REVIEW

The Effects of Psychological and Environmental Stress on Micronutrient Concentrations in the Body: A Review of the Evidence

Adrian L Lopresti

School of Psychology and Exercise Science, Murdoch University, Perth, Australia; and Clinical Research Australia, Duncraig, Australia

ABSTRACT

Stress is the nonspecific response of the body to any demand for change. Excess or chronic psychological or environmental stress is associated with an increased risk of mental and physical diseases, with several mechanisms theorized to be associated with its detrimental effects. One underappreciated potential mechanism relates to the effects of psychological and environmental stress on micronutrient concentrations. Micronutrients (vitamins and minerals) are essential for optimal physical and mental function, with deficiencies associated with an array of diseases. In this article, animal and human studies investigating the effects of various psychological and environmental stressors on micronutrient concentrations are reviewed. In particular, the effects of psychological stress, sleep deprivation, and physical exercise on micronutrient concentrations and micronutrient excretion are summarized. Micronutrients identified in this review include magnesium, zinc, calcium, iron, and niacin. Overall, the bulk of evidence suggests stress can affect micronutrient concentrations, often leading to micronutrient depletion. However, before definitive conclusions about the effects of stress can be made, the impact of different stressors, stress severity, and acute versus chronic stress on micronutrient concentrations requires investigation. Moreover, the impact of stress on micronutrients in different populations varying in age, gender, and premorbid health status and the durability of changes after a stressor is resolved require examination. The medical, physical, and psychological implications of nutrient changes caused by a stressor also remain to be determined. *Adv Nutr* 2020;11:103–112.

Keywords: stress, nutrients, magnesium, zinc, calcium, iron, sleep, exercise, review

Introduction

Stress is a general term defined by Hans Selye (1) in 1936 as the nonspecific response of the body to any demand for change. According to Chrousos (2), all living organisms maintain a complex dynamic equilibrium, or homeostasis, that is constantly challenged by internal or external adverse effects, termed stressors. He defined stress as a state in which homeostasis is threatened by real or perceived stressors. Attempts for homeostasis are then enacted by a complex repertoire of behavioral and physiological adaptive responses of the organism. Stressors can be physical or emotional, real or perceived, and acute or chronic, and they can vary tremendously in their intensity. The impact of a stressor on an individual can also vary widely, ranging from negligible effects to life-threatening impacts.

From a biological standpoint, the stress response comprises a series of reactions involving the hypothalamic–pituitary–adrenocortical and sympatho-adrenomedullary axes. A series of hormones are released, leading to increases in adrenaline, noradrenaline, and cortisol (or corticosterone in most animals). Although this stress response is essential for human functioning, excess acute activation or chronic activation is associated with several physical and mental disturbances. Acute stress is associated with allergic manifestations, such as asthma, eczema, or urticaria; migraines and headaches; hypertensive or hypotensive attacks; different types of pain conditions; gastrointestinal symptoms such as pain, indigestion, diarrhea, and constipation; and mental health disturbances such as panic attacks and psychotic episodes (3–5). Chronic stress is also associated with several disorders and diseases, including mental health disturbances such as anxiety and depression (6); neurodegenerative diseases such as Alzheimer's disease (7); cardiovascular diseases (8); metabolic disorders such as obesity, metabolic syndrome, and type 2 diabetes mellitus (9);

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Address correspondence to ALL (e-mail: a.lopresti@murdoch.edu.au).

sleep disorders such as insomnia and restless leg syndrome (10, 11); and several cancers (12, 13).

Physiological mechanisms associated with the damaging effects of stress on the body are often attributed to excess or chronic levels of stress hormones such as cortisol. Its acute elevation or chronic overproduction can have detrimental effects on all body organs, leading to tissue destruction over time (14–16). Excess or chronic stress can also adversely influence the negative feedback response associated with the regulation of the hypothalamus–pituitary–adrenal response, resulting in excess cortisol production (2). Stress exposure, and the resultant excess cortisol production, also contributes to elevations in inflammatory markers, oxidative stress, mitochondrial disturbances, and thyroid and sex hormone dysfunction (17–21). Another potential and possibly underappreciated mechanism associated with the damaging effects of stress may be via its influence on nutrient stores in the body. Nutrients such as vitamins, minerals, proteins, and fatty acids are essential for enzymatic activity, energy production, immunity, hormone synthesis, tissue growth and repair, and a large array of other biological processes (22).

