolytic agent is important and may be involved in the neurobiological mechanisms that impact mental health. Another study conducted with male Wistar rats treated with zinc histidine dehydrate found that the impact on anxiety was dose dependent. A zinc dose of 20 mg/kg was found to have an anxiolytic effect; however, a dose of 30 mg/kg was found to have an anxiogenic effect, demonstrating the influence of zinc homeostasis on anxiety-like behavior [45]. Zinc hydroaspartate administration in male albino Swiss mice and male Wistar rats also revealed a dose-dependent anxiolytic effect in the treatment group [46]. Zinc oxide nanoparticles represent another potential therapy option for anxiety. Although conventional zinc oxide has been shown to have moderate anxiolytic effects, it was discovered that a treatment of zinc oxide nanoparticles outperformed conventional zinc oxide for the reduction of anxiety-like behavior in adult male Wistar rats [47,48]. This nanoparticle delivery method provides evidence for a unique and more effective form of zinc-based treatment for anxiety. However, more research is needed to understand the safety and biological mechanisms of zinc oxide nanoparticles as a form of mental health therapy, after which clinical trials should be conducted.

Although there is compelling evidence to support the claim that zinc status is inversely associated with anxiety, other studies have shown conflicting results. For example, no correlation was found between serum zinc concentration and anxiety in older community-dwelling Australians [49] nor in Polish postmenopausal women [50]. A cross-sectional study in elderly Iranians found no association between anxiety and dietary zinc nor serum zinc [51]. In a prospective analysis, Australian adolescents were evaluated for potential

associations between various mental health issues and dietary zinc. Anxiety was assessed using the Youth Self-Report and dietary zinc using a semi-quantitative food frequency questionnaire. Although the results were trending toward statistical significance, there was no confirmed association between dietary zinc and anxiety [52]. A study with Australian women ranging from 20–94 years old also indicated no association between dietary zinc intake and anxiety [53]. Although there is substantial evidence that zinc supplementation frequently has an anxiolytic effect, a study in women with postpartum depression showed a different result. In this randomized controlled clinical trial, the women with postpartum depression and anxiety were treated with 27 mg of zinc sulfate supplements for eight weeks but did not experience a significant improvement in state anxiety or trait anxiety [54].

Overall, the current scientific literature suggests a relationship between zinc and anxiety. Most of the evidence shows that there is an association between zinc deficiency and anxiety, and that zinc repletion may alleviate the symptoms. However, other studies show that there is no connection. A summary of clinical evidence for the relationship between zinc and anxiety is shown in Table 1. Due to variations in genetics, age, sex, and study design, it is not surprising that there are conflicting results. More research is needed to establish a true cause-and-effect relationship between zinc deficiency and anxiety. Additionally, determining the proper dose and form of zinc for clinical supplementation is important. More investigation is needed to understand how zinc dysregulation impacts different brain regions, such as the amygdala and hippocampus, how zinc supplementation influences HGF levels and other neurotrophic factors, and how zinc-dependent antioxidants may play a role in the development of anxiety disorders.

**Table 1.** Summary of clinical evidence for the relationship between zinc (Zn) and anxiety.

| Participants | Measures | Key Results | Authors and Year |
|---|---|---|---|
| Female high school students | Hospital Anxiety and Depression Scale; serum Zn | Inverse association between serum Zn and anxiety | Tahmasebi et al., 2017 [28] |
| Female university students | Beck Anxiety Inventory survey; dietary Zn assessment using a 12-month food frequency questionnaire | Inverse association between dietary Zn intake and anxiety | Hajianfar et al., 2021 [29] |
| Adult Japanese Workers | Kessler Psychological Distress Scale; dietary Zn assessed using three-month food frequency questionnaire | Inverse association between dietary Zn and anxiety symptoms | Nakamura et al., 2019 [30] |
| Children and adolescents with ADHD | Conners' Parent Rating Scale, Conners' Teacher Rating Scale; serum Zn | Low serum Zn correlates with higher anxiety and conduct issues | Oner et al., 2010 [32] |
| Male Chinese individuals | Self-Rating Anxiety Scale; cerebrospinal fluid Zn concentration | Cerebrospinal fluid Zn was negatively correlated with anxiety symptoms | Song et al., 2016 [33] |
| Adults from Bangladesh with generalized anxiety disorder | Patients previously diagnosed with generalized anxiety disorder were recruited; serum Zn | Participants with anxiety had low serum concentrations of Zn | Islam et al., 2013 [34] |
| Patients with CHD and T2DM | Beck Anxiety Inventory; serum Zn | Zn sulfate and magnesium oxide supplementation reduced anxiety symptoms. | Hamedifard at al., 2020 [35] |
| Iranian Females | Premenstrual Symptoms Screening Tool-Adolescent questionnaire; 220 mg/day elemental zinc supplement for 24 weeks | Zn supplementation reduced anxiety and other symptoms related to PMS | Ahmadi et al., 2022 [36] |

**Table 1.** *Cont.*

| Participants | Measures | Key Results | Authors and Year |
|---|---|---|---|
| Guatemalan school-aged children | Psychological questionnaire; serum Zn | Increased serum Zn was associated with reduced anxiety symptoms | DiGirolamo et al., 2010 [22] |
| Patients with anxiety | Modified Hamilton Scale; plasma Zn and Cu | Patients with anxiety had lower serum Zn concentrations compared to control. Anxiety symptoms were reduced after Zn/antioxidant supplementation. | Russo., 2011 [38] |
| Patients with anxiety and depression | Modified Hamilton Scale; plasma Zn and Cu | Zn/antioxidant treatment reduced anxiety and normalized plasma Zn | Russo., 2011 [39] |
| Individuals with anxiety | Hamilton Rating Scale; serum Zn | Individuals with anxiety had lower levels of serum HGF and Zn compared to control. Eight-week Zn/antioxidant supplementation correlated with increased serum HGF and zinc. | Russo., 2010 [40] |
| Community dwelling Australian Adults | Hospital Anxiety and Depression Scale; serum Zn | No correlation between serum Zn and anxiety | Mravunac et al., 2019 [49] |
| Polish postmenopausal women | Primary Care Evaluation of Mental Disorders and State-Trait Anxiety Inventory; serum Zn | No correlation between serum Zn concentration and anxiety | Wieder-Huszla et al., 2020 [50] |
| Elderly Iranians | Hamilton Anxiety Rating Scale; dietary Zn and serum Zn analysis | No association between anxiety and dietary Zn nor serum Zn | Anbari-Nogyni et al., 2020 [51] |
| Australian Adolescents | Youth-Self Report; semi-quantitative food frequency questionnaire to assess dietary Zn | No confirmed association between dietary Zn and anxiety | Black et al., 2015 [52] |
| Australian women (20–94 yrs) | General Health Questionnaire and clinical interviews; food frequency questionnaire to assess dietary Zn | No association between dietary Zn intake and anxiety | Jacka et al., 2012 [53] |
| Women with postpartum depression | Spielberger State-Trait Anxiety Inventory; 24 h dietary questionnaire, serum Zn | Daily 27-mg Zn sulfate supplementation for eight weeks showed no significant improvement in state anxiety or trait anxiety | Fard et al., 2017 [54] |

Abbreviations: Zn = zinc, Cu = copper, ADHD = attention deficit hyperactivity disorder, CHD = coronary heart disease, T2DM = Type 2 Diabetes Mellitus, PMS = premenstrual syndrome, HGF = human growth factor.

## 4. Copper

Copper is an essential trace mineral involved in energy production, iron metabolism, neuropeptide activation, and neurotransmitter synthesis. It also plays a role in neurohormone homeostasis, brain development, and immune system function. The RDA for copper is 900 mcg/day for adult men and women [55]. Rich sources of copper include meat, shellfish, nuts, seeds, legumes, and dried fruit. Other sources include potatoes, whole grains, and cocoa [26]. Copper deficiency can lead to health issues such as anemia, connective tissue abnormalities, impaired growth, nervous system degeneration, and weakened immune

system [23]. Although copper deficiency is not common in the United States, people at risk for potential deficiency include those with Celiac disease and Menkes disease. Additionally, excess zinc intake, especially in the form of dietary supplements, can lead to copper deficiency since zinc can interfere with copper absorption [55].

Copper is required for normal physiological function. It acts as an antioxidant as a component of cytoplasmic superoxide dismutase and metallothionein [26]. Copper also functions within metallothionein to regulate the bioavailability and absorption of zinc [56]. It is a key component of ceruloplasmin and hephaestin, ferroxidase proteins that are required for iron utilization [26]. A key physiological function of copper related to mood is its role as a cofactor for dopaminemonooxygenase, which converts dopamine to norepinephrine. Copper is also a cofactor for a variety of amine oxidases responsible for oxidizing biogenic amines such as dopamine, serotonin, and norepinephrine. In addition to its role as an enzyme cofactor, copper participates in nerve myelination and endorphin action. Thus, a copper imbalance can lead to the potential dysfunction of several neurological and physiological processes. A summary of clinical research that examines the impact of copper on anxiety is shown in Table 2.

Currently, there is limited research that links copper deficiency with anxiety disorders. One preclinical study using male Wistar rats found that copper injections had an anxiolytic effect when assessing behaviors in the elevated plus maze and light-dark box tests [57]. A cross-sectional study in adult Japanese workers mentioned previously in this review found an inverse association of both zinc and copper dietary intake with anxiety and depression symptoms [30]. To the best of our knowledge, this was the only current study in humans that linked copper deficiency to anxiety disorders, possibly due to the fact that the incidence of copper deficiency is rare.

