National Institutes of Health
Office of Dietary Supplements

Vitamin C

Fact Sheet for Health Professionals

For information on Vitamin C and COVID-19, see the NIH COVID-19 Treatment Guidelines on Vitamin C (https://www.covid19treatmentguidelines.nih.gov/adjunctive-therapy/vitamin-c/).

Introduction

Vitamin C, also known as L-ascorbic acid, is a water-soluble vitamin that is naturally present in some foods, added to others, and available as a dietary supplement. Humans, unlike most animals, are unable to synthesize vitamin C endogenously, so it is an essential dietary component [1].

Vitamin C is required for the biosynthesis of collagen, L-carnitine, and certain neurotransmitters; vitamin C is also involved in protein metabolism [1,2]. Collagen is an essential component of connective tissue, which plays a vital role in wound healing. Vitamin C is also an important physiological antioxidant [3] and has been shown to regenerate other antioxidants within the body, including alpha-tocopherol (vitamin E) [4]. Ongoing research is examining whether vitamin C, by limiting the damaging effects of free radicals through its antioxidant activity, might help prevent or delay the development of certain cancers, cardiovascular disease, and other diseases in which oxidative stress plays a causal role. In addition to its biosynthetic and antioxidant functions, vitamin C plays an important role in immune function [4] and improves the absorption of nonheme iron [5], the form of iron present in plant-based foods. Insufficient vitamin C intake causes scurvy, which is characterized by fatigue or lassitude, widespread connective tissue weakness, and capillary fragility [1,2,4,6-9].

The intestinal absorption of vitamin C is regulated by at least one specific dose-dependent, active transporter [4]. Cells accumulate vitamin C via a second specific transport protein. In vitro studies have found that oxidized vitamin C, or dehydroascorbic acid, enters cells via some facilitated glucose transporters and is then reduced internally to ascorbic acid. The physiologic importance of dehydroascorbic acid uptake and its contribution to overall vitamin C economy is unknown.

Oral vitamin C produces tissue and plasma concentrations that the body tightly controls. Approximately 70%–90% of vitamin C is absorbed at moderate intakes of 30–180 mg/day. However, at doses above 1 g/day, absorption falls to less than 50% and absorbed, unmetabolized ascorbic acid is excreted in the urine [4]. Results from pharmacokinetic studies indicate that oral doses of 1.25 g/day ascorbic acid produce mean peak plasma vitamin C concentrations of 135 micromol/L, which are about two times higher than those produced by consuming 200–300 mg/day ascorbic acid from vitamin C-rich foods [10]. Pharmacokinetic modeling predicts that even doses as high as 3 g ascorbic acid taken every 4 hours would produce peak plasma concentrations of only 220 micromol/L [10].

The total body content of vitamin C ranges from 300 mg (at near scurvy) to about 2 g [4]. High levels of vitamin C (millimolar concentrations) are maintained in cells and tissues, and are highest in

leukocytes (white blood cells), eyes, adrenal glands, pituitary gland, and brain. Relatively low levels of vitamin C (micromolar concentrations) are found in extracellular fluids, such as plasma, red blood cells, and saliva [4].

Recommended Intakes

Intake recommendations for vitamin C and other nutrients are provided in the Dietary Reference Intakes (DRIs) developed by the Food and Nutrition Board (FNB) at the Institute of Medicine (IOM) of the National Academies (formerly National Academy of Sciences) [8]. DRI is the general term for a set of reference values used for planning and assessing nutrient intakes of healthy people. These values, which vary by age and gender [8], include:

- Recommended Dietary Allowance (RDA): Average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals; often used to plan nutritionally adequate diets for individuals.
- Adequate Intake (AI): Intake at this level is assumed to ensure nutritional adequacy; established when evidence is insufficient to develop an RDA.
- Estimated Average Requirement (EAR): Average daily level of intake estimated to meet the requirements of 50% of healthy individuals; usually used to assess the nutrient intakes of groups of people and to plan nutritionally adequate diets for them; can also be used to assess the nutrient intakes of individuals.
- Tolerable Upper Intake Level (UL): Maximum daily intake unlikely to cause adverse health effects.