The purpose of this article is to review human and animal research examining the impact of psychological and environmental stressors on micronutrient concentrations and distribution in the body. A search of research databases was conducted to examine the effects of acute and chronic stressors (defined as a physical, mental, and/or emotional demand) on micronutrient changes and distribution in the body. Although a search of the effects of stress on all micronutrients was conducted, those identified included magnesium, zinc, iron, calcium, and niacin.

Methods

Information for this review was compiled by searching PubMed (https://www.ncbi.nlm.nih.gov/pubmed), Google Scholar (https://scholar.google.com.au), PsycINFO (https://search.proquest.com/psycinfo), Scopus (https://www.scopus.com), and the Cochrane Library databases (http://www.cochranelibrary.com) and also by examining reference lists of relevant articles to locate additional studies that were not identified by the database searches. Databases were scanned from all years of study until March 2019 for animal or human studies. A systematic search of databases with the use of the terms (nutrient* or magnesium or zinc or calcium or iron or B vitamin or mineral or vitamin) and (stress or sleep restriction or cortisol) and (deplet* or reduc* or excret* or absorption) was completed.

Magnesium

Magnesium is an essential mineral used as a cofactor in more than 300 enzymatic systems. For example, it is involved in ATP metabolism, fatty acid synthesis and breakdown, glucose metabolism, protein synthesis, and DNA and RNA metabolism. Total magnesium concentrations are most commonly assessed in serum, which can provide a useful estimate of total magnesium stores, particularly in people with magnesium deficiency. However, serum magnesium concentrations may not reflect true total body magnesium concentrations because only 1% is present in serum and >99% is present in bone or intracellularly. Other measurement options include red blood cells, blood leukocytes, and muscle; however, no perfect measure has been identified (23). Urinary measures present another option that can provide an indication of magnesium excretion associated with medication use or exposure to environmental or psychological stressors (23, 24).

An examination of animal studies suggests magnesium concentrations are altered in animals exposed to acute and chronic stress. For example, when healthy adult dogs were subjected to forced exercise using a treadmill, a significant reduction in serum magnesium was observed. Moreover, magnesium concentrations were lower in winter compared with summer months, and this was negatively correlated with plasma adrenaline and noradrenaline concentrations (25). In rats, a combination of restraint stress plus ethanol administration reduced serum magnesium concentrations, although no change was observed when rats were subjected to restraint stress or ethanol administration alone (26). In rats exposed to acute cold-restraint stress, the magnesium content in both the stomach and the duodenum was reduced, although there was no change in serum levels. However, whether changes were due to exposure to cold, stress, or the combination could not be determined (27). Finally, exposure to cold and a deficient dietary intake synergistically reduced plasma magnesium concentrations in sheep (28). Sleep disturbances are common during times of stress, and 1 animal study was identified examining the effects of sleep restriction on magnesium concentrations. In this study, there was no change in magnesium hippocampal concentrations after sleep deprivation in rats (29). Concentrations of hippocampal magnesium are positively associated with synaptic plasticity, learning, and memory (30).

Results from investigations on various stressors in human populations are generally consistent with those obtained from animal studies. For example, increased urinary magnesium excretion was reported in university students during their examination period compared with the beginning of their academic term. This increased excretion positively correlated with increases in self-reported anxiety but not stress levels (31). Whether increased urinary excretion was associated with lower serum magnesium concentrations is uncertain because this was not investigated. Furthermore, changes in the diet were also not examined, which may have contributed to the reduced urinary concentrations over time. In another study, measures taken before and immediately after a 4-wk final-term examination in college students were associated with decreased erythrocyte (intracellular) magnesium concentrations. All students during this period also experienced chronic sleep deprivation, which may have also influenced stress levels and magnesium concentrations (32). Cernak et al. (33) investigated magnesium status in young volunteers exposed to chronic stress (e.g., political intolerance, awareness of potential military attacks, permanent stand-by duty, and reduced holidays >10 y) or subchronic

