Zinc

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Summary

- Zinc is a nutritionally essential mineral needed for catalytic, structural, and regulatory functions in the body. *(More information)*

- Severe zinc deficiency is rare and caused by an inherited condition called acrodermatitis enteropathica. Acquired zinc deficiency is primarily due to malabsorption syndromes and chronic alcoholism. *(More information)*
- Dietary zinc deficiency is quite common in the developing world, affecting an estimated 2 billion people. Consumption of diets high in phytate and lacking foods from animal origin drive zinc deficiency in these populations. *(More information)*
- The recommended dietary allowance (RDA) for adult men and women is 11 mg/day and 8 mg/day of zinc, respectively. *(More information)*
- Long-term consumption of zinc in excess of the tolerable upper intake level (UL; 40 mg/day for adults) can result in copper deficiency. *(More information)*
- Dietary zinc deficiency has been associated with impaired growth and development in children, pregnancy complications, and immune dysfunction with increased susceptibility to infections. *(More information)*
- Supplementation with doses of zinc in excess of the UL is effective to reduce the duration of common cold symptoms. The use of zinc at daily doses of 50 to 180 mg for one to two weeks has not resulted in serious side effects. *(More information)*
- Current evidence suggests that supplemental zinc may be useful in the management of chronic conditions, such as age-related macular degeneration, diabetes mellitus, Wilson's disease, and HIV/AIDS. *(More information)*
- Zinc bioavailability is relatively high in meat, eggs, and seafood; zinc is less bioavailable from whole grains and legumes due to their high content in phytate that inhibits zinc absorption. *(More information)*

Zinc is an essential trace element for all forms of life. Clinical zinc deficiency in humans was first described in 1961, when the consumption of diets with low zinc bioavailability due to high phytate content (see Food sources) was associated with "adolescent nutritional dwarfism" in the Middle East (1). Since then, zinc insufficiency has been recognized by a number of experts as an important public health issue, especially in low-resource countries (2, 3).

Function

Numerous aspects of cellular metabolism are zinc-dependent. Zinc plays important roles in growth and development, immune function, neurotransmission, vision, reproduction, and intestinal ion transport (4). Using data mining approaches, it has been estimated that over 3,000 proteins in humans have functional zinc-binding sites (5). At the cellular level, the function of zinc can be divided into three categories: (1) catalytic, (2) structural, and (3) regulatory (6).

Catalytic role

Over 50 different enzymes depend on zinc for their ability to catalyze vital chemical reactions (7). Zinc-dependent enzymes can be found in all six classes of enzymes (8), as defined by the International Union of Biochemistry and Molecular Biology (9). During enzymatic reactions, zinc may have either a direct catalytic role or a structural role (i.e., stabilizing the structure of catalytic enzymes; see below).

Structural role

Zinc plays an essential role in the folding of some proteins. A finger-like structure, known as a zinc finger motif, stabilizes the structure several proteins. Examples of zinc finger proteins include the superfamily of nuclear receptors that bind and respond to steroids and other molecules, such as estrogens, thyroid hormones, vitamin D, and vitamin A (10). Zinc finger motifs in the structure of nuclear receptors allow them to bind to DNA and act as transcription factors to regulate gene expression (see Regulatory role). Zinc finger motifs are also involved in interactions of proteins with other proteins, ribonucleotides, and lipids (6). Removal of zinc from zinc-containing proteins results in protein misfolding and loss of function.

Metallothioneins are examples of proteins with a zinc-binding motif. Metallothioneins are small metal-binding cysteine-rich proteins with a high affinity for zinc. They work in concert with zinc transporters, regulating free zinc concentrations in the cytosol (11). Metallothioneins are also involved in the regulation of metal ion homeostasis, cellular defense against oxidative stress, and detoxification of heavy metals (11, 12).

The antioxidant enzyme, copper-zinc superoxide dismutase 1 (SOD 1), is made of two identical dimers, each including an active site with a catalytic copper ion and a structural zinc iron. Demetalation of SOD1 has been implicated in the formation of amyloid aggregates in some forms of inherited amyotrophic lateral sclerosis (ALS) — a motor neuron disease leading to muscle atrophy and paralysis (13).

Regulatory role

Zinc finger proteins have been found to regulate gene expression by acting as transcription factors (see above). Zinc also plays a role in cell signaling via the metal-response element (MRE)-binding transcription factor 1 (MTF1); MTF1 has a zinc finger domain that allows its binding to MRE sequences in the promoter of target genes and the subsequent expression of zinc-responsive genes (6). Zinc may also have a direct regulatory function, modulating the activity of cell-signaling enzymes and transcription factors (6). Extracellular zinc can also stimulate a zinc-sensing receptor that triggers the release of intracellular calcium, a second messenger in signaling pathways (14). Zinc has been found to influence hormone release (see Type 2 diabetes mellitus) (15) and nerve impulse transmission (16).

Nutrient interactions

Copper

Taking large quantities of zinc (50 mg/day or more) over a period of weeks can interfere with copper bioavailability. High intake of zinc induces the intestinal synthesis of a copper-binding protein called metallothionein (see the article on Copper). Metallothionein traps copper within intestinal cells and prevents its systemic absorption (see Wilson's disease). More typical intakes of zinc do not affect copper absorption, and high copper intakes do not affect zinc absorption (17).

Iron

Iron and zinc compete for absorptive pathways (18). Supplemental (38-65 mg/day of elemental iron) but not dietary levels of iron may decrease zinc absorption (18, 19). This interaction is of concern in the management of iron supplementation during pregnancy and lactation and has led some experts to recommend zinc supplementation for pregnant and

lactating women taking iron supplements (20, 21). Food fortification with iron has not been shown to negatively affect zinc absorption (22). In a placebo-controlled study, supplementation with zinc (10 mg/day) for three months in children aged eight to nine years significantly decreased serum iron concentrations, yet not to the extent of causing anemia (23). Additional randomized controlled studies have reported a worsening of nutritional iron status with chronic zinc supplementation (24, 25).

Calcium

High levels of dietary calcium impair zinc absorption in animals, but it is uncertain whether this occur in humans (17). One study showed that increasing the calcium intake of postmenopausal women by 890 mg/day in the form of milk or calcium phosphate (total calcium intake, 1,360 mg/day) reduced zinc absorption and zinc balance in postmenopausal women (26). However, another study found that increasing the calcium intake of adolescent girls by 1,000 mg/day in the form of calcium citrate malate (total calcium intake, 1,667 mg/day) did not affect zinc absorption or balance (27). Calcium in combination with phytate might affect zinc absorption, which would be particularly relevant to individuals who very frequently consume tortillas made with lime (i.e., calcium oxide). A study in 10 healthy women (age range, 21-47 years) found that high intake of dietary calcium (~1,800 mg/day) did not impair zinc absorption regardless of the phytate content of the diet (28). For more information on phytate, see Food sources.