Rather than deficiency, there is more evidence to support a relationship between anxiety symptoms and copper overload. For example, male and female adults from Bangladesh with generalized anxiety disorder had significantly higher serum copper and iron levels compared to a control group [34]. In a cross-sectional case–control study with male participants, the relationship between anxiety and serum copper was examined in patients with type 2 diabetes mellitus and a control group. The Hamilton Anxiety Rating Scale was used for the anxiety assessment. They found a positive association between copper and anxiogenic behaviors in all subjects [58]. The anxiogenic effects of excess serum copper could be explained by oxidative stress or disruptions in neurotransmitter synthesis. In the presence of biological reducing agents, cupric ion ($Cu^{2+}$) can be reduced to cuprous ion ($Cu^{+}$), which can catalyze the formation of hydroxyl radicals from hydrogen peroxide via the Haber-Weiss reaction [59]. The resulting damage to various biomolecules and cellular membranes could lead to neurodegeneration or disruptions in neurotransmitter synthesis, potentially manifesting as anxiety or other mood disorders. The impact of copper on anxiety in rodents can vary depending on the route of copper exposure. For example, although male Wistar rats injected with copper displayed anxiolytic behaviors [57], rats exposed to excess copper via drinking water showed anxiogenic behaviors using the elevated plus maze test [60]. Both studies found that copper intoxication induced a serotonergic modification in the dorsal raphe nucleus manifested as increased serotonin levels [57,60]. This increased concentration of serotonin may result from an upstream effect on tryptophan hydroxylase activity, the rate-limiting copper-dependent enzyme required for serotonin synthesis. Serotonin is one of many neurotransmitters implicated in the pathophysiology of anxiety disorders [61], thus disturbances in serotonin-related enzyme activity via cofactor dysregulation may provide a mechanism for understanding the biological triggers of anxiety and potential treatments through diet intervention and medication.

Although there is evidence to support the relationship between anxiety and copper overload, other studies show that there is no significant correlation. A randomized controlled trial with older community-dwelling Australians found no association between anxiety and blood copper, zinc, or copper/zinc levels [49]. A cross-sectional study in pregnant Iranian adolescents found that participants with depression had elevated copper, however, there was no association between serum copper and anxiety [62]. In Polish postmenopausal women, no relationship

was found between anxiety and serum copper levels [50]. A case–control study mentioned previously in this review evaluated the effect of an eight-week zinc supplementation and antioxidant therapy on anxiety symptoms, plasma zinc, plasma copper, and copper/zinc ratio [38]. Patients with anxiety were found to have higher copper and copper/zinc levels but had reduced zinc concentrations compared to the control group before the treatment was administered. Although the zinc/antioxidant therapy improved anxiety symptoms and restored plasma zinc levels to a normal level, plasma copper was unchanged after the treatment. This reduction in anxiety with no concurrent change in plasma copper suggests that zinc has a greater impact on anxiety symptoms or that zinc could be a better indicator of anxiety compared to copper. In a similar study, participants with a combination of anxiety and depression or anxiety only were found to have lower levels of plasma zinc and higher plasma copper compared to the control group before treatment [39]. After the eight-week zinc/antioxidant therapy, zinc levels were normalized, anxiety symptoms were reduced, but there was an unexpected increase in plasma copper for patients with a combination of anxiety and depression. For patients with anxiety only, plasma copper decreased, but not with statistical significance. Like the previous study, these results suggest that biological zinc has more influence on anxiety compared to copper. Since zinc and copper can compete for transporters and share cofactor roles in enzymes such as metallothionein and cytoplasmic superoxide dismutase, it is still worth investigating both trace elements considering that both impact the nervous system and may play a role in stabilizing mental health.

In conclusion, the current evidence suggests that copper overload is a more substantial concern than copper deficiency as it relates to anxiety disorders. There is also evidence to show that there is no relationship between copper and anxiety. However, there is limited research that specifically quantifies dietary copper intake and the subsequent impact on anxiety, thus providing an opportunity for continued research to understand if there is a significant relationship between this trace element and anxiety disorders.

**Table 2.** Summary of clinical evidence for the relationship between copper (Cu) and anxiety.

| Participants | Measures | Key Results | Authors and Year |
|---|---|---|---|
| Adult Japanese workers | Kessler Psychological Distress Scale; dietary Cu assessed using three-month food frequency questionnaire | Inverse association of Cu and Zn dietary intake with anxiety and depression symptoms | Nakamura et al., 2019 [30] |
| Adults from Bangladesh with generalized anxiety disorder | Patients previously diagnosed with generalized anxiety disorder were recruited; serum Cu | Participants had significantly higher serum Cu levels compared to control group | Islam et al., 2013 [34] |
| T2DM males | Hamilton Anxiety Rating Scale; serum Cu | Positive association between Cu and anxiogenic behaviors | Al Hakeim et al., 2022 [58] |
| Community dwelling Australian Adults | Hospital Anxiety and Depression Scale; plasma Cu and serum Zn | No association between anxiety and Cu or Cu/Zn levels | Mravunac et al., 2019 [49] |
| Pregnant adolescents | Depression Anxiety Stress Scale-21; serum Cu | No association between anxiety and serum Cu | Bahramy et al., 2020 [62] |
| Polish postmenopausal women | State-Trait Anxiety Inventory; serum Cu | No association between anxiety and serum Cu | Wieder-Huszla et al., 2020 [50] |
| Patients with anxiety | Modified Hamilton Scale; plasma Cu and Zn | Participants with anxiety had higher Cu and Cu/Zn levels compared to control group. Zn/antioxidant treatment had no effect on plasma Cu. | Russo, 2011 [38] |
| Patients with anxiety and depression | Modified Hamilton Scale; plasma Cu and Zn | Participants with anxiety and depression had higher plasma Cu and lower plasma Zn compared to the control group | Russo, 2011 [39] |

Abbreviations: Cu = copper, Zn = zinc, T2DM = Type 2 Diabetes Mellitus.

## 5. Iron

Iron is a vital trace element required for good health and red blood cell function. This element plays a crucial role in the early developmental stages of life and is required for proper growth and oxygen transport. The RDA for iron depends on gender and developmental stage of life: 8 mg daily for adult men, 18 mg for adult women, 27 mg during pregnancy, 9–10 mg while lactating, 8 mg for elderly, and 7–15 mg for children and adolescents. Iron is more bioavailable in the heme form obtained from animal sources versus the non-heme form. The richest sources of this mineral are from lean meat and seafood. Non-heme iron is provided by nuts, beans, vegetables, and fortified grains. Although the body does not absorb non-heme iron as easily, these sources of iron can be paired with foods high in vitamin C to improve bioavailability and help achieve the RDA [63]. Iron deficiency is one of the most common dietary mineral deficiencies worldwide [64]. Populations at higher risk for iron deficiency include infants, young children, and adolescents due to rapid growth rate, women who are menstruating due to blood loss, and pregnant women due to expanding blood volume and demands of the fetus and placenta [26]. In addition to health issues related to insufficient iron intake, such as iron deficiency anemia (IDA), iron overload is also a major health concern. Iron overload is implicated in the process of neurodegeneration and common brain-targeted diseases such as Alzheimer's, Parkinson's, and Huntington's disease [65]. Considering the biological significance of iron, maintaining iron homeostasis through proper diet is critical for health promotion and disease prevention.

Iron-dependent proteins serve many diverse roles throughout the body. Key heme proteins include hemoglobin, myoglobin, and cytochromes. Amino acid metabolism depends on iron for the proper function of dioxygenase enzymes, including tryptophan dioxygenase and homogentisate dioxygenase for tyrosine metabolism. Iron is required by various peroxidases such as the antioxidant catalase, myeloperoxidase, and thyroperoxidase for the synthesis of thyroid hormones [26]. It is also required by tyrosine hydroxylase for the synthesis of catecholamines that impact behavior, such as dopamine, epinephrine, and norepinephrine [66].

Several studies have examined the relationship between iron and anxiety. Many of these studies focused on patients with IDA, a common type of anemia where the blood lacks a sufficient amount of healthy red blood cells [67]. Low iron status is often associated with higher risk for anxiety behaviors in both humans and animals. In one rodent study, male and female weanling rats were fed either an iron-deficient diet or control diet for six weeks. The iron-deficient rats showed significantly increased anxiety-like behaviors and reductions in brain iron content and dopamine receptors in the corpus striatum, prefrontal cortex, and midbrain [68]. In a Chilean cohort, participants with iron deficiency with or without anemia in infancy were reported to have greater self-reported anxiety symptoms during adolescence [69]. Taiwanese children and adolescents with IDA were also correlated with an increased risk for anxiety disorder [70]. A recent study showed that serum ferritin in adolescent females was inversely correlated with both anxiety and depressive symptom severity [71]. In a cross-sectional sleep study in Turkish adults, patients with IDA had higher levels of anxiety compared to the control group [72]. Interestingly, a group of medical technology students attending the University of Santo Tomas in the Philippines showed a significant association between symptom-based IDA and anxiety for females but not for males [73], suggesting a potential sex difference in the development of anxiety traits. Furthermore, a sleep study with male Japanese students found that low dietary intake of iron was associated with poor sleep quality, and that poor sleep was associated with higher anxiety [74].

Maternal diets that are iron-deficient can significantly impact offspring behaviors such as anxiety. For example, pregnant Long-Evans hooded rats fed a low-iron diet led to offspring with higher anxiety-like traits [75]. Another rodent study investigated the behavior of adult Wistar male and female rats exposed to iron deficiency during the fetal and lactational periods and subsequent impact of dietary iron replacement after the weaning period. The iron-deficient progeny displayed higher levels of anxiety-like behavior compared to the control group and

did not benefit from the post-weaning iron-supplemented diet [21]. These pre-clinical studies emphasize the consequence of an iron-deficient diet during pregnancy and lactation, as it can lead to future psychological impairments. In a scoping review regarding maternal nutrition and neurodevelopment, it was reported that inadequate nutrient intake during pregnancy, including lack of dietary iron, was associated with brain defects, such as diminished cerebral volume and alteration of hypothalamic and hippocampal pathways, and an increased risk of neuropsychiatric disorders such as anxiety and depression [76]. The authors stress that important developmental processes, such as myelination, dendritogenesis, synaptogenesis, and neurotransmission, are dependent on iron-containing enzymes and hemoproteins. It is therefore evident that sufficient dietary iron intake is critical in the maternal and developmental phases of life to preserve both physical and mental health.