stress consisting of everyday mortal danger in military actions lasting >3 mo. Significant decreases in plasma ionized magnesium and total magnesium concentrations were found in both groups. In a study by Piruzian and colleagues (34), a 6-man crew was isolated in a chamber for 105 d. The scenario was designed to simulate a Mars mission comprising various experiments and realistic mission scenarios. Total and ionized magnesium in serum and daily urine were measured before and on days 30, 60, and 105 of the experiment. Hair magnesium concentrations were also measured before and on day 105 of the experiment. Reductions in serum magnesium (total and ionized) were observed over time, with the greatest changes occurring during the first 30 d of the experiment. Changes in urinary magnesium were also observed, as demonstrated by an initially increased excretion followed by reduced excretion at day 105. Moreover, hair concentrations of magnesium were lower at day 105. These findings suggest stress has a larger impact on magnesium excretion during early exposure (up to 30 d) and then stabilizes over time. Alternatively, reduced magnesium excretion over time may result from stress-induced magnesium depletion. Finally, changes in blood and urine concentrations of magnesium were measured after a 4-h exposure to noise in an industrial plant. Serum levels of magnesium increased the evening after noise exposure. However, urinary concentrations remained the same the evening after noise exposure but significantly increased 1 and 2 d post-noise exposure, suggesting increased excretion over time (35). The results of this study suggest an acute 4-h exposure to a stressor can alter magnesium concentrations, with varying effects on serum and urine over time. However, how magnesium concentrations in blood and urine change following acute compared with chronic stress exposure was not examined.

Several studies were identified examining the relation between sleep quality and sleep restriction on blood and urinary concentrations of magnesium. In 1 study, healthy male college students were monitored over a 4-wk period, commencing 4 wk prior to their final exams. Compared with nonstressed periods (defined as 1 d that followed at least 1 wk of sleeping well), erythrocyte magnesium concentrations during chronic-stress periods (defined as a time of high mental stress due to final exams and 80% less sleep compared with nonstress periods) were significantly lower. Moreover, plasma concentrations of adrenaline and noradrenaline were higher, and heart rate variability was lower (suggesting increased autonomic arousal) (32, 36). Whether changes in magnesium concentrations were due to reduced sleep duration, stress associated with exams, or the combination was not adequately evaluated. Tanabe et al. (37) measured erythrocyte magnesium concentrations in healthy men after exposure to 3 conditions comprising 1 d following a night of good sleep (control condition), 1 d preceded by <3 h of sleep (temporary sleep deprivation), and 1 d preceded by 1 mo during which sleep was <60% of the control condition (chronic sleep deprivation). Erythrocyte magnesium concentrations were lower after temporary sleep restriction compared with the control condition. Moreover, chronic sleep deprivation was associated with even greater reductions in magnesium concentrations as levels were lower than both the control and temporary sleep restriction conditions. In a study comparing sleep-deprived men with a control group, there were differences in the 24-h pattern of urinary magnesium excretion after acute, whole-body cold exposure (38). However, there were no differences in total magnesium excretion during this period.

As a physical stressor, investigations into the effects of physical exercise on magnesium concentrations have also been conducted. Blood and urine concentrations of magnesium decreased significantly following the completion of a marathon in endurance athletes (39). In another exercise study, blood samples were taken before and 3 min after completion of a 40-min run. Post-exercise plasma magnesium concentrations were significantly lower than pre-exercise concentrations, which coincided with increases in plasma adrenaline (40).

Definitive conclusions about the effect of psychological and environmental stress on magnesium concentrations cannot be made due to significant variability in the type of stress exposure (e.g., noise, exams, sleep restriction, endurance exercise, and war/political stress), duration of stress exposure (e.g., acute 4-h stress, 4 wk of stress exposure, and chronic war exposure), and type of magnesium measurement (e.g., serum, erythrocyte, urine, and hair). However, the bulk of evidence suggests that both acute and chronic exposure to psychological and environmental stress are associated with lower blood magnesium concentrations and increased urinary excretion. The greatest effects of stress on magnesium concentrations seem to occur in the first month of exposure, with no further reductions after this time. However, this requires further investigation.

Zinc

Zinc is vital for the function of >300 enzymes. It plays a key role in gene expression; immune function; and the synthesis or decomposition of carbohydrates, fats, proteins, and nucleic acids (41, 42). Zinc status in humans can be assessed in plasma, serum, erythrocytes, neutrophils, lymphocytes, urine, and hair (43). Because <1% of total zinc stores are in the blood, accurate measurement of blood samples is difficult. However, total blood plasma zinc can provide a simple and useful measure of zinc deficiency (44). Other blood measures can also provide an indication of total zinc status, and urinary zinc can provide a marker of zinc excretion. However, weaknesses are associated with all the aforementioned measurements.