Folate

The bioavailability of dietary folate (vitamin B_9) is increased by the action of a zinc-dependent enzyme. Accordingly, some studies found low zinc intake decreased folate absorption. It was also suggested that supplementation with folic acid — the synthetic form of folate — might impair zinc utilization in individuals with marginal zinc status (17, 29). However, one study reported that supplementation with a relatively high dose of folic acid (800 µg/day) for 25 days did not alter zinc absorption or status in a group of students being fed a low-zinc diet (3.5 mg/day) (30).

Vitamin A

Zinc and vitamin A interact in several ways. Zinc is a component of retinol-binding protein, a protein necessary for transporting vitamin A in the blood. Zinc is also required for the enzyme that converts retinol (vitamin A) to retinal. This latter form of vitamin A is necessary for the synthesis of rhodopsin, a protein in the eye that absorbs light and thus is involved in dark adaptation. Zinc deficiency has been associated with a decreased release of vitamin A from the liver, which may contribute to symptoms of night blindness that are seen with zinc deficiency (31, 32).

Deficiency

Inherited zinc deficiency

Much of what is known about severe zinc deficiency was derived from the study of individuals born with acrodermatitis enteropathica, a genetic disorder resulting from the impaired uptake and transport of zinc (33). The symptoms of severe zinc deficiency include the slowing or cessation of growth and development, delayed sexual maturation, characteristic

skin rashes, chronic and severe diarrhea, immune system deficiencies, impaired wound healing, diminished appetite, impaired taste sensation, night blindness, swelling and clouding of the cornea, and behavioral disturbances. Before the cause of acrodermatitis enteropathica was known, patients typically died in infancy. Oral zinc therapy results in the complete remission of symptoms, though it must be maintained indefinitely in individuals with the genetic disorder (33, 34).

Acquired zinc deficiency

It is now recognized that milder zinc deficiency contributes to a number of health problems, especially common in children who live in low-resource countries. An estimated 2 billion people worldwide are affected by dietary zinc deficiency (3). The lack of a sensitive and specific indicator of marginal zinc deficiency hinders the scientific study of its health implications (8). However, controlled trials of moderate zinc supplementation have demonstrated that marginal zinc deficiency contributes to impaired physical and neuropsychological development and increased susceptibility to life-threatening infections in young children (34). In fact, zinc deficiency has been estimated to cause more than 450,000 deaths annually in children under five years of age, comprising 4.4% of global childhood deaths (35). For a more detailed discussion of the relationship of zinc deficiency to health problems, see the section on Disease Prevention.

In industrialized countries, dietary zinc deficiency is unlikely to cause severe zinc deficiency in individuals without a genetic disorder, zinc malabsorption or conditions of increased zinc loss, such as severe burns or prolonged diarrhea. Severe zinc deficiency has also been reported in individuals undergoing total parenteral nutrition without zinc, in those who abuse alcohol, and in those who are taking certain medications like penicillamine (see Drug interactions) (36).

Individuals at risk of zinc deficiency (6, 36-38):

- Premature and low-birth-weight infants
- Older breast-fed infants and toddlers with inadequate intake of zinc-rich complementary foods
- Children and adolescents
- Pregnant and lactating (breast-feeding) women, especially adolescents
- Patients receiving total parenteral nutrition (intravenous feedings)
- Malnourished individuals, including those with protein-energy malnutrition and anorexia nervosa
- Individuals with severe or persistent diarrhea
- Individuals with malabsorption syndromes, including celiac disease and short bowel syndrome
- Individuals with inflammatory bowel disease, including Crohn's disease and ulcerative colitis
- Alcoholics and those with alcoholic liver disease who have increased urinary zinc excretion and low liver zinc levels
- Individuals with chronic renal disease
- Individuals with sickle cell anemia
- Individuals who use medications that decrease intestinal zinc absorption, increase zinc excretion, or impair zinc utilization (see Drug interactions)
- Older adults (65 years and older)

- Vegetarians: The requirement for dietary zinc may be as much as 50% greater for vegetarians whose major food staples are grains and legumes, because high levels of phytate in these foods reduce zinc absorption (see Food sources) (29).

Biomarkers of zinc status

Currently, there is not a sensitive and specific biomarker to detect zinc deficiency in humans. Low plasma or serum zinc concentrations are typically used as indicators of zinc status in populations and in intervention studies, but they have a number of limitations, including lack of sensitivity to detect marginal zinc deficiency, diurnal variations, and confounding by inflammation, stress, and hormones (38, 39).

The Recommended Dietary Allowance (RDA)

The recommended dietary allowance (RDA) for zinc is listed by gender and age group in **Table 1**. Infants, children, adolescents, and pregnant and lactating women are at increased risk of zinc deficiency. Since a sensitive indicator of zinc nutritional status is not readily available, the RDA for zinc is based on a number of different indicators of zinc nutritional status and represents the daily intake likely to prevent deficiency in nearly all individuals in a specific age and gender group (29).

Table 1. The Recommended Dietary Allowance (RDA) for Zinc

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	2 (AI)	2 (AI)
Infants	7-12 months	3	3
Children	1-3 years	3	3
Children	4-8 years	5	5
Children	9-13 years	8	8
Adolescents	14-18 years	11	9
Adults	19 years and older	11	8
Pregnancy	18 years and younger	-	12
Pregnancy	19 years and older	-	11
Breast-feeding	18 years and younger	-	13
Breast-feeding	19 years and older	-	12

Prevention of Diseases or Conditions Related to Zinc Deficiency

Pregnancy complications and adverse pregnancy outcomes

Estimates based on national food supply indicate that dietary zinc intake is likely inadequate in most low- and middle-income countries, especially those in Sub-Saharan Africa and South Asia (40). Inadequate zinc status during pregnancy interferes with fetal development, and preterm neonates from zinc-deficient mothers suffer from growth retardation and dermatitis and are at risk of infections, necrotizing enterocolitis, chronic lung disease, and retinopathy of prematurity (4). Maternal zinc deficiency has also been associated with a number of pregnancy complications and poor outcomes. A recent case-control study conducted in an

Iranian hospital reported higher odds of congenital malformations in newborns of mothers with low serum zinc concentrations during the last month of pregnancy (41). A 2016 review of 64 observational studies found an inverse relationship between maternal zinc status and the severity of preeclampsia, as well as between maternal zinc intake and the risk of low-birth-weight newborns (42). There were no apparent associations between maternal zinc status and the risk of gestational diabetes mellitus and preterm birth. However, the conclusions of this analysis were limited by the fact that most observational studies were conducted in women from populations not at risk for zinc deficiency (42).