Interventions with various iron supplementation treatments have proven to have a significant anxiolytic effect in many cases. For example, in a 16-week intervention study, elderly Canadians were assigned randomly to either a liquid nutritional supplement group or a control group. Iron serum increased in the treatment group, and values from the General Well-Being Questionnaire improved for anxiety and general well-being [77]. A prospective multicenter observational study in patients with inflammatory bowel disease and IDA evaluated the efficacy and tolerability of Sucrosomial® iron as an alternative to conventional iron supplements. The new Sucrosomial® iron supplement was not only effective at treating inflammatory bowel disease and IDA, but also improved anxiety symptoms [78]. A clinical study in Italy evaluated the effect of Sideremil™, a liposomal iron pyrophosphate/ascorbic acid supplement, on clinical and psychological outcomes in pregnant women with IDA. They found that this form of iron supplementation was effective at reducing anxiety and increasing key iron-related proteins such as hemoglobin, ferritin, and transferrin [79]. In a prospective randomized controlled intervention trial, South African anemic mothers were given iron sulfate supplements and followed from 10 weeks of pregnancy to nine months postpartum. Iron status for these women was inversely associated with stress and anxiety [80]. Premenopausal Turkish women with IDA were treated with oral or parenteral iron agents for three months, and anxiety was assessed using the Beck Anxiety Inventory. Anxiety scores improved and serum iron was increased after the treatment [81]. A retrospective population-based cohort study in Taiwan compared psychiatric disorders in patients with IDA compared to a control group. The IDA group was associated with significantly higher incidence of anxiety disorders. Iron supplementation in these IDA patients was associated with a lower risk of psychiatric disorders compared to non-iron supplementation in IDA participants [82]. Furthermore, a prospective study evaluated Japanese children and adolescents with hypoferritinemia who received an oral iron administration for 12 weeks. The results showed that the iron supplemented group had increased ferritin levels and had significantly improved hypoferritinemia-related psychological symptoms, including anxiety and depression [83]. Novel treatments using nanoparticle technology have also been evaluated preclinically. Similar to the zinc oxide nanoparticle treatment mentioned earlier in this review, iron oxide nanoparticles show promise as a treatment method capable of crossing the blood–brain barrier to induce anxiolytic effects. In a study with male Sprague Dawley rats, injection of iron oxide nanoparticles conjugated with antisauvagine-30 peptide, a peptide shown to reduce anxiety in rodent models, was found to significantly reduce anxiety-like behavior [84].

Although the majority of research provides evidence that iron deficiency increases the risk for anxiety disorders, other studies have revealed different results. For example, a study in young women ranging from 20–32 years old that used electroencephalographic psychometric data to assess anxiety found that iron-depleted females did not differ from the iron-sufficient group in anxiety traits [85]. In a multicenter randomized control trial in nonanemic adult French women with fatigue, women were assigned 80 mg/day oral ferrous sulfate or placebo for 12 weeks. The Current and Past Psychological Scale was used to evaluate fatigue as the main outcome, and anxiety and depression as secondary outcomes. Although the iron supplementation effectively decreased fatigue, there was

no significant change in anxiety or depression [86]. However, in a similar randomized control trial in Switzerland, women who were assigned 80 mg/day oral ferrous sulfate for four weeks had significantly improved fatigue and anxiety symptoms, but no change in depression [87]. As mentioned previously in this review, adults from Bangladesh with generalized anxiety disorder had significantly higher serum iron and copper levels compared to a control group [34]. A cross-sectional study in adult Japanese workers found an inverse association between dietary zinc and copper and anxiety symptoms, but no association between anxiety and iron [30]. In a study with children, healthy Chilean infants free of IDA at age six months were randomly assigned to either an iron supplemented formula or a control formula from ages six to 12 months. At 10 years of age, the children were evaluated for various social-emotional outcomes. Although the treatment group was associated with more adaptive behavior at age 10, especially in response to reward, there were no differences in behaviors related to behavioral inhibition, such as anxiety, depression, or social problems [88].

Elucidating the mechanisms of iron metabolism in the brain and the neuronal pathways involved in anxiety provocation are important for the development of specifically targeted dietary treatments, nutraceuticals, or pharmaceuticals for the alleviation of anxiety. It was discovered recently that axonal iron transport along a neuronal pathway from the ventral hippocampus to the medial prefrontal cortex and to the substantia nigra modulates anxiety-like behaviors in male C57BL/6J mice [89]. Additionally, it has been proposed that mechanisms of iron-impacted behavior change include altered functions in the hippocampus, the corpus striatum, and neurotransmitter metabolism [90]. One study evaluated the impact of ceruloplasmin deficiency on anxiety in male three-month-old ceruloplasmin knockout mice. Ceruloplasmin is a copper-dependent ferroxidase involved in regulating cellular iron efflux. It was discovered that iron levels in the hippocampus were significantly reduced in ceruloplasmin knockout mice and that ceruloplasmin deficiency resulted in higher anxiety-like behavior in the open field and elevated plus maze tests. Additionally, it was found that levels of serotonin and norepinephrine, and the expression of brain-derived neurotrophic factor (BDNF) and its receptor, were significantly reduced in the hippocampus of ceruloplasmin knockout mice. This suggests that the anxiety phenotype resulting from ceruloplasmin deficiency involves mechanisms that include reduced levels of iron, serotonin, norepinephrine, and BDNF expression in the hippocampus [91]. For a more in-depth discussion related to iron metabolism and potential biological mechanisms related to behaviors impacted by iron dysregulation, several relevant scientific publications are available [92–96].

In sum, the current evidence demonstrates that iron status has an impact on anxiety as revealed through both human and animal models. A summary of clinical research investigating the relationship between zinc and anxiety is shown in Table 3. Consuming the recommended amount of dietary iron through food or supplements is critical for both physical and mental health and is especially important during the early stages of life. Although many studies have been published on the topic of IDA and anxiety or iron supplementation for the attenuation of anxiety, there are limited studies focused on the relationship between dietary iron and anxiety disorder. Future investigations could include iron-fortified diet interventions for iron-deficient individuals for the potential improvement of anxiety symptoms. Furthermore, investigating gender differences in effectiveness of iron supplementation or iron-fortified diets for the mitigation of anxiety would be valuable. These gaps in the scientific literature present an opportunity for future research to better understand the relationship between dietary or supplemental iron and anxiety disorder, providing an opportunity for safe, alternative treatment options or adjunctive diet-based treatments for the improvement of mental health.

**Table 3.** Summary of clinical evidence for the relationship between iron (Fe) and anxiety.

| Participants | Measures | Key Results | Authors and Year |
|---|---|---|---|
| Chilean children (infancy–adolescence) | Youth Self Report by adolescents and the Child Behavior Checklist by parents; blood Fe at 12 and 18 months | Greater self-reported anxiety symptoms during adolescence for participants with Fe deficiency as an infant | Doom et al., 2018 [69] |
| Taiwanese children and adolescents with IDA | National Health Insurance Database from 1996 to 2008 used to identify children and adolescents with IDA; coexisting anxiety disorders were determined by specific diagnostic codes | IDA correlated with an increased risk for anxiety disorder | Chen et al., 2013 [70] |
| Adolescent females | Psychiatric assessment to determine anxiety status; serum ferritin | Serum ferritin was inversely correlated with both anxiety and depressive symptom severity | Abbas et al., 2021 [71] |
| Turkish adults | Hospital Anxiety and Depression Scale; diagnosis of IDA | Patients with IDA had higher levels of anxiety compared to the control group | Semiz et al., 2015 [72] |
| Students from the University of Santo Tomas in Sampaloc, Manila | General Anxiety Disorder-7 questionnaire; symptom-based IDA questionnaire | Positive association between symptom-based IDA and anxiety for females but not for males | Buita et al., 2021 [73] |
| Male Japanese students | State-Trait Anxiety Inventory A-Trait scale; brief-type self-administered diet history questionnaire | Low dietary Fe intake was associated with poor sleep quality and poor sleep was associated with higher anxiety | Matsunaga et al., 2021 [74] |
| Elderly Canadians | General Well-Being Questionnaire; liquid nutritional supplement; serum Fe | Supplemented group had increased serum Fe and improved anxiety and general well-being scores | Krondl et al., 1999 [77] |
| Patients with inflammatory bowel disease and IDA | EuroQoL questionnaire to assess anxiety; one capsule/day for 12 weeks Sucrosomial® Fe supplement | Sucrosomial® Fe supplement improved anxiety symptoms | Bastida et al., 2021 [78] |
| Italian pregnant women with IDA | State-Trait Anxiety Inventory; one capsule/day for one year of Sideremil™ liposomal Fe pyrophosphate/ascorbic acid supplement | Fe supplementation reduced anxiety and increased key Fe-related proteins hemoglobin, ferritin, and transferrin | Vitale et al., 2022 [79] |
| South African anemic mothers | Edinburgh Postnatal Depression Scale and State-Trait Anxiety Inventory; 125 mg Fe sulfate supplements from 10 weeks of pregnancy to nine months postpartum; Fe status assessed using hemoglobin, mean corpuscular volume, and transferrin saturation | Fe status was inversely associated with stress and anxiety and Fe supplementation improved stress scores | Beard et al., 2005 [80] |