There are several animal studies examining the effects of stress on zinc stores. Tao et al. (45) assessed the effects of repeated psychological stress (electrical shocks) on zinc metabolism in rats. Rats exposed to stress experienced increases in serum cortisol and decreases in serum zinc concentrations after 7 and 14 d. In the liver, zinc concentrations increased at day 14, whereas its concentration in the hippocampus was decreased after 7 and 14 d of

stress exposure. Moreover, a decrease in zinc absorption in the small intestine was observed at days 7 and 14, which recovered to normal concentrations 7 d after stress exposure. There were no significant changes in zinc concentrations in the heart, spleen, kidney, duodenum, cerebral cortex, and cerebellum. In another animal study, exposure to 7 and 14 d of psychological stress-induced hypozincemia was related to liver zinc accumulation believed to result from an increased concentration of metallothionein, a zinc-binding protein (46). Teng et al. (47) exposed mice to single or repeated restraints to induce acute or chronic stress. Blood zinc concentrations of restrained rats in both the acute-stress and the chronic-stress groups were significantly lower than in the control groups. Finally, in rats exposed to 1-h restraint stress, hippocampal zinc release was stimulated by 167% (48).

Stress effects on zinc concentrations in human populations are limited, although most studies have confirmed stress-induced zinc depletion. In 1 study, serum zinc concentrations were measured in 34 apparently healthy male prisoners of war immediately upon release from a detention camp. Zinc concentrations were lower in former prisoners compared with a healthy-matched control group. The authors argued that because the BMI of the former prisoners was in the normal range (average 23.4 kg/m^2) and the nomogram showed no indication of malnutrition, lower zinc concentrations were likely the result of increased psychological stress induced by conditions during imprisonment (49). Singh et al. (50) measured plasma zinc concentrations before and after a 5-d period of sustained physical and psychological stress in Navy SEAL trainees. Physical stressors included simulated combat exercises and obstacle courses, running, swimming, and boat races. Trainees were also only allowed ~5 h of sleep during the entire 5-d period. Psychological stressors comprised increases in performance anxiety, verbal confrontations, activities with no-win situations, and increased anxiety associated with the uncertainty of the nature of events. Plasma zinc levels decreased by 33% at the end of the 5 d but returned to baseline 7 d later. In contrast to these findings, salivary zinc concentrations did not significantly change in dental students from 1 wk before to immediately prior to the completion of a comprehensive English test (51). However, the reliability of saliva as a measure of zinc status remains questionable (52). Studies on the effects of exercise on zinc concentrations have generally confirmed zinc-altering effects, although changes vary based on the time of collection. In a meta-analysis, it was concluded that serum zinc concentrations decrease significantly during exercise recovery compared to pre-exercise levels (53). However, an increase in serum zinc immediately after exercise was reported by the same authors in a separate meta-analysis (54).

Overall, given the paucity of studies conducted, a definitive conclusion about the effects of environmental and psychological stress on zinc concentrations cannot be made. However, the bulk of evidence from animal studies suggests acute and chronic stress ranging from 1 h to 14 d is associated with reduced blood and tissue concentrations. Results from human studies also indicate that acute stress exposure (physical and psychological) lasting up to 5 d, severe chronic stress (prisoners of war), and endurance exercise are associated with lower serum and plasma zinc concentrations. How zinc concentrations vary over time and once the stressor is resolved requires further investigation.

Iron

Iron is an essential element involved in a wide variety of metabolic processes, including oxygen transport, DNA synthesis, and electron transport. Almost two-thirds of body iron is located in the blood as a component of hemoglobin, an oxygen-binding protein, present in erythrocytes; 25% is contained in ferritin, a readily mobilized iron-binding protein; and the remaining 15% is bound to myoglobin, an oxygen-binding protein, which is found in muscle tissue and a variety of enzymes involved in oxidative metabolism and many other cellular functions (55). In humans, iron concentrations are most commonly measured in plasma or serum. Serum ferritin provides a good measure of iron stores, although it is an acute-phase reactant protein, so concentrations can be elevated by infection or inflammation. Plasma or serum iron reflects the fraction of all iron in the body that circulates, bound primarily to transferrin, but does not provide an accurate measure of iron stores (56).

Results from animal studies suggest iron concentrations may be altered by stress exposure. For example, rats that underwent psychological stress for 14 d experienced a significant decrease in femoral bone marrow iron, in addition to a 28.6% and 27.5% reduction in serum iron and a 10% and 12.5% reduction in hemoglobin after days 7 and 14, respectively. There were no changes in serum ferritin, transferrin receptor, and erythropoietin at day 7, although serum ferritin and erythropoietin decreased by 23.8% and 12.3% at day 14, respectively. Also, transferrin receptor increased by 31.5% after 14 d (57). In another study, single or repeat restraints were applied to mice to induce acute or chronic stress. The concentration of whole blood iron in both acute stress and chronic stress groups was significantly lower compared with that in the control groups (47).