To date, available evidence from maternal zinc intervention trials conducted worldwide does not support the recommendation of routine zinc supplementation during pregnancy. A 2015 systematic review and meta-analysis of 21 randomized controlled trials in over 17,000 women and their babies found a 14% reduction in premature deliveries with zinc supplementation during pregnancy, mainly in low-income women (43). This analysis, however, did not find zinc supplementation to benefit other indicators of maternal or infant health, including stillbirth or neonatal death, low birth weight, small-for-gestational age, and pregnancy-induced hypertension. There was also no effect of supplemental zinc on postpartum hemorrhage, maternal infections, congenital malformations, and child development outcomes (43). A recent review of 17 trials (of which 15 were conducted in low- and middle-income countries) found that maternal supplementation with multiple micronutrients (including, among others, zinc, iron, and folic acid) reduced the risk of low-birth-weight newborns and small-for-gestational age infants when compared to supplemental iron with or without folic acid (44). While multiple micronutrient supplementation would likely benefit pregnant women with coexisting micronutrient deficiencies in low- and middle-income countries, there is no evidence to recommend zinc supplementation in isolation in pregnant women from any settings (43, 45).

Impaired growth and development

Growth retardation

Significant delays in linear growth and weight gain, known as growth retardation or failure to thrive, are common features of mild zinc deficiency in children. In the 1970s and 1980s, several randomized, placebo-controlled studies of zinc supplementation in young children with significant growth delays were conducted in Denver, Colorado. Modest zinc supplementation (5.7 mg/day) resulted in increased growth rates compared to placebo (46). Several meta-analyses of growth data from zinc intervention trials have confirmed the widespread occurrence of growth-limiting zinc deficiency in young children, especially in low- and middle-income countries (47-49). A 2018 systematic review and meta-analysis identified 54 trials that examined the impact of zinc supplementation during infancy (on average, 7.6 mg/day for 30.9 weeks) or childhood (on average, 8.5 mg/day for 38.9 weeks) on child anthropometric measurements (50). There was evidence of a positive effect of supplemental zinc on children's height, weight, and weight-for-age Z score (WAZ), but neither on height-for-age Z score (HAZ) or weight-for-height Z score (WHZ). In addition, zinc supplementation did not reduce the risks of underweight (WAZ<-2 standard deviation [SD]), wasting (WHZ<-2 SD), or stunting (HAZ<-2 SD) in children (50). Although the exact mechanisms for the growth-limiting effect of zinc deficiency are not known, research indicates that zinc availability affects cell-signaling systems that coordinate the response to the growth-regulating hormone, insulin-like growth factor-1 (IGF-1) (51).

Delayed mental and psychomotor development in young children

Adequate nutrition in essential for brain growth and development, especially during the first 1,000 days of life — a critical period of development for all organs and systems spanning from conception to 24 months of age (52). Animal studies have established that zinc deficiency in early life interferes with normal brain development and cognitive functions (reviewed in 53). Data on the effect of zinc supplementation during pregnancy on infants' neurologic and psychomotor outcomes is very limited. In a randomized, placebo-controlled trial in African-American women, daily maternal supplementation with 25 mg of zinc from about 19 weeks' gestation had no effect on neurologic development test scores in their children at five years of age (54).

Several studies have reported on the effect of postnatal zinc supplementation on mental and motor development. Two early randomized controlled trials, one conducted in India and the other in Guatemala, suggested that postnatal supplementation with 10 mg/day of zinc resulted in toddlers being more vigorous (55) and functionally active (56). In one trial conducted in Brazilian newborns from low-income families and weighing between 1,500 g and 2,499 g at birth, neither zinc supplementation for eight weeks with 1 mg/day or 5 mg/day improved mental and psychomotor development at 6 or 12 months of age compared to a placebo and assessed using the Bayley Scales of Infant Development (BSID) for Mental Development Index (MDI) and Psychomotor Development Index (PDI) (57). Additionally, a randomized, placebo-controlled, double-blind trial in Chilean newborns (birth weights >2,300 g) from low-income families reported no effect of zinc supplementation (5 mg/day) on mental and psychomotor development indices at 6 and 12 months (58). Two other trials found that supplemental zinc failed to improve MDI or PDI at 12 months of age when zinc (10 mg/day) was given to six-month-old infants for six months (59) or at the end of the intervention in toddlers aged 12-18 months when zinc (30 mg/day) was given for four months (60). A 2012 Cochrane review of eight clinical trials found no evidence that postnatal zinc supplementation improves mental or motor development of infants and children from populations with presumably inadequate zinc status (61).

Impaired immune system function

Adequate zinc intake is essential in maintaining the integrity of the immune system (62), specifically for normal development and function of cells that mediate both innate (neutrophils, macrophages, and natural killer cells) and adaptive (B-lymphocytes and T-lymphocytes) immune responses (63). Because pathogens also require zinc to thrive and invade, a well-established antimicrobial defense mechanism in the body sequesters free zinc away from microbes (64). Another opposite mechanism consists in intoxicating intracellular microbes within macrophages with excess zinc (65). Through weakening innate and adaptive immune responses, zinc deficiency diminishes the capacity of the body to combat pathogens (63, 64). As a consequence, zinc-deficient individuals experience an increased susceptibility to a variety of infectious agents (66).