**Table 3.** *Cont.*

| Participants | Measures | Key Results | Authors and Year |
|---|---|---|---|
| Premenopausal Turkish women with IDA | Beck Anxiety Inventory; treatment with oral or parenteral Fe agents for three months, serum Fe | Anxiety scores improved and serum Fe was increased after the treatment | Gulmez et al., 2014 [81] |
| Taiwanese patients with IDA | Longitudinal Health Insurance Database 2005 was used to recruit IDA patients and retrieve Fe supplementation data and anxiety disorder data; IDA status confirmed by measuring serum Fe, ferritin, and total iron binding capacity | IDA group was associated with higher incidence of anxiety disorders. Fe supplementation in IDA patients was associated with a lower risk of psychiatric disorders. | Lee et al., 2020 [82] |
| Japanese children and adolescents with hypoferritinemia | Profile of Mood States 2nd Edition Youth-Short; 25–100 mg oral Fe administration for 12 weeks; serum ferritin | Fe supplemented group had increased ferritin levels and had significantly improved hypoferritinemia-related psychological symptoms, including anxiety and depression | Mikami et al., 2022 [83] |
| Swiss women 18–55 years old | Validated 24-item self-administered questionnaire; 80 mg/day oral ferrous sulfate for four weeks; serum ferritin | Improved fatigue and anxiety symptoms for Fe treatment group | Verdon 2003 [87] |
| Non-anemic women 20–32 years old | Electroencephalographic psychometric data to assess anxiety; serum ferritin | Fe-depleted females did not differ from the Fe-sufficient group in anxiety traits | Dziembowska et al., 2019 [85] |
| Nonanemic adult French women with fatigue | Current and Past Psychological Scale; 80 mg/day oral ferrous sulfate for 12 weeks | No change in anxiety or depression with Fe supplementation | Vaucher et al., 2012 [86] |
| Adults from Bangladesh with generalized anxiety disorder | Patients previously diagnosed with generalized anxiety disorder were recruited; serum Fe | Participants with anxiety had higher serum Fe concentration | Islam et al., 2013 [34] |
| Adult Japanese Workers | Kessler Psychological Distress Scale; dietary Fe assessed using three-month food frequency questionnaire | No association between anxiety and Fe | Nakamura et al., 2019 [30] |
| Healthy Chilean infants free of IDA at age six months | Trier Social Stress Test for Children and Child Behavior Checklist; Fe-supplemented formula 12.7 mg/L from ages six to 12 months | No difference in behaviors related to behavioral inhibition, such as anxiety, depression, or social problems | Lozoff et al., 2014 [88] |

Abbreviations: Fe = iron, IDA = iron deficiency anemia.

## 6. Selenium

Selenium has many benefits as an essential nutrient in our diet. It functions as an antioxidant and helps regulate thyroid hormone metabolism, DNA synthesis, reproduction, and immune system support. The RDA for age 14 years and older is 55 mcg. Biological selenium status is commonly assessed using blood or urine for recent selenium intake or hair and nails for long-term intake. Selenium-rich foods include Brazil nuts, meat, grains, and seafood, such as tuna, halibut, sardines, and shrimp. Brazil nuts are considered the richest source as they supply 544 mcg per 6–8 nuts, providing 989% of the daily value [97]. The selenium content of plant foods, such as grains and seeds, depends on the selenium concentration of the soil in which they are grown. Hence, lower soil selenium levels in regions such as China can lead to dietary selenium deficiency [12]. It is critical to obtain the RDA for selenium since a deficiency has been associated with Keshan disease, male infertility, and cognitive decline [97].

Selenium plays a key role in several enzymes called selenoproteins, which function primarily as antioxidants. The most highly characterized of these proteins is glutathione peroxidase. Glutathione peroxidase is an important antioxidant that converts hydrogen peroxide, lipid peroxides, and organic peroxides to less harmful substances via a coupled reaction involving the conversion of reduced glutathione to oxidized glutathione. A dietary deficiency in selenium decreases the expression of glutathione peroxidase in favor of other selenoproteins, such as selenoprotein P, and can increase the risk for oxidative damage. Selenoprotein P contains up to 10 selenocysteine residues, transports selenium to tissues, and acts as an additional antioxidant, quenching peroxynitrate radicals which can damage DNA and lipid membranes. Selenoprotein M is found in neuronal cells and may protect against oxidative stress caused by hydrogen peroxide. Selenium is also required for iodine metabolism for the regulation of thyroid hormone synthesis [26]. The various biological roles and mechanistic actions of selenium and selenoproteins are not completely understood and require more investigation.

Research involving the impact of selenium on anxiety is relatively recent. Overall, the majority of evidence reveals an inverse association between selenium and anxiety, and a promising effect of selenium supplementation to alleviate anxiety symptoms. For example, in Portuguese adults with chronic renal failure under hemodialysis, higher anxiety levels were associated with selenium deficiency based on nutrient intake analysis [98]. A study involving 831 Chinese children used the Screen for Child Anxiety Related Disorders questionnaire and serum selenium concentrations to assess the relationship between selenium and anxiety. It was found that lower selenium levels were associated with higher anxiety symptoms [99]. Recently, two randomized, double-blinded, placebo-controlled clinical trials revealed a promising effect of combining a probiotic with selenium for the reduction of anxiety symptoms in women with polycystic ovary syndrome [100] and adult patients with both type 2 diabetes and coronary heart disease [20]. Both studies found an increase in total antioxidant capacity and glutathione levels in the treatment group, suggesting that the effect of selenium to reduce anxiety could be a result of improved antioxidant activity. Furthermore, it was found in older reports that selenium supplementation or a selenium-fortified diet may improve anxious mood [101,102]. More research should be conducted to understand the impact of selenium supplementation on the reduction of anxiety symptoms in patients diagnosed with anxiety disorders to broaden current treatment options.

Preclinical research has also shown that selenium-based treatments are effective for mitigating anxiety. In several of these studies, 7-chloro-4-phenylselanylquinoline (4-PSQ), a new quinoline derivative containing selenium, shows promise as an anxiolytic agent in rodents [103–106]. One of these studies found that 4-PSQ exhibited antioxidant activity and protected against memory impairment and anxiety in a mouse model of Alzheimer's disease [104]. Another showed that the anxiolytic effect of 4-PSQ in male adult Swiss mice may be associated with its ability to modulate serotonergic and GABAergic systems [105]. A third study using obese male Wistar rats discovered that 4-PSQ mitigated anxiety-like and depression-like behaviors induced by neonatal administrations of monosodium glutamate [106]. Similar to the

anxiolytic actions of 4-PSQ, another potential therapeutic agent for the attenuation of anxiety is the selenium-based compound 6-((4-fluorophenyl) selanyl)-9H-purine. This compound was found to reduce anxiety-like behaviors in male adult Swiss mice [107]. Furthermore, the efficacy of a pyrazole-containing selenium compound to treat anxiety caused by acute restraint stress was assessed in adult male Swiss mice. The selenium-based treatment was successful in decreasing plasma corticosterone and reducing lipid peroxidation by modulating oxidative pathways and neuroendocrine responses. It alleviated anxiety-like behavior and restored the activity of superoxide dismutase and catalase in the hippocampus and prefrontal cortex [108]. Although not directly related to diet, these studies involving selenium-based pharmacological agents provide evidence that selenium is involved mechanistically in the process of reducing anxiety, likely through its antioxidant properties. The impact of selenium on anxiety provoked by arsenic exposure has also been investigated. Arsenic has been linked to oxidative stress and anxiety symptoms in humans and animals and can be used as a method to study potential anxiety treatments in a rodent model [109]. For example, one research team investigated the effect of selenium on arsenic-induced anxiety-like behavior in male Albino Wistar rats [110]. The selenium treatment had an anxiolytic effect and increased the activity of glutathione peroxidase, superoxide dismutase, and catalase in the hippocampus. This recent evaluation of selenium as a protective agent against arsenic toxicity and consequent neurological disruptions suggests a promising treatment for anxiety and other mental health disorders caused by arsenic poisoning. Overall, these rodent studies demonstrate the beneficial impact of selenium on anxiety and its positive influence on endogenous antioxidants to reduce oxidative stress and neurological damage that can lead to mental health disorders.

There is evidence that demonstrates the connection between thyroid function and mental health [111]. As selenium plays an important role in thyroid hormone metabolism, it is postulated that a selenium imbalance occurring in thyroid disease may promote anxiety disorder as a comorbidity. To investigate this possible connection, one cross-sectional study examined the relationship between selenium and anxiety in patients with euthyroid nodular goiter. There was a significant correlation between selenium deficiency and anxiety symptoms independent of thyroid hormone status [112]. Based on these results, patients with euthyroid nodular goiter may benefit from selenium-enriched diets or selenium supplementation.

Although most of the scientific literature suggests an inverse association between selenium status and anxiety, there is some evidence that suggests that there is no association. For example, one study evaluated the relationship between serum selenium levels and anxiety symptoms in postmenopausal women using the State-Trait Anxiety Inventory questionnaire. There was no observed correlation between selenium concentrations and the corresponding anxiety level of the individual. The same lack of association with anxiety was also found for zinc, copper, and magnesium for the women in this study [50].

Overall, there appears to be a positive correlation between dietary selenium intake or selenium-based treatments and reduced anxiety. A summary of clinical evidence for the relationship between selenium and anxiety is shown in Table 4. To the best of our knowledge, there was only one study that found no association, and no evidence to suggest that dietary selenium or high selenium serum levels can lead to increased anxiety. It is possible that the beneficial influence of selenium on anxiety symptoms results from a combination of reduced oxidative stress, improved regulation of thyroid function, and optimized function of selenoproteins. Several clinical and preclinical studies described above found increased antioxidant capacity after selenium supplementation, suggesting that the anxiolytic effect of selenium is mainly attributed to its protective function against oxidative stress. One limitation when drawing conclusions regarding selenium status and anxiety is the lack of research in humans that have anxiety disorder as their primary health concern. Several of the studies reviewed here were conducted in patients with comorbidities, such as chronic renal failure, polycystic ovary syndrome, and euthyroid nodular goiter. Further investigation of the impact of dietary selenium on patients with anxiety disorder alone would help clarify the relationship between this trace element and mental health. Another limitation is that animal studies have mainly involved selenium

derivatives such as 4-PSQ and 6-((4-fluorophenyl) selanyl)-9H-purine rather than dietary selenium. Future research in animals could include selenium-enriched or selenium-deficient diets compared to a control diet to provide a more translatable evaluation of the impact of dietary selenium on anxiety-like behavior. In conclusion, the evidence thus far supports that proper intake of selenium can have a positive impact on mental health by alleviating anxiety. However, the connection between selenium and anxiety is just beginning to gain the attention of the research community, with much to be learned from further research.