Table 1 lists the current RDAs for vitamin C [8]. The RDAs for vitamin C are based on its known physiological and antioxidant functions in white blood cells and are much higher than the amount required for protection from deficiency [4,8,11]. For infants from birth to 12 months, the FNB established an AI for vitamin C that is equivalent to the mean intake of vitamin C in healthy, breastfed infants.

Table 1: Recommended Dietary Allowances (RDAs) for Vitamin C [8]

Age	Male	Female	Pregnancy	Lactation
0–6 months	40 mg*	40 mg*		
7–12 months	50 mg*	50 mg*		
1–3 years	15 mg	15 mg		
4–8 years	25 mg	25 mg		
9–13 years	45 mg	45 mg		
14–18 years	75 mg	65 mg	80 mg	115 mg
19+ years	90 mg	75 mg	85 mg	120 mg
Smokers	Individuals who smoke require 35 mg/day more vitamin C than nonsmokers.			

* Adequate Intake (AI)

Sources of Vitamin C

Food

Fruits and vegetables are the best sources of vitamin C (see Table 2) [12]. Citrus fruits, tomatoes and tomato juice, and potatoes are major contributors of vitamin C to the American diet [8]. Other good food sources include red and green peppers, kiwifruit, broccoli, strawberries, Brussels sprouts, and cantaloupe (see Table 2) [8,12]. Although vitamin C is not naturally present in grains, it is added to some fortified breakfast cereals. The vitamin C content of food may be reduced by prolonged storage and by cooking because ascorbic acid is water soluble and is destroyed by heat [6,8]. Steaming or microwaving may lessen cooking losses. Fortunately, many of the best food sources of vitamin C, such as fruits and vegetables, are usually consumed raw. Consuming five varied servings of fruits and vegetables a day can provide more than 200 mg of vitamin C.

Table 2: Selected Food Sources of Vitamin C [12]

Food	Milligrams (mg) per serving	Percent (%) DV*
Red pepper, sweet, raw, ½ cup	95	106
Orange juice, ¾ cup	93	103
Orange, 1 medium	70	78
Grapefruit juice, ¾ cup	70	78
Kiwifruit, 1 medium	64	71
Green pepper, sweet, raw, ½ cup	60	67
Broccoli, cooked, ½ cup	51	57
Strawberries, fresh, sliced, ½ cup	49	54
Brussels sprouts, cooked, ½ cup	48	53
Grapefruit, ½ medium	39	43
Broccoli, raw, ½ cup	39	43
Tomato juice, ¾ cup	33	37
Cantaloupe, ½ cup	29	32
Cabbage, cooked, ½ cup	28	31
Cauliflower, raw, ½ cup	26	29
Potato, baked, 1 medium	17	19
Tomato, raw, 1 medium	17	19
Spinach, cooked, ½ cup	9	10
Green peas, frozen, cooked, ½ cup	8	9

*DV = Daily Value. The U.S. Food and Drug Administration (FDA) developed DVs to help consumers compare the nutrient contents of foods and dietary supplements within the context of a total diet. The DV for vitamin C on the new Nutrition Facts and Supplement Facts labels and used for the values in Table 2 is 90 mg for adults and children age 4 years and older [14]. FDA required manufacturers to use these new labels starting in January 2020, but companies with annual sales of less than $10 million may continue to use the old labels that list a vitamin C DV of 60 mg until January 2021 [13,15]. FDA does not require the new food food labels to list vitamin C content unless vitamin C has been added to the food. Foods providing 20% or more of the DV are

considered to be high sources of a nutrient, but foods providing lower percentages of the DV also contribute to a healthful diet.

The U.S. Department of Agriculture's (USDA's) FoodData Central (https://fdc.nal.usda.gov/) lists the nutrient content of many foods and provides a comprehensive list of foods containing vitamin C arranged by nutrient content and by food name.