Increased susceptibility to infectious disease in children

Diarrhea: Zinc promotes mucosal resistance to infections by supporting the activity of immune cells and the production of antibodies against invading pathogens (63, 64, 67). Therefore, a deficiency in zinc increases the susceptibility to intestinal infections and constitutes a major contributor to diarrheal diseases in children (66). In turn, persistent diarrhea contributes to zinc deficiency and malnutrition (66). Research indicates that zinc deficiency may also potentiate the effects of toxins produced by diarrhea-causing bacteria like

E. coli (68). It is estimated that diarrheal diseases are responsible for the deaths of about 500,000 children under five years of age annually in low- and middle-income countries (69). Zinc supplementation in combination with oral rehydration therapy has been shown to significantly reduce the duration and severity of acute and persistent childhood diarrhea and to increase survival in a number of randomized controlled trials (70). A 2016 meta-analysis of randomized controlled trials found that zinc supplementation reduced the duration of acute diarrhea by one day in children aged >6 months who presented signs of malnutrition (5 trials; 419 children) (71). However, there was little evidence to suggest that zinc could be as efficacious to reduce the duration of acute diarrheal episodes in children aged <6 months and in well-nourished children aged >6 months. Zinc supplementation also reduced the duration of persistent diarrhea in children by more than half a day (5 trials; 529 children) (71).

The World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) currently recommend supplementing young children with 10 to 20 mg/day of zinc as part of the treatment for acute diarrheal episodes and to prevent further episodes in the two to three months following zinc supplementation (72).

Pneumonia: Pneumonia — caused by lower respiratory tract viral or bacterial infections (LRTIs) — accounts for nearly 1 million deaths among children annually, primarily in low- and middle-income countries (69). Vaccinations against *Haemophilus influenzae* type B, pneumococcus, pertussis (whooping cough), and measles can help prevent pneumonia (73). According to a 2009 WHO report on disease risk factors, zinc deficiency may be responsible for 13% of all LRTI cases, primarily pneumonia and flu cases, in children younger than 5 years (74). Accordingly, a 2016 meta-analysis of six trials found that zinc supplementation in children under 5 years old reduced the risk of pneumonia by 13% (75). However, it remains unclear whether supplemental zinc, in conjunction with antibiotic therapy, is beneficial in the treatment of pneumonia. A recent randomized, placebo-controlled trial conducted in Gambian children who were not zinc deficient failed to show any benefit of zinc supplementation (10 mg/day or 20 mg/day [depending on child's age] for 7 days) given alongside antibiotics in the treatment of severe pneumonia (76). A 2018 meta-analysis of five trials (1,822 participants) found no improvement when zinc was used as an adjunct to antibiotic treatment in children with pneumonia (77). There was, however, evidence that supplemental zinc reduced the risk of pneumonia-related mortality (3 trials; 1,318 participants) (77).

Malaria: Early studies have indicated that zinc supplementation may reduce the incidence of clinical attacks of malaria in children (78). A placebo-controlled trial in preschool-aged children in Papua New Guinea found that zinc supplementation reduced the frequency of health center attendance due to *Plasmodium falciparum* malaria by 38% (79). Additionally, the number of malaria episodes accompanied by high circulating parasite concentrations was reduced by 68%, suggesting that zinc supplementation may be of benefit in preventing more severe episodes of malaria. However, a six-month trial in more than 700 West African children did not find any difference in the frequency or severity of malaria episodes between children supplemented with zinc and those given a placebo (80). Another randomized controlled trial reported that zinc supplementation did not benefit preschool-aged children with acute, uncomplicated malaria (81). There is also little evidence to suggest that zinc supplementation could reduce the risk of malaria-related mortality in children (82). At present, there is not enough evidence to suggest a prophylactic and/or therapeutic role for supplemental zinc in the management of childhood malaria (48). A recent randomized, placebo-controlled trial did not provide clear-cut evidence of a protective effect of zinc (25

mg/day) administered to Tanzanian women during their first gestational trimester until delivery on the risk of placental malaria infection (83).

Age-related decline in immune function

Inadequate zinc status in elderly subjects is not uncommon and is thought to exacerbate the age-related decline in immune function (84). In one study, low serum zinc concentrations in nursing home residents were associated with higher risks of pneumonia and pneumonia-related and all-cause mortality (85). Trials examining the effects of zinc supplementation on immune function in middle-aged and elderly adults have given mixed results (reviewed in 86). Some studies showed mixed or no effects of zinc supplementation on parameters of immune function (87-89). However, zinc supplementation was found to have a positive impact on certain aspects of immune function that are affected by zinc deficiency, such as the decline in T-cell (a type of lymphocyte) function (90). For example, a randomized, placebo-controlled study in adults over 65 years of age found that zinc supplementation (25 mg/day) for three months increased blood concentrations of helper T-cells and cytotoxic T-cells (91). Additionally, a randomized, double-blind, placebo-controlled trial in 101 older adults (aged 50-70 years) with normal blood zinc concentrations showed that zinc supplementation at 15 mg/day for six months improved the helper T-cells/cytotoxic T-cells ratio, which tends to decline with age and is a predictor of survival (92). However, the study also suggested that a dose of 30 mg/day of zinc might reduce the number of B-lymphocytes, which play a central role in humoral immunity. Further, zinc supplementation had no effect on various immune parameters, including markers of inflammation, measures of granulocyte and monocyte phagocytic capacity, or cytokine production by activated monocytes (92).

A more recent trial examined the effect of daily supplementation with a multiple micronutrients, including 5 mg or 30 mg of zinc for three months, on zinc status and markers of immune function in institutionalized elderly participants (mean age, >80 years) with low serum zinc concentrations (93). Zinc status was improved with the 30 mg/day dose — but not with 5 mg/day — yet the most zinc-deficient individuals failed to achieve normal serum zinc concentrations within the intervention period. The number of circulating T-cells was also significantly increased in those who took the micronutrient supplement with the higher versus low dose of zinc (93).

More research is warranted before zinc supplementation could be recommended to older adults, especially those with no symptoms of declining immunity. Nonetheless, the high prevalence of zinc deficiency among institutionalized elderly adults should be addressed and would likely improve the performance of their immune systems (86).