The effects of stress on iron concentrations in human populations are limited and contradictory. After 5 d of physical and psychological stress in Navy SEAL trainees, iron concentrations decreased by 44% and ferritin concentrations increased by 59% but returned to baseline 7 d later (50). However, there were no changes in salivary concentrations of iron during a 1-wk period in students undergoing a comprehensive English test (51). In 1 interesting study on pregnant mothers, umbilical cord blood hemoglobin, zinc protoporphyrin/heme (ZnPP/H; to evaluate concentrations of erythrocyte iron), and plasma ferritin (to evaluate iron stores) were measured. Maternal recall of distress and health concerns during pregnancy positively correlated with cord blood ZnPP/H (indicating low erythrocyte iron). At 1 y, 24% of infants who were breastfed had a moderate iron deficiency, with higher cord blood ZnPP/H predictive of this moderate iron deficiency. In mothers with similar levels of cord blood ZnPP/H, the likelihood of low plasma ferritin at 1 y in infants

increased 36-fold in higher stressed mothers compared with low-stress mothers (58). These results suggest stress levels in mothers are associated with altered iron concentrations in infants, even 1 y after their birth.

There have been several studies examining the effects of physical exercise on iron concentrations. After participation in a strength training program comprising 2-h sessions, 4 times a week, for 6 wk, serum ferritin decreased by 35% in healthy untrained males. There were no changes in transferrin, serum iron, and iron saturation of transferrin (59). In another study, 2 h of moderate-intensity exercise by recreational cyclists resulted in a 3% and 1% loss of the recommended daily intake of iron through sweat in men and women, respectively (60). Martinez et al. (61) examined the effect of both acute exercise and maintained training during a period of competition (3 mo at the start of the season) on iron metabolism in sportsmen on a professional volleyball team. Participants completed an exercise test, and a range of hematological parameters were measured at rest, just after exercise, and after recovery, including serum iron, ferritin, and cortisol. The exercise tests resulted in several changes in hematological and biochemical variables that were related to iron metabolism. The researchers concluded that athletes, after a period of adaptation, with a good plan of work/recovery series, undergo a biological redistribution of hematological and biochemical parameters concerning iron metabolism during the training and competition period.

Overall, the results from both animal and human studies suggest psychological and environmental stress can alter iron concentrations. However, whether such stressors are associated with increases or decreases requires further investigation. The measures used to assess iron concentrations (e.g., ferritin, serum iron, and serum transferrin, saliva, and tissue stores) add to the variability of findings. Because ferritin is an acute-phase reactant protein, caution is warranted with its interpretation as a marker of iron stores due to the fact that it can be increased by inflammation.

Calcium

Calcium has many essential roles in the body, including being involved in muscle contraction, oocyte activation, bone and teeth development, blood clotting, nerve impulse and transmission, heart regulation, and cellular fluid balance. Approximately 99% of the body's calcium is stored in teeth and bones, and ~1% is found in blood (62). Calcium concentrations can be measured in serum, whole blood, urine, and hair. Although these provide an indication of body calcium status, interpretation is hindered by the body's tight regulation of blood concentrations, which do not necessarily reflect tissue concentrations (63).

In the single identified animal study, the concentrations of whole blood calcium were higher in rats exposed to chronic stress (but not acute stress) compared with control rats (47). The effects of stress on calcium concentrations have been investigated in several human studies. Significant decreases in plasma calcium concentrations were found in young volunteers exposed to chronic and sub-chronic stress (33). In a study designed to investigate the social and individual psychological conditions associated with a long-term space mission to Mars, participants' total serum calcium concentrations decreased by 16% from baseline after 30 d of isolation (although they remained within physiological norms) and stabilized at these lower concentrations during the remaining 75 d. However, there were no significant changes in urinary and hair concentrations (64). Changes in blood and urine concentrations of calcium were measured after a 4-h exposure to noise in an industrial plant. Serum levels of calcium increased the evening after noise exposure. However, there were no changes in urinary calcium concentrations (35). Contrary to these findings, some studies have demonstrated no impact of stress on calcium concentrations. In a study on university students during the examination period, despite self-reported increases in anxiety (but not stress), there were no changes in urinary calcium excretion during the examination period compared with the beginning of the academic term (31). Moreover, there were no changes in serum calcium concentrations after a marathon run in endurance athletes (39).