Dietary supplements

Supplements typically contain vitamin C in the form of ascorbic acid, which has equivalent bioavailability to that of naturally occurring ascorbic acid in foods, such as orange juice and broccoli [16-18]. Other forms of vitamin C supplements include sodium ascorbate; calcium ascorbate; other mineral ascorbates; ascorbic acid with bioflavonoids; and combination products, such as Ester-C®, which contains calcium ascorbate, dehydroascorbate, calcium threonate, xylonate and lyxonate [19].

A few studies in humans have examined whether bioavailability differs among the various forms of vitamin C. In one study, Ester-C® and ascorbic acid produced the same vitamin C plasma concentrations, but Ester-C® produced significantly higher vitamin C concentrations in leukocytes 24 hours after ingestion [20]. Another study found no differences in plasma vitamin C levels or urinary excretion of vitamin C among three different vitamin C sources: ascorbic acid, Ester-C®, and ascorbic acid with bioflavonoids [19]. These findings, coupled with the relatively low cost of ascorbic acid, led the authors to conclude that simple ascorbic acid is the preferred source of supplemental vitamin C [19].

Vitamin C Intakes and Status

According to the 2001–2002 National Health and Nutrition Examination Survey (NHANES), mean intakes of vitamin C are 105.2 mg/day for adult males and 83.6 mg/day for adult females, meeting the currently established RDA for most nonsmoking adults [21]. Mean intakes for children and adolescents aged 1-18 years range from 75.6 mg/day to 100 mg/day, also meeting the RDA for these age groups [21]. Although the 2001–2002 NHANES analysis did not include data for breastfed infants and toddlers, breastmilk is considered an adequate source of vitamin C [8,16]. Use of vitamin C-containing supplements is also relatively common, adding to the total vitamin C intake from food and beverages. NHANES data from 1999–2000 indicate that approximately 35% of adults take multivitamin supplements (which typically contain vitamin C) and 12% take a separate vitamin C supplement [22]. According to 1999–2002 NHANES data, approximately 29% of children take some form of dietary supplement that contains vitamin C [23].

Vitamin C status is typically assessed by measuring plasma vitamin C levels [4,16]. Other measures, such as leukocyte vitamin C concentration, could be more accurate indicators of tissue vitamin C levels, but they are more difficult to assess and the results are not always reliable [4,9,16].

Vitamin C Deficiency

Acute vitamin C deficiency leads to scurvy [7,8,11]. The timeline for the development of scurvy varies, depending on vitamin C body stores, but signs can appear within 1 month of little or no vitamin C intake (below 10 mg/day) [6,7,24,25]. Initial symptoms can include fatigue (probably the result of impaired carnitine biosynthesis), malaise, and inflammation of the gums [4,11]. As vitamin

C deficiency progresses, collagen synthesis becomes impaired and connective tissues become weakened, causing petechiae, ecchymoses, purpura, joint pain, poor wound healing, hyperkeratosis, and corkscrew hairs [1,2,4,6-8]. Additional signs of scurvy include depression as well as swollen, bleeding gums and loosening or loss of teeth due to tissue and capillary fragility [6,8,9]. Iron deficiency anemia can also occur due to increased bleeding and decreased nonheme iron absorption secondary to low vitamin C intake [6,11]. In children, bone disease can be present [6]. Left untreated, scurvy is fatal [6,9].

Until the end of the 18th century, many sailors who ventured on long ocean voyages, with little or no vitamin C intake, contracted or died from scurvy. During the mid-1700s, Sir James Lind, a British Navy surgeon, conducted experiments and determined that eating citrus fruits or juices could cure scurvy, although scientists did not prove that ascorbic acid was the active component until 1932 [26-28].

Today, vitamin C deficiency and scurvy are rare in developed countries [8]. Overt deficiency symptoms occur only if vitamin C intake falls below approximately 10 mg/day for many weeks [5-8,24,25]. Vitamin C deficiency is uncommon in developed countries but can still occur in people with limited food variety.