Type 2 diabetes mellitus

There is a close relationship between zinc and insulin action. Specifically, in pancreatic β-cells, zinc is involved in insulin synthesis and storage in secretory vesicles. Zinc is released with the hormone when blood glucose concentrations increase (15). Zinc is also understood to stimulate glucose uptake and metabolism by insulin-sensitive tissues through triggering the intracellular insulin signaling pathway (94). Single-nucleotide polymorphisms (SNPs) in the *SLC30A8* (solute carrier family 30 member 8) gene, coding for a zinc transporter that co-localizes with insulin in β-cells, have been associated with higher risks of type 1 and type 2 diabetes mellitus (95), though the risk for type 2 diabetes mellitus was found to be reduced with rare protein-truncating variants of the gene (96). The first prospective cohort study to

examine the risk of type 2 diabetes in relation to zinc intakes — the Nurses' Health Study (NHS) — followed 82,297 US registered female nurses for 24 years. The data analysis showed an 8% lower risk of type 2 diabetes with the highest versus lowest intake of dietary zinc (median values, 11.8 mg/day versus 4.9 mg/day) (97). This finding was consistent with the result of the Australian Longitudinal Study on Women's Health (ALSWH) that enrolled 8,921 women for six years and showed a 50% lower risk of diabetes with the highest versus lowest intake of energy-adjusted dietary zinc (98). Both NHS and ALSWH studies also reported a reduced risk of diabetes with higher versus lower zinc-to-heme iron ratios in the diet (97, 98), although the significance is unclear as nonheme iron, rather than heme iron, is known to interfere with dietary zinc absorption (see Nutrient interactions). Heme iron may be an indicator of red meat consumption, which has been positively associated with the risk of type 2 diabetes (99). However, two other prospective cohort studies — the Multi-Ethnic Study of Atherosclerosis (MESA; 4,982 participants) and the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study (232,007 participants) — failed to find evidence for an association between zinc intake and risk of type 2 diabetes (100, 101). Another recent prospective cohort study, the Malmo Diet and Cancer Study in 26,132 middle-aged Swedish participants followed for 19 years, found an increased risk of diabetes with higher dietary zinc intakes yet a lower risk of diabetes in zinc supplement users (versus non-users) and in those with a higher zinc-to-iron intake ratio (102). The authors reported a stronger inverse association between zinc-to-iron intake ratio and risk of diabetes among obese participants carrying a specific *SLC30A8* genotype (102).

The results of a few short-term intervention studies suggest that zinc supplementation may improve glucose handling in subjects with prediabetes. A 2015 systematic review identified three short trials (4 to 12 weeks) conducted in adults with prediabetes and found little evidence of an improvement in insulin resistance with zinc supplementation (103). However, a 2016 randomized, placebo-controlled trial in 55 Bangladeshi with prediabetes showed that daily supplementation with zinc sulfate (30 mg/day for 6 months) improved fasting blood glucose, as well as measures of β-cell function and insulin sensitivity (104). Similar observations were made in another recent trial in 100 Sri Lankan randomized to receive daily supplementation with zinc (20 mg of elemental zinc) or a placebo for one year (105). Supplemental zinc improved zinc status and measures of glycemic control (105). Large-scale, long-term studies are necessary to provide definite conclusions regarding the potential benefit of zinc supplementation in subjects at risk of type 2 diabetes.

Disease Treatment

Doses of supplemental zinc in many of the below-mentioned clinical trials exceeded the tolerable upper intake level (UL). Such high intake of supplemental zinc may lead to adverse health effects with prolonged use (see Safety).

Wilson's disease

The protein, ATP7B, is responsible for the excretion of hepatic copper into the biliary tract, and its impairment in Wilson's disease results in an increased concentration of 'free' copper (i.e., not bound to the copper-carrying protein, ceruloplasmin) in blood, an increased excretion of copper in the urine (hypercupriuria), the deposition of copper in part of the cornea (forming Kayser-Fleischer rings), and the accumulation of copper in the liver and brain (106). This inherited condition is progressive and fatal if untreated. The standard-of-care for symptomatic patients usually includes an initial phase (around 2-6 months) of copper chelation with agents

such as penicillamine or trientine (triethylenetetramine) followed by lifelong maintenance therapy with penicillamine and/or trientine and/or zinc salts (107). Patients presenting without symptoms can be treated with maintenance therapeutic doses of a chelating agent or with zinc (108). Zinc-induced metallothionein in the intestinal mucosa binds copper and prevents its absorption (see Nutrient interactions). There is growing evidence to suggest that zinc salts are a safer, much cheaper, and efficacious alternative to metal-chelating agents — which have been associated with a worsening of symptoms during the initial phase of treatment in some patients (109). The use of zinc is advocated as safe and efficacious in both pediatric (110, 111) and adult patients (112-114).

Common cold

Zinc lozenges

There is no proven treatment for common cold (115). The use of zinc lozenges within 24 hours of the onset of cold symptoms, and continued intake every two to three hours while awake until symptoms resolve, have been advocated for reducing the duration of the common cold (116). Several clinical trials examining the effect of zinc have been published to date. A 2012 systematic review and meta-analysis of 13 randomized controlled trials reported that zinc supplementation in the form of lozenges or syrup shortened the duration of cold symptoms, but there was significant heterogeneity (inconsistent effects across the included studies) for the primary outcomes (117). A 2013 Cochrane review confirmed that oral zinc administrated within 24 hours of symptom onset could reduce the duration of cold symptoms (14 trials, 1,656 participants) (118). Subgroup analyses also suggested that oral zinc was effective regardless of the age of participants (children or adults) and the type of zinc formulation (gluconate/acetate lozenges or sulfate syrup). In addition, beneficial effects on cold duration were seen in trials that provided more than 75 mg/day of zinc but not in trials that used lower doses. The pooled analysis of five trials found no evidence of an effect of oral zinc on the severity of cold symptoms. The analysis of secondary trial outcomes suggested a faster resolution of specific cold symptoms (cough, nasal congestion, nasal drainage, sore throat) and a lower proportion of participants exhibiting cold symptoms after seven days of treatment in zinc- versus placebo-supplemented participants (118).

Inconsistent findings among trials have been partly attributed to different amounts of zinc released from various forms used in the lozenges (particularly zinc acetate and zinc gluconate) (119, 120). It has been argued that the unpleasant taste of zinc gluconate forming complexes with carbohydrates may have led to poor compliance, thereby explaining negative trial results (119, 121). However, when a meta-analysis was recently conducted on results from seven trials (575 participants) that employed zinc lozenges at doses >75 mg/day, there was no evidence of a difference in efficacy observed between trials that used either zinc acetate (3 trials) or zinc gluconate (4 trials) (122).

With numerous well-controlled trials and meta-analyses, the efficacy of zinc lozenges or syrup in treating common cold symptoms is no longer questionable. A meta-analysis of seven trials recently reported a 33% reduction in the duration of cold symptoms with the intake of zinc lozenges (>75 mg/day of elemental zinc) (122). However, many supplemental zinc formulations available over-the-counter have been found to release zero zinc ions (i.e., the biologically active form of zinc) or to contain additives (e.g., magnesium, certain amino acids, citric acid) that either cancel out the benefit of zinc or worsen cold symptoms (119).