If psychological and environmental stress negatively impacts on calcium concentrations in the body, it would be prudent to expect lower bone mineral densities (BMDs) in people experiencing chronic psychological stress. This has been observed in some human and animal studies. For example, an examination of ~16,000 adults demonstrated a significant negative correlation between BMD (femoral neck, lumbar spine, and total femur) and psychological stress, particularly in men and premenopausal women (65). Moreover, in a cross-sectional study on 135 postmenopausal women, BMD in the spine and right and left hip was negatively associated with depression, anxiety, and stress (66). Results from animal studies have also confirmed that prenatal stress (67) and chronic psychological stress (68) can negatively affect BMD.

Niacin (vitamin B-3)

Niacin is converted in the body into its primary metabolically active form, coenzyme NAD. Because >400 enzymes require NAD to catalyze reactions in the body, niacin is involved in ATP production, cellular maintenance and communication, and the synthesis of cholesterol and fatty acids (69). Concentrations of niacin in the blood are unreliable indicators of niacin status, with the most sensitive and reliable measure of niacin status believed to be the urinary excretion of its two major methylated metabolites, *N*(1)-methyl-nicotinamide and *N*(1)-methyl-2-pyridone-5-carboxamide (69, 70).

One study was identified examining the effects of stress on concentrations of the B vitamin, niacin. In this study, the effects of cold exposure (classified as a physical stressor), calculation exercise (classified as a mental stressor), and dark exposure (classified as an emotional stressor) on the metabolism of niacin in female adults were examined. Cold exposure significantly increased the urinary excretory output of niacin metabolites, although no change in urinary niacin

concentrations was found after exposure to the mental or emotional stress (71).

Conclusions

Although research is somewhat limited and the robustness of research is variable, the bulk of evidence suggests psychological and physical stress can influence concentrations of several micronutrients. A summary of stress studies in humans is provided in **Table 1**. The largest body of evidence demonstrates stress-induced depletion of magnesium and zinc, although several studies (both human and animal) demonstrate the effects of stress on calcium and iron concentrations. One study was identified suggesting that physical stress, but not emotional stress, can lead to increased excretion of niacin metabolites. Investigations into the effects of stress on other important vitamins and minerals were not identified. These preliminary findings have potentially significant clinical and health implications because the mentioned micronutrients have many essential roles in the body.

However, before definitive conclusions about the micronutrient-depleting effects of stress can be made, further investigations are essential. Although there is evidence that stress can influence micronutrient stores, the impact of diverse physical and psychological stressors is yet to be determined. Research to date provides little indication of the impact of different stressors on micronutrient concentrations, the severity of stress required to induce nutrient changes, and the impact of acute versus chronic stress on nutrient concentrations. Moreover, questions remain about the impact of stress on micronutrients in different populations varying in age, gender, and premorbid health status and also about the durability of changes after a stressor is resolved. The medical, physical, and psychological implications of nutrient changes caused by a stressor also remain to be determined. It is possible that micronutrient alterations are adaptive responses and/or are of negligible significance, thereby having little clinical or health implications. Alternatively, micronutrient alterations during times of stress may be associated with increased disease risk, particularly because greater nutritional stores may be required during times of high mental or physical demands. Greater understanding of these processes can only be obtained from research examining the impact of diverse physical and psychological stressors, with varying severity, over variable time periods, and utilizing differing populations.

To further elucidate the impact of stress on micronutrients, it is important to consider appropriate measures of change. Options include blood assessments of specific micronutrients (e.g., whole blood, plasma, and erythrocyte) and urinary (urine collection times require consideration), salivary, and hair measurements. Functional markers or metabolite measures may also be helpful to identify nutritional deficiencies, including methylmalonic acid as a measure of vitamin B-12 deficiency, xanthurenic acid as a measure of vitamin B-6 deficiency, and formiminoglutamate as a measure of folate deficiency (72). It will also be important to examine the effects of a stressor on collective nutrients (e.g., vitamins, minerals, amino acids, and fatty acids) rather than its impact on 1 nutrient in isolation. This will help elucidate the effect of a stressor on nutrients as a whole, the nutrients most impacted by a stressor, and the relation between changes in nutrients over time.