**Table 4.** Summary of clinical evidence for the relationship between selenium (Se) and anxiety.

| Participants | Measures | Key Results | Authors and Year |
|---|---|---|---|
| Portuguese adults with chronic renal failure under hemodialysis | EuroQoL anxiety assessment; DIETPLAN5 2003 nutrient intake analysis for Se | Higher anxiety associated with Se deficiency | Raimundo et al., 2006 [98] |
| Chinese children | Screen for Child Anxiety Related Disorders questionnaire; serum Se | Lower serum Se associated with higher anxiety symptoms | Portnoy et al., 2022 [99] |
| Women 18–40 years old with polycystic ovary syndrome | Depression Anxiety and Stress scale, General Health Questionnaire-28; probiotic supplement with 200 µg/day Se for 12 weeks | Se/probiotic treatment was associated with reduced anxiety symptoms | Jamilian et al., 2018 [100] |
| Adults 45–85 years old diagnosed with both T2DM and CHD | Beck Anxiety Inventory; probiotic supplement with 200 µg/day Se for 12 weeks | Se/probiotic treatment was associated with improved Beck Anxiety Inventory scores | Raygan et al., 2019 [20] |
| Females and males 14–74 years old | Profile of Mood States questionnaire; 100 µg Se supplementation daily for five weeks | Se supplementation associated with decreased anxious mood | Benton and Cook, 1990 [101] |
| Healthy men 18–45 years old | Profile of Mood States-Bi Polar questionnaire; formulated diets containing low (32.6 µg) or high (226.5 µg) Se/day for 105 days and plasma Se | High Se diet associated with improved anxiety scores | Finley and Penland, 1998 [102] |
| Adults 18–80 years old with Euthyroid Nodular Goiter | Beck Anxiety Inventory; serum Se | Negative correlation between serum Se and anxiety | Turan and Karaaslan, 2020 [112] |

Abbreviations: Se = selenium, T2DM = Type 2 Diabetes Mellitus, CHD = coronary heart disease.

## 7. Conclusions

Based on the current peer-reviewed scientific literature, there is evidence to suggest an inverse association between anxiety and dietary trace minerals zinc, iron, and selenium. Improved dietary patterns that include a variety of foods or treatments plans to supplement mineral deficiencies are potential strategies to optimize both physical and mental health. Although there is some evidence that a deficiency in copper may be correlated with anxiety, there is more evidence to suggest that copper overload has a greater influence on the development of anxiety. More research is needed to understand the specific neurobiological mechanisms involved. Overall, the collective findings demonstrate the importance of optimizing trace mineral homeostasis for the mitigation of anxiety disorders and preservation of mental health.

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## References

1. Penninx, B.W.; Pine, D.S.; Holmes, E.A.; Reif, A. Anxiety Disorders. *Lancet* **2021**, *397*, 914–927. [CrossRef] [PubMed]
2. World Health Organization Mental Disorders. Available online: https://www.who.int/news-room/fact-sheets/detail/mental-disorders (accessed on 24 June 2022).
3. Prevalence of Any Anxiety Disorder. Available online: https://www.nimh.nih.gov/health/statistics/any-anxiety-disorder (accessed on 22 June 2022).
4. Ströhle, A.; Gensichen, J.; Domschke, K. The Diagnosis and Treatment of Anxiety Disorders. *Dtsch. Ärztebl. Int.* **2018**, *115*, 611–620. [CrossRef]
5. Logan, A.C.; Jacka, F.N. Nutritional Psychiatry Research: An Emerging Discipline and Its Intersection with Global Urbanization, Environmental Challenges and the Evolutionary Mismatch. *J. Physiol. Anthropol.* **2014**, *33*, 22. [CrossRef] [PubMed]
6. Marx, W.; Moseley, G.; Berk, M.; Jacka, F. Nutritional Psychiatry: The Present State of the Evidence. *Proc. Nutr. Soc.* **2017**, *76*, 427–436. [CrossRef] [PubMed]
7. Adan, R.A.H.; van der Beek, E.M.; Buitelaar, J.K.; Cryan, J.F.; Hebebrand, J.; Higgs, S.; Schellekens, H.; Dickson, S.L. Nutritional Psychiatry: Towards Improving Mental Health by What You Eat. *Eur. Neuropsychopharmacol.* **2019**, *29*, 1321–1332. [CrossRef]
8. Firth, J.; Gangwisch, J.E.; Borsini, A.; Wootton, R.E.; Mayer, E.A. Food and Mood: How Do Diet and Nutrition Affect Mental Wellbeing? *Food Thought* **2020**, *369*, 4. [CrossRef]
9. Godos, J.; Currenti, W.; Angelino, D.; Mena, P.; Castellano, S.; Caraci, F.; Galvano, F.; Del Rio, D.; Ferri, R.; Grosso, G. Diet and Mental Health: Review of the Recent Updates on Molecular Mechanisms. *Antioxidants* **2020**, *9*, 346. [CrossRef]
10. Kris-Etherton, P.M.; Petersen, K.S.; Hibbeln, J.R.; Hurley, D.; Kolick, V.; Peoples, S.; Rodriguez, N.; Woodward-Lopez, G. Nutrition and Behavioral Health Disorders: Depression and Anxiety. *Nutr. Rev.* **2021**, *79*, 247–260. [CrossRef]
11. Aucoin, M.; LaChance, L.; Naidoo, U.; Remy, D.; Shekdar, T.; Sayar, N.; Cardozo, V.; Rawana, T.; Chan, I.; Cooley, K. Diet and Anxiety: A Scoping Review. *Nutrients* **2021**, *13*, 4418. [CrossRef]
12. Shayganfard, M. Are Essential Trace Elements Effective in Modulation of Mental Disorders? Update and Perspectives. *Biol. Trace Elem. Res.* **2022**, *200*, 1032–1059. [CrossRef]
13. Hassan, W.; Barroso Silva, C.; Mohammadzai, I.U.; Teixeira da Rocha, J.; Landeira-Fernandez, J. Association of Oxidative Stress to the Genesis of Anxiety: Implications for Possible Therapeutic Interventions. *Curr. Neuropharmacol.* **2014**, *12*, 120–139. [CrossRef] [PubMed]
14. *Dietary Guidelines for Americans, 2020–2025*, 9th ed.; U.S. Department of Agriculture; U.S. Department of Health and Human Services: Washington, DC, USA, 2020.
15. Blampied, M.; Bell, C.; Gilbert, C.; Rucklidge, J.J. Broad Spectrum Micronutrient Formulas for the Treatment of Symptoms of Depression, Stress, and/or Anxiety: A Systematic Review. *Expert Rev. Neurother.* **2020**, *20*, 351–371. [CrossRef] [PubMed]
16. Kimball, S.; Mirhosseini, N.; Rucklidge, J. Database Analysis of Depression and Anxiety in a Community Sample—Response to a Micronutrient Intervention. *Nutrients* **2018**, *10*, 152. [CrossRef] [PubMed]
17. Rucklidge, J.J.; Blampied, N.; Gorman, B.; Gordon, H.A.; Sole, E. Psychological Functioning 1 Year after a Brief Intervention Using Micronutrients to Treat Stress and Anxiety Related to the 2011 Christchurch Earthquakes: A Naturalistic Follow-up. *Hum. Psychopharmacol. Clin. Exp.* **2014**, *29*, 230–243. [CrossRef] [PubMed]
18. Zhang, L.; Kleiman-Weiner, M.; Luo, R.; Shi, Y.; Martorell, R.; Medina, A.; Rozelle, S. Multiple Micronutrient Supplementation Reduces Anemia and Anxiety in Rural China's Elementary School Children. *J. Nutr.* **2013**, *143*, 640–647. [CrossRef]
19. Boyle, N.; Lawton, C.; Dye, L. The Effects of Magnesium Supplementation on Subjective Anxiety and Stress—A Systematic Review. *Nutrients* **2017**, *9*, 429. [CrossRef]
20. Raygan, F.; Ostadmohammadi, V.; Asemi, Z. The Effects of Probiotic and Selenium Co-Supplementation on Mental Health Parameters and Metabolic Profiles in Type 2 Diabetic Patients with Coronary Heart Disease: A Randomized, Double-Blind, Placebo-Controlled Trial. *Clin. Nutr.* **2019**, *38*, 1594–1598. [CrossRef]
21. Bonuti, R.; Horiquini-Barbosa, E.; Morato, S. Late Effects of Iron Deficiency during Gestation and Lactation Followed by Iron Replacement on Anxiety-Related Behaviors and Brain Morphology of Young Adult Rats. *Psychol. Neurosci.* **2020**, *13*, 516–530. [CrossRef]