Finally, although taking zinc lozenges for a cold every two to three hours while awake will result in daily zinc intakes well above the tolerable upper intake level (UL) of 40 mg/day for adults (see Safety), the use of zinc at daily doses of 50 to 180 mg for one to two weeks has not resulted in serious side effects (117). Bad taste and nausea were the most frequent adverse effects reported in therapeutic trials (117). Use of zinc lozenges for prolonged periods (e.g., 6-8 weeks) is likely to result in copper deficiency (see Nutrient interactions and Safety).

Intranasal zinc (zinc nasal gels and nasal sprays)

Intranasal zinc preparations, designed to be applied directly to the nasal epithelium (cells lining the nasal passages), are marketed as over-the-counter cold remedies. While two placebo-controlled trials found that intranasal zinc gluconate modestly shortened the duration of cold symptoms (123, 124), another one found intranasal zinc to be of no benefit (125). The pooled analysis of these three trials showed no overall benefit of intranasal zinc on the risk of still experiencing cold symptoms by day 3 (126). The existence of a mouth-nose biologically close electric circuit (BCEC) has been proposed to explain the efficacy of oral rather than intranasal zinc delivery (119). Specifically, it is suggested that the positively charged interior of the nose repels ionic zinc (Zn^{2+}) such that ionic zinc delivered by throat lozenges and migrating from the mouth to the nose are more effective against rhinovirus infection than those directly delivered into the nose (119). Of serious concern are several case reports of individuals experiencing loss of the sense of smell (anosmia) after using intranasal zinc as a cold remedy (127). Since zinc-associated anosmia may be irreversible, intranasal zinc preparations should be avoided.

Age-related macular degeneration

Age-related macular degeneration (AMD) is a degenerative disease of the macula and a leading cause of blindness in people aged >65 years in the US (128). The macula is the portion of the retina in the back of the eye involved with central vision. Zinc is hypothesized to play a role in the development of AMD for several reasons: (1) zinc is found at high concentrations in the part of the retina affected by AMD, (2) retinal zinc content has been shown to decline with age, and (3) the activities of some zinc-dependent retinal enzymes have been shown to decline with age. To date, prospective cohort studies have shown limited evidence suggesting an association between dietary zinc intake and the incidence of AMD (129-131).

However, an early randomized controlled trial provoked interest when it found that 200 mg/day of zinc sulfate (81 mg/day of elemental zinc) over two years limited the loss of vision in patients with AMD (132). Yet a later trial using the same dose and duration found no benefit to patients with a more advanced form of AMD in one eye (133). Small trials have generally not reported a protective effect of vitamin and mineral supplementation on AMD (134, 135). However, a randomized, double-blind, placebo-controlled trial in 74 patients with AMD reported that supplementation with 50 mg/day of zinc monocysteine for six months improved measures of macular function, including visual acuity, contrast sensitivity, and photorecovery (136). A large randomized, placebo-controlled trial of daily supplementation with antioxidants (500 mg of vitamin C, 400 IU of vitamin E, and 15 mg of β-carotene) and high-dose zinc (80 mg of zinc as zinc oxide and 2 mg of copper as cupric oxide) — the Age-Related Eye Disease Study (AREDS) — found that administration of high-dose zinc alone or with the antioxidant combination to individuals with signs of moderate-to-severe macular degeneration significantly reduced the risk of developing advanced macular degeneration over

a mean follow-up of 6.3 years (137). A follow-up analysis conducted four years after the cessation of the trial in 2001, including nearly 85% of the surviving participants, found that the benefit of the AREDS (combined antioxidants plus zinc) formulation had persisted (138). Indeed, the odds of developing late AMD, especially neovascular AMD, was lower in both participants with a low risk of developing AMD and those who were at risk and recommended to continue taking the AREDS formulation after the trial ended. There was, however, no effect of AREDS formulation on the risk of developing central geographic atrophy (138). Another trial, AREDS2, examined the effect of an AREDS formulation without β-carotene and/or containing 25 mg instead of 80 mg of zinc (139). The trial showed no apparent difference in the risk of developing advanced AMD with the use of AREDS formulations containing either 25 mg or 80 mg of zinc and/or β-carotene (140). A recent meta-analysis of five trials (including the original AREDS study) confirmed the protective effect of supplemental zinc against neovascular and advanced AMD (141).

In conclusion, the AREDS formulation combining antioxidants and zinc (25 mg or 80 mg) may delay the progression of the disease in patients with AMD. Patients, especially smokers and those with vascular disease, are advised to discuss with their physician the benefits versus potential harms that could be associated with the long-term use of high-dose antioxidant vitamins and carotenoids (141).

Diabetes mellitus

Type 2 diabetes mellitus

Poor glycemic control and frequent urination in patients with diabetes mellitus may be driving urinary loss of zinc and contribute to marginal zinc deficiency (142, 143). Yet, because of the role of zinc in β-cell function and insulin action (see Disease Prevention), a number of randomized controlled trials have examined whether supplementation with zinc (alone or with other minerals and vitamins) could play a role in diabetes management, especially by improving glycemic control in people with type 2 diabetes (15). Out of the 12 trials that measured participants' zinc status at baseline, supplementation with zinc (20-240 mg/day) for 4 to 16 weeks improved fasting blood glucose in patients who presented with zinc deficiency (6 studies). Supplemental zinc also reduced the proportion of glycated hemoglobin (HbA1c) in two trials conducted in zinc-deficient participants, yet not in four studies including participants without zinc deficiency (15). Patients with type 2 diabetes should ensure that their diet provides enough zinc to cover their needs, especially if their blood glucose is poorly controlled.

Gestational diabetes mellitus

Gestational diabetes mellitus is defined as hyperglycemia that is first diagnosed during pregnancy. The condition is associated with an increased risk for adverse pregnancy outcomes (144). A group of investigators in Iran conducted two small randomized, placebo-controlled trials to examine the effect of zinc supplementation in pregnant women with gestational diabetes. Supplemental zinc (30 mg/day) for six weeks during pregnancy improved zinc status, reduced fasting blood glucose, and improved insulin sensitivity in women with gestational diabetes but had no impact on pregnancy outcomes, including the need for cesarean section, need for insulin therapy, newborn's birth size and Apgar scores, or incidence of hyperbilirubinemia (145, 146). Similar improvements of markers of glycemic control were reported in another placebo-controlled trial that randomized pregnant women

with gestational diabetes to receive zinc (4 mg) together with magnesium (100 mg), calcium (400 mg), and vitamin D (200 IU) twice a day for six weeks (147). There was also some evidence suggesting that supplemental zinc might help correct other metabolic disorders (e.g., abnormal blood lipid profile) associated with gestational diabetes (147, 148).