Because stress is associated with changes in several stress-related hormones, such as cortisol, adrenaline, and noradrenaline, determining the relation between these hormones and micronutrient changes will also be helpful. Examining stress hormone concentrations can also provide an objective measure of stress and can help clarify their impact on nutritional alterations. Other markers that are often elevated during times of stress and that may influence nutrient absorption and excretion include those associated with inflammation and oxidative stress (17, 73). Because stress can alter digestive function and microbial populations, nutrient absorption from foods eaten and/or nutrient production may be affected. Therefore, examining the relation between stress, gastrointestinal function, and nutrient status will also be helpful.

From a medical and psychological standpoint, deficiencies in several micronutrients have been associated with several physical and mental disorders. For example, lower magnesium and zinc concentrations have been confirmed in people with depression (74, 75), of which stress can be a major trigger. Magnesium and zinc have antidepressant and antistress effects (76, 77); therefore, depletion during times of stress may contribute to, or exacerbate, depressive symptoms. Supplementation with magnesium, zinc, and other micronutrients depleted during times of stress has the potential to prevent or reduce depressive symptoms (and other diseases). However, this requires further examination in robustly designed studies. There is evidence confirming the benefits of magnesium supplementation during times of stress (77), although it is uncertain whether such benefits are the result of its repletion during times of stress.

Finally, if it is confirmed that stress significantly impacts nutrient concentrations, understanding the mechanisms associated with these changes will be important. A redistribution of nutrients from tissues/organs to blood, or vice versa, in response to metabolic demands activated by stress is possible. This is demonstrated by studies confirming increased concentrations of metallothionein, a mineral-binding protein in the liver, intestine, and kidneys, after stress exposure (78, 79). Increased metabolic and enzymatic demands during times of stress may also be associated with increased micronutrient utilization and subsequent depletion. Moreover, stress is associated with increased oxidative stress and inflammation. Through their anti-inflammatory and antioxidant mechanisms, nutrients may be utilized at greater concentrations in response to these processes. It is also possible that increased micronutrient excretion through urine and sweat may contribute to reduced bodily nutrient stores. Perspiration is increased during times of physical and psychological stress, possibly accounting for increased

TABLE 1 Summary of human studies examining the effects of psychological and environmental stress on nutrient concentrations[1]

Reference; year	Population	Stressor	Control	Measure	Findings
Examination stress					
Grases et al. (31); 2006	35 university students aged 18–20 y Country: Spain	Examination period	Beginning of academic course	Urine Stress measures: STAI, Perceived Stress Questionnaire	Compared to beginning of academic course, the examination period was associated with the following: ↑ anxiety (83% increase in STAI, trait score), → stress, ↑ magnesium excretion, → calcium excretion
Sheibaninia (51); 2014	12 dental students with an average age of 27 y Country: Iran	Immediately prior to a comprehensive English test	1 wk before a comprehensive English test	Saliva Stress measure: none	Compared to 1 wk before the exam, there was a nonsignificant increase in salivary zinc and iron.
Takase et al. (32); 2004	30 healthy, male college students with an average age of 22 y Country: Japan	High-stress period—time of high mental stress due to final exams and 80% less sleep compared to nonstress period	Low-stress period—4 wk prior to examination period	Red blood cells (erythrocyte) Stress measure: none	Compared to low-stress period, there were the following: ↓ magnesium, ↑ plasma adrenaline and noradrenaline, ↓ heart rate variability (i.e., ↑ autonomic activity)
Cold exposure					
Fiorica et al. (38); 1968	6 healthy, sleep-deprived men with an average age of 25 y Country: United States	Acute whole-body cold exposure	6 non-sleep-deprived age-matched men	Urine Stress measure: none	Compared to non-sleep-deprived men, there were the following: differences in the pattern of 24-h urinary magnesium excretion; no difference in total 24-h magnesium urinary excretion
Okamoto et al. (71); 2002	12 women living in same facility for 12 d with an average age of 21 y Country: Japan	Cold exposure (as a typical physical stress), calculation exercise (a typical mental stress), and dark exposure (a typical emotional stress)	Before exposure to stressors	Urine Stress measure: none	Following cold exposure only, there was an ↑ in urinary excretory output of niacin metabolites [*N*(1)-methylnicotinamide, *N*(1)-methyl-2-pyridone-5-carboxamide, and *N*(1)-methyl-4-pyridone-3-carboxamide].
Exposure to war and violence					
Cernak et al. (33); 2000	35 men aged 18–38 y Country: Serbia	Exposure to chronic stress (political intolerance, awareness of potential military attacks, permanent stand-by duty, and reduced holidays for >10 y) or subchronic stress consisting of everyday mortal danger in military actions lasting >3 mo	10 age-matched male volunteers without major stress	Plasma Stress measure: none	Compared to matched controls, stressed group had the following: ↓ ionized plasma magnesium, ↓ total plasma magnesium, ↓ ionized plasma calcium
Pizent et al. (49); 1999	34 apparently healthy male prisoners of war Country: Croatia	Prisoners of war immediately after release from a detention camp	85 healthy, male matched controls of comparable age and BMI not exposed to a war combat zone	Serum Stress measure: none	Compared to control group, the prisoners of war had ↓ serum zinc. The authors claim analyses indicate this was not due to malnutrition.