22. DiGirolamo, A.M.; Ramirez-Zea, M.; Wang, M.; Flores-Ayala, R.; Martorell, R.; Neufeld, L.M.; Ramakrishnan, U.; Sellen, D.; Black, M.M.; Stein, A.D. Randomized Trial of the Effect of Zinc Supplementation on the Mental Health of School-Age Children in Guatemala. *Am. J. Clin. Nutr.* **2010**, *92*, 1241–1250. [CrossRef]
23. Smolin, L.A.; Grosvenor, M.B. *Nutrition: Science and Applications*; Wiley: Hoboken, NJ, USA, 2016; ISBN 978-1-119-08710-6.
24. U.S. Department of Health and Human Services Office of Dietary Supplements—Zinc. Available online: https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/ (accessed on 25 June 2022).
25. Młyniec, K.; Gaweł, M.; Doboszewska, U.; Starowicz, G.; Nowak, G. The Role of Elements in Anxiety. *Vitam. Horm.* **2017**, *103*, 295–326. [CrossRef]
26. Gropper, S.S.; Smith, J.L.; Carr, T.P. *Advanced Nutrition and Human Metabolism*, 8th ed.; Cengage: Mason, OH, USA, 2022; ISBN 978-0-357-70932-0.
27. Cope, E.C.; Levenson, C.W. Role of Zinc in the Development and Treatment of Mood Disorders. *Curr. Opin. Clin. Nutr. Metab. Care* **2010**, *13*, 685–689. [CrossRef] [PubMed]
28. Tahmasebi, K.; Amani, R.; Nazari, Z.; Ahmadi, K.; Moazzen, S.; Mostafavi, S.-A. Association of Mood Disorders with Serum Zinc Concentrations in Adolescent Female Students. *Biol. Trace Elem. Res.* **2017**, *178*, 180–188. [CrossRef] [PubMed]
29. Hajianfar, H.; Mollaghasemi, N.; Tavakoly, R.; Campbell, M.S.; Mohtashamrad, M.; Arab, A. The Association between Dietary Zinc Intake and Health Status, including Mental Health and Sleep Quality, among Iranian Female Students. *Biol. Trace Elem. Res.* **2021**, *199*, 1754–1761. [CrossRef] [PubMed]
30. Nakamura, M.; Miura, A.; Nagahata, T.; Shibata, Y.; Okada, E.; Ojima, T. Low Zinc, Copper, and Manganese Intake Is Associated with Depression and Anxiety Symptoms in the Japanese Working Population: Findings from the Eating Habit and Well-Being Study. *Nutrients* **2019**, *11*, 847. [CrossRef] [PubMed]
31. Grabrucker, S.; Boeckers, T.M.; Grabrucker, A.M. Gender Dependent Evaluation of Autism like Behavior in Mice Exposed to Prenatal Zinc Deficiency. *Front. Behav. Neurosci.* **2016**, *10*, 37. [CrossRef] [PubMed]
32. Oner, O.; Oner, P.; Bozkurt, O.H.; Odabas, E.; Keser, N.; Karadag, H.; Kızılgün, M. Effects of Zinc and Ferritin Levels on Parent and Teacher Reported Symptom Scores in Attention Deficit Hyperactivity Disorder. *Child Psychiatry Hum. Dev.* **2010**, *41*, 441–447. [CrossRef]
33. Song, N.; Yu, D.; Kang, Y.; Cao, Z.; Yang, X.; Wang, J.; Liu, Y.; Wang, F. Negative Correlation between CSF Zinc Level and Anxiety in Male Chinese Subjects. *Psychiatry Res.* **2016**, *246*, 841–843. [CrossRef]
34. Islam, M.R.; Ahmed, M.U.; Mitu, S.A.; Islam, M.S.; Rahman, G.K.M.M.; Qusar, M.M.A.S.; Hasnat, A. Comparative Analysis of Serum Zinc, Copper, Manganese, Iron, Calcium, and Magnesium Level and Complexity of Interelement Relations in Generalized Anxiety Disorder Patients. *Biol. Trace Elem. Res.* **2013**, *154*, 21–27. [CrossRef]
35. Hamedifard, Z.; Farrokhian, A.; Reiner, Ž.; Bahmani, F.; Asemi, Z.; Ghotbi, M.; Taghizadeh, M. The Effects of Combined Magnesium and Zinc Supplementation on Metabolic Status in Patients with Type 2 Diabetes Mellitus and Coronary Heart Disease. *Lipids Health Dis.* **2020**, *19*, 112. [CrossRef]
36. Ahmadi, M.; Khansary, S.; Parsapour, H.; Alizamir, A.; Pirdehghan, A. The Effect of Zinc Supplementation on the Improvement of Premenstrual Symptoms in Female University Students: A Randomized Clinical Trial Study. *Biol. Trace Elem. Res.* **2023**, *201*, 559–566. [CrossRef]
37. Zinc Supplementation in the Treatment of Anorexia Nervosa. *Rev. Assoc. Médica Bras. Engl. Ed.* **2013**, *59*, 321–324. [CrossRef] [PubMed]
38. Russo, A.J. Decreased Zinc and Increased Copper in Individuals with Anxiety. *Nutr. Metab. Insights* **2011**, *4*, 1–5. [CrossRef] [PubMed]
39. Russo, A.J. Analysis of Plasma Zinc and Copper Concentration, and Perceived Symptoms, in Individuals with Depression, Post Zinc and Anti-Oxidant Therapy. *Nutr. Metab. Insights* **2011**, *4*, NMI-S6760. [CrossRef]
40. Russo, A.J. Decreased Serum Hepatocyte Growth Factor (HGF) in Individuals with Anxiety Increases after Zinc Therapy. *Nutr. Metab. Insights* **2010**, *3*, NMI-S5495. [CrossRef] [PubMed]
41. Nakamura, T.; Mizuno, S. The Discovery of Hepatocyte Growth Factor (HGF) and Its Significance for Cell Biology, Life Sciences and Clinical Medicine. *Proc. Jpn. Acad. Ser. B* **2010**, *86*, 588–610. [CrossRef]
42. Barkus, C.; McHugh, S.B.; Sprengel, R.; Seeburg, P.H.; Rawlins, J.N.P.; Bannerman, D.M. Hippocampal NMDA Receptors and Anxiety: At the Interface between Cognition and Emotion. *Eur. J. Pharmacol.* **2010**, *626*, 49–56. [CrossRef]
43. Ghasemi, M.; Navidhamidi, M.; Rezaei, F.; Azizikia, A.; Mehranfard, N. Anxiety and Hippocampal Neuronal Activity: Relationship and Potential Mechanisms. *Cogn. Affect. Behav. Neurosci.* **2022**, *22*, 431–449. [CrossRef]
44. Cavalcanti, C.L.; Gonçalves, M.C.R.; Alves, A.F.; de Araújo, E.V.; Carvalho, J.L.P.; Lins, P.P.; Alves, R.C.; Soares, N.L.; Pordeus, L.C.M.; Aquino, J.S. Antidepressant, Anxiolytic and Neuroprotective Activities of Two Zinc Compounds in Diabetic Rats. *Front. Neurosci.* **2020**, *13*, 1411. [CrossRef]
45. Samardzic, J.; Savic, K.; Stefanovic, N.; Matunovic, R.; Baltezarevic, D.; Obradovic, M.; Jancic, J.; Opric, D.; Obradovic, D. Anxiolytic and Antidepressant Effect of Zinc on Rats and Its Impact on General Behavioural Parameters. *Vojnosanit. Pregl.* **2013**, *70*, 391–395. [CrossRef]
46. Partyka, A.; Jastrzębska-Więsek, M.; Szewczyk, B.; Stachowicz, K.; Sławińska, A.; Poleszak, E.; Doboszewska, U.; Pilc, A.; Nowak, G. Anxiolytic-like Activity of Zinc in Rodent Tests. *Pharmacol. Rep.* **2011**, *63*, 1050–1055. [CrossRef]