HIV/AIDS

Sufficient zinc is essential to maintain immune system function, and HIV-infected individuals are particularly susceptible to zinc deficiency. In HIV-infected patients, low serum zinc concentrations have been associated with disease progression and increased mortality (149, 150). In one study conducted in AIDS patients, 45 mg/day of zinc for one month resulted in a decreased incidence of opportunistic infections compared to placebo (151). A placebo-controlled trial in 231 HIV-positive adults with low zinc status found that zinc supplementation (12 mg/day for women and 15 mg/day for men) for 18 months reduced the incidence of immunological failure (defined by a $CD4^+$ count <200 cells/mm^3) by 76% and the rate of diarrhea by 60% (152). A 2011 systematic review that identified three randomized controlled trials in primarily resource-poor settings concluded that zinc supplementation was safe and efficacious in reducing opportunistic infections in HIV-positive adults (153).

Evidence of benefits of zinc supplementation in HIV-positive pregnant women and children is very limited. In a double-blind, randomized, placebo-controlled trial in Tanzania, the administration of zinc (25 mg/day) to women between 12 and 27 weeks' gestation until six months after delivery failed to reduce maternal viral load or limit mother-to-child HIV transmission (154). A randomized placebo-controlled trial of zinc supplementation (10 mg/day for 6 months) in 96 HIV-positive children (6 months to 5 years old) in South Africa showed no effect on $CD4^+$ count and viral load (155). There was evidence showing a reduction in the incidence of watery diarrhea in zinc-supplemented children compared to those taking a placebo, yet no differences in the incidence of pneumonia, ear infection, or upper respiratory tract infection (155). Another trial in Uganda showed that supplemental zinc in children with severe pneumonia effectively reduced case fatality regardless of children's HIV status (156). While zinc supplementation during pregnancy and infancy is recommended in populations likely to be zinc deficient (43, 71, 75), its use in HIV infection management requires further investigation (157).

Alzheimer's disease

Abnormal homeostasis of trace metals, in particular copper and zinc, has been reported in individuals affected by Alzheimer's disease — the most common form of dementia. Specifically, results from case-control studies have shown higher serum copper concentrations and lower serum zinc concentrations in people with Alzheimer's disease compared to cognitively healthy controls (158-160). Based on the utilization of zinc salts in Wilson's disease, it has been proposed that zinc supplementation could improve zinc and copper status and limit further cognitive deterioration in individuals with Alzheimer's disease. The use of slow-release zinc acetate (150 mg/day for six months) in a randomized, placebo-controlled study of 60 patients with mild-to-moderate Alzheimer's disease corrected low zinc status and decreased serum 'free' copper (i.e., unbound to ceruloplasmin) (161). Moreover, when a post-hoc analysis was restricted to participants over 70 years of age (N=29), it was found that zinc supplementation prevented the deterioration of cognition scores over the trial period (161). Additional evidence is needed to confirm whether zinc supplementation could play a role in stabilizing cognitive deficits in older adults with dementia.

Depression

A data analysis of the Boston Area Community Health (BACH) survey, including 3,708 participants (ages, 30-79 years), reported higher odds of depression symptoms in women (but not in men) in the lowest versus highest quartiles of total (median values, 8.7 mg/day versus 26.8 mg/day) and dietary (median values, 7.6 mg/day versus 13.1 mg/day) zinc intakes (162). The possibility that zinc could play a role in preventing or alleviating depression has been explored in two trials conducted by one research group. The data from these trials were analyzed following a per-protocol approach (i.e., restricted to the participants who completed the studies). A preliminary randomized, double-blind, placebo-controlled trial in 20 subjects (mean age, 43 years) treated for major depression showed that supplementation with 25 mg/day of zinc reduced depression symptoms at 6 and 12 weeks as assessed by the Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI) scores (163). A second placebo-controlled trial in 60 participants treated with the antidepressant imipramine (Tofranil; 100-200 mg/day) assessed the therapeutic response to supplemental zinc (25 mg/day) using HDRS, BDI, Clinical Global Impression scale (CGI), and Montgomery-Åsberg Depression Rating Scale (MADRS) scores (164). Zinc supplementation improved score-based measures of therapeutic response and remission after six weeks but only when the analysis was restricted to participants resistant to imipramine. There was, however, no evidence of an effect of zinc after 12 weeks (164).

Neonatal sepsis

Sepsis is a life-threatening condition that causes organ dysfunction as a consequence of a dysregulated host's response to infection (165). Sepsis is accompanied by changes in zinc homeostasis characterized in particular by a decrease in serum zinc concentration and an increase in liver zinc concentration (166). These changes in zinc distribution are thought to be part of a host's defense mechanism whereby the host can limit zinc availability to pathogens, as well as stimulate the immune system. Such a mechanism has been described for other transition metals, including iron and manganese (167). However, lower serum zinc concentrations in critically ill patients at high risk of organ failure have been associated with recurrent sepsis episodes and poorer outcomes (168, 169). A 2018 systematic review identified four trials that examined the effect of zinc supplementation in newborns with sepsis (166). Zinc supplementation was found to result in decreased inflammation (170) and better neurological development (171, 172). Three out of four trials that examined the rate of mortality showed no effect of zinc supplementation (170, 172, 173).

Sources

Food sources

Shellfish, beef, and other red meats are rich sources of zinc; nuts and legumes are relatively good plant sources of zinc. Zinc bioavailability (the fraction of zinc retained and used by the body) is relatively high in meat, eggs, and seafood because of the relative absence of compounds that inhibit zinc absorption and the presence of sulfur-containing amino acids (cysteine and methionine) that improve zinc absorption. Zinc in whole-grain products and plant proteins is less bioavailable due to their relatively high content of phytate, which inhibits zinc absorption (174). The enzymatic action of yeast reduces the level of phytate in foods; therefore, leavened whole-grain breads have more bioavailable zinc than unleavened whole-grain breads.

National dietary surveys in the US estimate that average dietary zinc intake from naturally and fortified food is about 12.3 mg/day in adults, with about 12% of the adult population being at risk for inadequate intake (175). The zinc content of some foods relatively rich in zinc is listed in **Table 2** in milligrams (mg). For more information on the nutrient content of specific foods, search the USDA food composition database (176).