(*Continued*)

TABLE 1 (*Continued*)

Reference; year	Population	Stressor	Control	Measure	Findings
Other psychological and environmental stressors					
Mocci et al. (35); 2001	25 healthy, male volunteers aged 26–41 y Country: Italy	Immediately after noise exposure and 2 d later. Noise exposure comprised 4 h of noise in an industrial plant.	Before noise exposure	Urine and serum (serum measured only immediately after exposure) Stress measure: none	Immediately after noise exposure, there were the following: ↑ serum magnesium, → urine magnesium, ↑ serum calcium, → urine catecholamines 1 d after noise exposure, there were the following: ↑ urine magnesium, → urine calcium, → urine catecholamines
Piruzian et al. (34); 2015	6 healthy, male volunteers aged 25–40 y Country: Russia	30, 60, and 105 d after isolation and confinement	Before isolation	Serum, urine, and hair Stress measure: none	Isolation was associated with the following: ↓ total and ionized serum magnesium (largest drop during initial 30 d), ↑ urine magnesium (largest drop during initial 30 d), ↓ hair magnesium after 105 d, ↓ serum calcium, → urinary and hair calcium
Rendina et al. (58); 2018	245 mothers and 79 breastfed infants aged 1 y Country: United States	High-stressed, pregnant mothers	Low-stressed, pregnant mothers	Umbilical cord blood hemoglobin; ZnPP/H (measure of erythrocyte iron); plasma ferritin Stress measure: Perceived Stress During Pregnancy questionnaire	Compared with low-stressed mothers, breastfed infants from high-stressed mothers had a 36-fold increased likelihood of low plasma ferritin at age 1 y (despite mothers having similar cord blood ZnPP/H)
Singh et al. (50); 1991	66 men (Navy SEALs) with an average age of 21 y Country: United States	5 d after a period of sustained physical and psychological stress called "Hell Week"	Before Hell Week	Plasma Stress measure: none	After 5-d stressor there were the following: 33% ↓ plasma zinc, 44% ↓ plasma iron, 58% ↑ plasma ferritin
Tanabe et al. (37); 1997	16 healthy, male college students with an average age of 22 y Country: Japan	Temporary sleep deprivation: 1 d preceded by <3 h of sleep OR Chronic sleep deprivation: 1 d preceded by 1 mo during which sleep was <60% of the control condition	A day following a night of good sleep	Red blood cells (erythrocyte) Stress measure: none	Compared with control condition, magnesium levels were lower after temporary sleep restriction. Compared with control and temporary sleep restriction, magnesium concentrations were lower after chronic sleep deprivation

[1] STAI, State–Trait Anxiety Inventory; ZnPP/H, zinc protoporphyrin/heme; ↑, statistically significant increase; ↓, statistically significant decrease; →, no statistically significant change.

excretion of certain micronutrients through sweat. Stress and increased cortisol output via its effect on aldosterone levels may also contribute to changes in the urinary excretion of associated minerals and electrolytes, thereby modifying nutrient concentrations (80). Finally, stress is also associated with appetite changes; therefore, reduced nutrient concentrations could be an artifact of dietary changes (81). Monitoring dietary changes during times of stress will be important to help elucidate the impact of dietary intake on nutrient levels. As also previously discussed, gastrointestinal activity can be adversely impacted by stress, potentially presenting as another contributor to nutritional alterations during times of stress.

In summary, although there is evidence from animal and human studies that stress can alter micronutrient concentrations, further research is essential to help elucidate the significance of these changes, the nutrients impacted, and the effect of different stressors on nutrient concentrations. These examinations are important given the strong association of stress with mental and physical disease and also the crucial role micronutrients play in optimizing biological activity.

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