47. Kesmati, M.; Varzi, H.; Harooni, H.; Torabi, M. Effects of Nano and Conventional Zinc Oxide on Anxiety-like Behavior in Male Rats. *Indian J. Pharmacol.* **2013**, *45*, 508. [CrossRef] [PubMed]
48. Torabi, M.; Kesmati, M.; Pourreza, N.; Najafzadeh Varzi, H.; Galehdari, H. Neurobehavioral and Biochemical Modulation Following Administration of MgO and ZnO Nanoparticles in the Presence and Absence of Acute Stress. *Life Sci.* **2018**, *203*, 72–82. [CrossRef] [PubMed]
49. Mravunac, M.; Szymlek-Gay, E.; Daly, R.M.; Roberts, B.R.; Formica, M.; Gianoudis, J.; O'Connell, S.L.; Nowson, C.A.; Cardoso, B.R. Greater Circulating Copper Concentrations and Copper/Zinc Ratios Are Associated with Lower Psychological Distress, But Not Cognitive Performance, in a Sample of Australian Older Adults. *Nutrients* **2019**, *11*, 2503. [CrossRef] [PubMed]
50. Wieder-Huszla, S.; Zabielska, P.; Kotwas, A.; Owsianowska, J.; Karakiewicz-Krawczyk, K.; Kowalczyk, R.; Jurczak, A. The Severity of Depressive and Anxiety Symptoms in Postmenopausal Women Depending on Their Magnesium, Zinc, Selenium and Copper Levels. *J. Elem.* **2020**, *25*, 1305–1317. [CrossRef]
51. Anbari-Nogyni, Z.; Bidaki, R.; Madadizadeh, F.; Sangsefidi, Z.S.; Fallahzadeh, H.; Karimi-Nazari, E.; Nadjarzadeh, A. Relationship of Zinc Status with Depression and Anxiety among Elderly Population. *Clin. Nutr. ESPEN* **2020**, *37*, 233–239. [CrossRef]
52. Black, L.J.; Allen, K.L.; Jacoby, P.; Trapp, G.S.; Gallagher, C.M.; Byrne, S.M.; Oddy, W.H. Low Dietary Intake of Magnesium Is Associated with Increased Externalising Behaviours in Adolescents. *Public Health Nutr.* **2015**, *18*, 1824–1830. [CrossRef]
53. Jacka, F.N.; Maes, M.; Pasco, J.A.; Williams, L.J.; Berk, M. Nutrient Intakes and the Common Mental Disorders in Women. *J. Affect. Disord.* **2012**, *141*, 79–85. [CrossRef]
54. Fard, F.E.; Mirghafourvand, M.; Mohammad-Alizadeh Charandabi, S.; Farshbaf-Khalili, A.; Javadzadeh, Y.; Asgharian, H. Effects of Zinc and Magnesium Supplements on Postpartum Depression and Anxiety: A Randomized Controlled Clinical Trial. *Women Health* **2017**, *57*, 1115–1128. [CrossRef]
55. U.S. Department of Health and Human Services Office of Dietary Supplements—Copper. Available online: https://ods.od.nih.gov/factsheets/Copper-HealthProfessional/ (accessed on 25 June 2022).
56. Ruttkay-Nedecky, B.; Nejdl, L.; Gumulec, J.; Zitka, O.; Masarik, M.; Eckschlager, T.; Stiborova, M.; Adam, V.; Kizek, R. The Role of Metallothionein in Oxidative Stress. *Int. J. Mol. Sci.* **2013**, *14*, 6044–6066. [CrossRef]
57. Abdellatif, A.; Omar, E.H.; Halima, G. The Neuronal Basis of Copper Induced Modulation of Anxiety State in Rat. *Acta Histochem.* **2017**, *119*, 10–17. [CrossRef]
58. Al-Hakeim, H.K.; Hadi, H.H.; Jawad, G.A.; Maes, M. Intersections between Copper, β-Arrestin-1, Calcium, FBXW7, CD17, Insulin Resistance and Atherogenicity Mediate Depression and Anxiety Due to Type 2 Diabetes Mellitus: A Nomothetic Network Approach. *J. Pers. Med.* **2022**, *12*, 23. [CrossRef]
59. Gaetke, L.M.; Chow-Johnson, H.S.; Chow, C.K. Copper: Toxicological Relevance and Mechanisms. *Arch. Toxicol.* **2014**, *88*, 1929–1938. [CrossRef]
60. Abbaoui, A.; Gamrani, H. Obvious Anxiogenic-like Effects of Subchronic Copper Intoxication in Rats, Outcomes on Spatial Learning and Memory and Neuromodulatory Potential of Curcumin. *J. Chem. Neuroanat.* **2019**, *96*, 86–93. [CrossRef] [PubMed]
61. Frick, A.; Åhs, F.; Engman, J.; Jonasson, M.; Alaie, I.; Björkstrand, J.; Frans, Ö.; Faria, V.; Linnman, C.; Appel, L.; et al. Serotonin Synthesis and Reuptake in Social Anxiety Disorder: A Positron Emission Tomography Study. *JAMA Psychiatry* **2015**, *72*, 794. [CrossRef] [PubMed]
62. Bahramy, P.; Mohammad-Alizadeh-Charandabi, S.; Ramezani-Nardin, F.; Mirghafourvand, M. Serum Levels of Vitamin D, Calcium, Magnesium, and Copper, and Their Relations with Mental Health and Sexual Function in Pregnant Iranian Adolescents. *Biol. Trace Elem. Res.* **2020**, *198*, 440–448. [CrossRef]
63. U.S. Department of Health and Human Services Office of Dietary Supplements—Iron. Available online: https://ods.od.nih.gov/factsheets/Iron-HealthProfessional/ (accessed on 25 June 2022).
64. Stoltzfus, R.J. Iron Deficiency: Global Prevalence and Consequences. *Food Nutr. Bull.* **2003**, *24*, S99–S103. [CrossRef] [PubMed]
65. Chen, P.; Totten, M.; Zhang, Z.; Bucinca, H.; Erikson, K.; Santamaría, A.; Bowman, A.B.; Aschner, M. Iron and Manganese-Related CNS Toxicity: Mechanisms, Diagnosis and Treatment. *Expert Rev. Neurother.* **2019**, *19*, 243–260. [CrossRef]
66. Daubner, S.C.; Le, T.; Wang, S. Tyrosine Hydroxylase and Regulation of Dopamine Synthesis. *Arch. Biochem. Biophys.* **2011**, *508*, 1–12. [CrossRef]
67. Iron Deficiency Anemia—Symptoms and Causes. Available online: https://www.mayoclinic.org/diseases-conditions/iron-deficiency-anemia/symptoms-causes/syc-20355034 (accessed on 28 June 2022).
68. Beard, J.L.; Erikson, K.M.; Jones, B.C. Neurobehavioral Analysis of Developmental Iron Deficiency in Rats. *Behav. Brain Res.* **2002**, *134*, 517–524. [CrossRef]
69. Doom, J.R.; Richards, B.; Caballero, G.; Delva, J.; Gahagan, S.; Lozoff, B. Infant Iron Deficiency and Iron Supplementation Predict Adolescent Internalizing, Externalizing, and Social Problems. *J. Pediatr.* **2018**, *195*, 199–205.e2. [CrossRef]
70. Chen, M.-H.; Su, T.-P.; Chen, Y.-S.; Hsu, J.-W.; Huang, K.-L.; Chang, W.-H.; Chen, T.-J.; Bai, Y.-M. Association between Psychiatric Disorders and Iron Deficiency Anemia among Children and Adolescents: A Nationwide Population-Based Study. *BMC Psychiatry* **2013**, *13*, 161. [CrossRef] [PubMed]
71. Abbas, M.; Gandy, K.; Salas, R.; Devaraj, S.; Calarge, C.A. Iron Deficiency and Internalizing Symptom Severity in Unmedicated Adolescents: A Pilot Study. *Psychol. Med.* **2021**, 1–11. [CrossRef] [PubMed]
72. Semiz, M.; Uslu, A.; Korkmaz, S.; Demir, S.; Parlak, I.; Sencan, M.; Aydin, B.; Uncu, T. Assessment of Subjective Sleep Quality in Iron Deficiency Anaemia. *Afr. Health Sci.* **2015**, *15*, 621. [CrossRef]