Table 2. Some Food Sources of Zinc

Food	Serving	Zinc (mg)
Oyster, cooked	6 medium	27-50
Beef, chuck, blade roast, cooked	3 ounces*	8.7
Beef, ground, 90% lean meat, cooked	3 ounces	5.4
Crab, Dungeness, cooked	3 ounces	4.7
Fortified, whole-grain toasted oat cereal	1 cup	3.8
Turkey, dark meat, cooked	3 ounces	3.0
Pork, loin, blade roast, cooked	3 ounces	2.7
Soybeans, dry roasted	½ cup	2.2
Chicken, roasting, dark meat, cooked	3 ounces	1.8
Pine nuts	1 ounce	1.8
Cashews	1 ounce	1.6
Yogurt, plain, low fat	6 ounces	1.5
Sunflower seed kernels	1 ounce	1.5
Pecans	1 ounce	1.3
Brazil nuts	1 ounce	1.2
Chickpeas (garbanzo beans), cooked	½ cup	1.2
Milk	1 cup (8 fl. oz.)	1.1
Cheese, cheddar	1 ounce	1.0
Almonds	1 ounce	0.9
Beans, baked	½ cup	0.9
*A three-ounce serving of meat is about the size of a deck of cards.		

Supplements

A number of zinc supplements are commercially available, including zinc acetate, zinc gluconate, zinc picolinate, and zinc sulfate. Zinc picolinate has been promoted as a more absorbable form of zinc, but there are few data to support this idea in humans. Limited work in animals suggests that increased intestinal absorption of zinc picolinate may be offset by increased elimination (29).

Safety

Toxicity

Acute toxicity

Isolated outbreaks of acute zinc toxicity have occurred as a result of the consumption of food or beverages contaminated with zinc released from galvanized containers. Signs of acute zinc toxicity are abdominal pain, diarrhea, nausea, and vomiting. Single doses of 225 to 450 mg of zinc usually induce vomiting. Milder gastrointestinal distress has been reported at doses of 50 to 150 mg/day of supplemental zinc. Metal fume fever has been reported after the inhalation of zinc oxide fumes. Specifically, profuse sweating, weakness, and rapid breathing may develop within eight hours of zinc oxide inhalation and persist for 12 to 24 hours after exposure is terminated (6, 29).

Adverse effects

The major consequence of long-term consumption of excessive zinc is copper deficiency. Total zinc intakes of 60 mg/day (50 mg supplemental and 10 mg dietary zinc) for up to 10 weeks have been found to result in signs of copper deficiency (29). Copper deficiency has also been reported following chronic use of excessive amounts of zinc-containing denture creams (≥2 tubes per week containing 17-34 mg/g of zinc) (177). In order to prevent copper deficiency, the US Food and Nutrition Board set the tolerable upper intake level (UL) for adults at 40 mg/day, including dietary and supplemental zinc (**Table 3**) (29).

Table 3. Tolerable Upper Intake Level (UL) for Zinc

Age Group	UL (mg/day)
Infants 0-6 months	4
Infants 7-12 months	5
Children 1-3 years	7
Children 4-8 years	12
Children 9-13 years	23
Adolescents 14-18 years	34
Adults 19 years and older	40

Intranasal zinc

Intranasal zinc is known to cause a loss of the sense of smell (anosmia) in laboratory animals (178), and there have been several case reports of individuals who developed anosmia after using intranasal zinc gluconate (127). Since zinc-associated anosmia may be irreversible, the use of zinc nasal gels and sprays should be avoided.

Drug interactions

The use of zinc supplements decrease the absorption of certain medications, including the antibiotics cephalexin (Keplex) and penicillamine (Cuprimine, Depen), as well as the antiretroviral drugs atazanavir (Reyataz) and ritonavir (Norvir) (179). Concomitant administration of zinc supplements with certain medications like tetracycline and quinolone antibiotics may decrease the absorption of both zinc and the medications, potentially reducing drug efficacy. Taking zinc supplements and these medications at least two hours apart should prevent this interaction.

The therapeutic use of metal-chelating agents, such as penicillamine (used to treat copper overload in Wilson's disease) and diethylenetriamine pentaacetate (DTPA; used to treat iron overload), has resulted in severe zinc deficiency. Anticonvulsant drugs, especially sodium valproate, may also precipitate zinc deficiency. Prolonged use of diuretics may increase urinary zinc excretion, resulting in increased loss of zinc. Because supplemental zinc can lower blood glucose, those taking anti-diabetic agents are advised to use zinc supplements with caution.

Linus Pauling Institute Recommendation

The RDA for zinc (8 mg/day for adult women and 11 mg/day for adult men) appears sufficient to prevent deficiency in most individuals, but the lack of sensitive indicators of zinc nutritional status in humans makes it difficult to determine the level of zinc intake most likely to promote optimum health. Following the Linus Pauling Institute recommendation to take a multivitamin/mineral supplement will generally provide at least the RDA for zinc. Daily total (supplemental + dietary) intakes of zinc should not exceed the UL (40 mg/day for adults) in order to limit the risk of copper deficiency in particular (see Safety).

Older adults (>50 years)

Although the requirement for zinc is not known to be higher for older adults, many have inadequate dietary zinc intakes (180, 181). A reduced capacity to absorb zinc, increased likelihood of disease states that alter zinc utilization, and increased use of drugs that decrease zinc bioavailability may all contribute to an increased risk of mild zinc deficiency in older adults. Adequate dietary intake of zinc is essential for older adults because the consequences of mild zinc deficiency, such as impaired immune system function, are especially relevant to maintenance of their health.

Authors and Reviewers

Originally written in 2001 by:
Jane Higdon, Ph.D.
Linus Pauling Institute
Oregon State University

Updated in December 2003 by:
Jane Higdon, Ph.D.
Linus Pauling Institute
Oregon State University

Updated in October 2007 by:
Victoria J. Drake, Ph.D.
Linus Pauling Institute
Oregon State University

Updated in June 2013 by:
Victoria J. Drake, Ph.D.

Linus Pauling Institute
Oregon State University

Updated in February 2019 by:
Barbara Delage, Ph.D.
Linus Pauling Institute
Oregon State University

Reviewed in May 2019 by:
Emily Ho, Ph.D.
Endowed Director, Moore Family Center for Whole Grain Foods,
Nutrition and Preventive Health
Professor, School of Biological and Population Health Sciences
Principal Investigator, Linus Pauling Institute
Oregon State University

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