73. Buita, E.; Castor, D.; Condat, E.; Cuaderno, M.; Cunan, J.; Danao, F.; Daya, M.; Villegas, V. Association of Symptoms-Based Iron Deficiency Anemia to Anxiety and Depression Related Criteria Symptoms among the 3rd Year Medical Technology Students of the University Of Santo Tomas during the COVID-19 Pandemic. *Int. J. Prog. Res. Sci. Eng.* **2021**, *2*, 62–71.
74. Matsunaga, T.; Nishikawa, K.; Adachi, T.; Yasuda, K. Associations between Dietary Consumption and Sleep Quality in Young Japanese Males. *Sleep Breath.* **2021**, *25*, 199–206. [CrossRef] [PubMed]
75. Eseh, R.; Zimmerberg, B. Age-Dependent Effects of Gestational and Lactational Iron Deficiency on Anxiety Behavior in Rats. *Behav. Brain Res.* **2005**, *164*, 214–221. [CrossRef]
76. Cortés-Albornoz, M.C.; García-Guáqueta, D.P.; Velez-van-Meerbeke, A.; Talero-Gutiérrez, C. Maternal Nutrition and Neurodevelopment: A Scoping Review. *Nutrients* **2021**, *13*, 3530. [CrossRef]
77. Krondl, M.; Coleman, P.H.; Bradley, C.L.; Lau, D.; Ryan, N. Subjectively Healthy Elderly Consuming a Liquid Nutrition Supplement Maintained Body Mass Index and Improved Some Nutritional Parameters and Perceived Well-Being. *J. Am. Diet. Assoc.* **1999**, *99*, 1542–1548. [CrossRef]
78. Bastida, G.; de Guise, C.H.; Algaba, A.; Ber Nieto, Y.; Soares, J.M.; Robles, V.; Bermejo, F.; Sáez-González, E.; Gomollón, F.; Nos, P. Sucrosomial Iron Supplementation for the Treatment of Iron Deficiency Anemia in Inflammatory Bowel Disease Patients Refractory to Oral Iron Treatment. *Nutrients* **2021**, *13*, 1770. [CrossRef]
79. Vitale, S.G.; Fiore, M.; La Rosa, V.L.; Rapisarda, A.M.C.; Mazza, G.; Paratore, M.; Commodari, E.; Caruso, S. Liposomal Ferric Pyrophosphate and Ascorbic Acid Supplementation in Pregnant Women with Iron Deficiency Anaemia: Haematochemical, Obstetric, Neonatal and Psychological Outcomes in a Prospective Observational Study. *Int. J. Food Sci. Nutr.* **2022**, *73*, 221–229. [CrossRef]
80. Beard, J.L.; Hendricks, M.K.; Perez, E.M.; Murray-Kolb, L.E.; Berg, A.; Vernon-Feagans, L.; Irlam, J.; Isaacs, W.; Sive, A.; Tomlinson, M. Maternal Iron Deficiency Anemia Affects Postpartum Emotions and Cognition. *J. Nutr.* **2005**, *135*, 267–272. [CrossRef] [PubMed]
81. Gulmez, H.; Akin, Y.; Savas, M.; Gulum, M.; Ciftci, H.; Yalcinkaya, S.; Yeni, E. Impact of Iron Supplementation on Sexual Dysfunction of Women with Iron Deficiency Anemia in Short Term: A Preliminary Study. *J. Sex. Med.* **2014**, *11*, 1042–1046. [CrossRef] [PubMed]
82. Lee, H.-S.; Chao, H.-H.; Huang, W.-T.; Chen, S.C.-C.; Yang, H.-Y. Psychiatric Disorders Risk in Patients with Iron Deficiency Anemia and Association with Iron Supplementation Medications: A Nationwide Database Analysis. *BMC Psychiatry* **2020**, *20*, 216. [CrossRef] [PubMed]
83. Mikami, K.; Akama, F.; Kimoto, K.; Okazawa, H.; Orihashi, Y.; Onishi, Y.; Takahashi, Y.; Yabe, H.; Yamamoto, K.; Matsumoto, H. Iron Supplementation for Hypoferritinemia-Related Psychological Symptoms in Children and Adolescents. *J. Nippon Med. Sch.* **2022**, *89*, 203–211. [CrossRef] [PubMed]
84. Vinzant, N.; Scholl, J.L.; Wu, C.-M.; Kindle, T.; Koodali, R.; Forster, G.L. Iron Oxide Nanoparticle Delivery of Peptides to the Brain: Reversal of Anxiety during Drug Withdrawal. *Front. Neurosci.* **2017**, *11*, 608. [CrossRef] [PubMed]
85. Dziembowska, I.; Kwapisz, J.; Izdebski, P.; Żekanowska, E. Mild Iron Deficiency May Affect Female Endurance and Behavior. *Physiol. Behav.* **2019**, *205*, 44–50. [CrossRef]
86. Vaucher, P.; Druais, P.-L.; Waldvogel, S.; Favrat, B. Effect of Iron Supplementation on Fatigue in Nonanemic Menstruating Women with Low Ferritin: A Randomized Controlled Trial. *Can. Med. Assoc. J.* **2012**, *184*, 1247–1254. [CrossRef] [PubMed]
87. Verdon, F. Iron Supplementation for Unexplained Fatigue in Non-Anaemic Women: Double Blind Randomised Placebo Controlled Trial. *BMJ* **2003**, *326*, 1124. [CrossRef]
88. Lozoff, B.; Castillo, M.; Clark, K.M.; Smith, J.B.; Sturza, J. Iron Supplementation in Infancy Contributes to More Adaptive Behavior at 10 Years of Age. *J. Nutr.* **2014**, *144*, 838–845. [CrossRef]
89. Wang, Z.; Zeng, Y.-N.; Yang, P.; Jin, L.-Q.; Xiong, W.-C.; Zhu, M.-Z.; Zhang, J.-Z.; He, X.; Zhu, X.-H. Axonal Iron Transport in the Brain Modulates Anxiety-Related Behaviors. *Nat. Chem. Biol.* **2019**, *15*, 1214–1222. [CrossRef]
90. Shah, H.E.; Bhawnani, N.; Ethirajulu, A.; Alkasabera, A.; Onyali, C.B.; Anim-Koranteng, C.; Mostafa, J.A. Iron Deficiency-Induced Changes in the Hippocampus, Corpus Striatum, and Monoamines Levels That Lead to Anxiety, Depression, Sleep Disorders, and Psychotic Disorders. *Cureus* **2021**, *13*, e18138. [CrossRef] [PubMed]
91. Texel, S.J.; Camandola, S.; Ladenheim, B.; Rothman, S.M.; Mughal, M.R.; Unger, E.L.; Cadet, J.L.; Mattson, M.P. Ceruloplasmin Deficiency Results in an Anxiety Phenotype Involving Deficits in Hippocampal Iron, Serotonin, and BDNF: Ceruloplasmin, Iron, BDNF and Anxiety. *J. Neurochem.* **2012**, *120*, 125–134. [CrossRef]
92. Koleini, N.; Shapiro, J.S.; Geier, J.; Ardehali, H. Ironing out Mechanisms of Iron Homeostasis and Disorders of Iron Deficiency. *J. Clin. Investig.* **2021**, *131*, e148671. [CrossRef]
93. Cerami, C. Iron Nutriture of the Fetus, Neonate, Infant, and Child. *Ann. Nutr. Metab.* **2017**, *71*, 8–14. [CrossRef] [PubMed]
94. Kim, J.; Wessling-Resnick, M. Iron and Mechanisms of Emotional Behavior. *J. Nutr. Biochem.* **2014**, *25*, 1101–1107. [CrossRef] [PubMed]
95. Beard, J.L.; Connor, J.R. Iron Status and Neural Functioning. *Annu. Rev. Nutr.* **2003**, *23*, 41–58. [CrossRef] [PubMed]
96. Burdo, J.R.; Connor, J.R. Brain Iron Uptake and Homeostatic Mechanisms: An Overview. *Biometals* **2003**, *16*, 63–75. [CrossRef]
97. U.S. Department of Health and Human Services Office of Dietary Supplements—Selenium. Available online: https://ods.od.nih.gov/factsheets/Selenium-HealthProfessional/ (accessed on 25 June 2022).
98. Raimundo, P.; Ravasco, P.; Proença, V.; Camilo, M. Does Nutrition Play a Role in the Quality of Life of Patients under Chronic Haemodialysis? *Nutr. Hosp.* **2006**, *21*, 139–144.

99. Portnoy, J.; Wang, J.; Wang, F.; Um, P.; Irving, S.Y.; Hackl, L.; Liu, J. Lower Serum Selenium Concentration Associated with Anxiety in Children. *J. Pediatr. Nurs.* **2022**, *63*, e121–e126. [CrossRef]
100. Jamilian, M.; Mansury, S.; Bahmani, F.; Heidar, Z.; Amirani, E.; Asemi, Z. The Effects of Probiotic and Selenium Co-Supplementation on Parameters of Mental Health, Hormonal Profiles, and Biomarkers of Inflammation and Oxidative Stress in Women with Polycystic Ovary Syndrome. *J. Ovarian Res.* **2018**, *11*, 80. [CrossRef]
101. Benton, D.; Cook, R. Selenium Supplementation Improves Mood in a Double-Blind Crossover Trial. *Psychopharmacology* **1990**, *102*, 549–550. [CrossRef] [PubMed]
102. Finley, J.W.; Penland, J.G. Adequacy or Deprivation of Dietary Selenium in Healthy Men: Clinical and Psychological Findings. *J. Trace Elem. Exp. Med.* **1998**, *11*, 11–27. [CrossRef]
103. Reis, A.S.; Pinz, M.; Duarte, L.F.B.; Roehrs, J.A.; Alves, D.; Luchese, C.; Wilhelm, E.A. 4-Phenylselenyl-7-Chloroquinoline, a Novel Multitarget Compound with Anxiolytic Activity: Contribution of the Glutamatergic System. *J. Psychiatr. Res.* **2017**, *84*, 191–199. [CrossRef] [PubMed]
104. Pinz, M.P.; dos Reis, A.S.; Vogt, A.G.; Krüger, R.; Alves, D.; Jesse, C.R.; Roman, S.S.; Soares, M.P.; Wilhelm, E.A.; Luchese, C. Current Advances of Pharmacological Properties of 7-Chloro-4-(Phenylselanyl) Quinoline: Prevention of Cognitive Deficit and Anxiety in Alzheimer's Disease Model. *Biomed. Pharmacother.* **2018**, *105*, 1006–1014. [CrossRef] [PubMed]
105. Paltian, J.J.; dos Reis, A.S.; de Oliveira, R.L.; da Fonseca, C.A.R.; Domingues, W.B.; Dellagostin, E.N.; Campos, V.F.; Kruger, R.; Alves, D.; Luchese, C.; et al. The Anxiolytic Effect of a Promising Quinoline Containing Selenium with the Contribution of the Serotonergic and GABAergic Pathways: Modulation of Parameters Associated with Anxiety in Mice. *Behav. Brain Res.* **2020**, *393*, 112797. [CrossRef] [PubMed]
106. Rodrigues, K.C.; Bortolatto, C.F.; da Motta, K.P.; de Oliveira, R.L.; Paltian, J.J.; Krüger, R.; Roman, S.S.; Boeira, S.P.; Alves, D.; Wilhelm, E.A.; et al. The Neurotherapeutic Role of a Selenium-Functionalized Quinoline in Hypothalamic Obese Rats. *Psychopharmacology* **2021**, *238*, 1937–1951. [CrossRef] [PubMed]
107. Pinz, M.P.; Vogt, A.G.; da Costa Rodrigues, K.; dos Reis, A.S.; Duarte, L.F.B.; Fronza, M.G.; Domingues, W.B.; Blodorn, E.B.; Alves, D.; Campos, V.F.; et al. Effect of a Purine Derivative Containing Selenium to Improve Memory Decline and Anxiety through Modulation of the Cholinergic System and Na+/K+-ATPase in an Alzheimer's Disease Model. *Metab. Brain Dis.* **2021**, *36*, 871–888. [CrossRef]
108. Birmann, P.T.; Domingues, M.; Casaril, A.M.; Smaniotto, T.Â.; Hartwig, D.; Jacob, R.G.; Savegnago, L. A Pyrazole-Containing Selenium Compound Modulates Neuroendocrine, Oxidative Stress, and Behavioral Responses to Acute Restraint Stress in Mice. *Behav. Brain Res.* **2021**, *396*, 112874. [CrossRef]
109. Tyler, C.R.; Allan, A.M. The Effects of Arsenic Exposure on Neurological and Cognitive Dysfunction in Human and Rodent Studies: A Review. *Curr. Environ. Health Rep.* **2014**, *1*, 132–147. [CrossRef]
110. Samad, N.; Rao, T.; ur Rehman, M.H.; Bhatti, S.A.; Imran, I. Inhibitory Effects of Selenium on Arsenic-Induced Anxiety-/Depression-Like Behavior and Memory Impairment. *Biol. Trace Elem. Res.* **2022**, *200*, 689–698. [CrossRef]
111. Bunevičius, R.; Prange, A.J. Thyroid Disease and Mental Disorders: Cause and Effect or Only Comorbidity? *Curr. Opin. Psychiatry* **2010**, *23*, 363–368. [CrossRef] [PubMed]
112. Turan, E.; Karaaslan, O. The Relationship between Iodine and Selenium Levels with Anxiety and Depression in Patients with Euthyroid Nodular Goiter. *Oman Med. J.* **2020**, *35*, e161. [CrossRef] [PubMed]