Groups at Risk of Vitamin C Inadequacy

Vitamin C *inadequacy* can occur with intakes that fall below the RDA but are above the amount required to prevent overt deficiency (approximately 10 mg/day). The following groups are more likely than others to be at risk of obtaining insufficient amounts of vitamin C.

Smokers and passive "smokers"

Studies consistently show that smokers have lower plasma and leukocyte vitamin C levels than nonsmokers, due in part to increased oxidative stress [8]. For this reason, the IOM concluded that smokers need 35 mg more vitamin C per day than nonsmokers [8]. Exposure to secondhand smoke also decreases vitamin C levels. Although the IOM was unable to establish a specific vitamin C requirement for nonsmokers who are regularly exposed to secondhand smoke, these individuals should ensure that they meet the RDA for vitamin C [4,8].

Infants fed evaporated or boiled milk

Most infants in developed countries are fed breastmilk and/or infant formula, both of which supply adequate amounts of vitamin C [8,16]. For many reasons, feeding infants evaporated or boiled cow's milk is not recommended. This practice can cause vitamin C deficiency because cow's milk naturally has very little vitamin C and heat can destroy vitamin C [6,12].

Individuals with limited food variety

Although fruits and vegetables are the best sources of vitamin C, many other foods have small amounts of this nutrient. Thus, through a varied diet, most people should be able to meet the vitamin C RDA or at least obtain enough to prevent scurvy. People who have limited food variety—including some elderly, indigent individuals who prepare their own food; people who abuse alcohol or drugs; food faddists; people with mental illness; and, occasionally, children—might not obtain sufficient vitamin C [4,6-9,11].

People with malabsorption and certain chronic diseases

Some medical conditions can reduce the absorption of vitamin C and/or increase the amount needed by the body. People with severe intestinal malabsorption or cachexia and some cancer patients might be at increased risk of vitamin C inadequacy [29]. Low vitamin C concentrations can also occur in patients with end-stage renal disease on chronic hemodialysis [30].

Vitamin C and Health

Due to its function as an antioxidant and its role in immune function, vitamin C has been promoted as a means to help prevent and/or treat numerous health conditions. This section focuses on four diseases and disorders in which vitamin C might play a role: cancer (including prevention and treatment), cardiovascular disease, age-related macular degeneration (AMD) and cataracts, and the common cold.

Cancer prevention

Epidemiologic evidence suggests that higher consumption of fruits and vegetables is associated with lower risk of most types of cancer, perhaps, in part, due to their high vitamin C content [1,2]. Vitamin C can limit the formation of carcinogens, such as nitrosamines [2,31], in vivo; modulate immune response [2,4]; and, through its antioxidant function, possibly attenuate oxidative damage that can lead to cancer [1].

Most case-control studies have found an inverse association between dietary vitamin C intake and cancers of the lung, breast, colon or rectum, stomach, oral cavity, larynx or pharynx, and esophagus [2,4]. Plasma concentrations of vitamin C are also lower in people with cancer than controls [2].

However, evidence from prospective cohort studies is inconsistent, possibly due to varying intakes of vitamin C among studies. In a cohort of 82,234 women aged 33–60 years from the Nurses' Health Study, consumption of an average of 205 mg/day of vitamin C from food (highest quintile of intake) compared with an average of 70 mg/day (lowest quintile of intake) was associated with a 63% lower risk of breast cancer among premenopausal women with a family history of breast cancer [32]. Conversely, Kushi and colleagues did not observe a significantly lower risk of breast cancer among postmenopausal women consuming at least 198 mg/day (highest quintile of intake) of vitamin C from food compared with those consuming less than 87 mg/day (lowest quintile of intake) [33]. A review by Carr and Frei concluded that in the majority of prospective cohort studies not reporting a significantly lower cancer risk, most participants had relatively high vitamin C intakes, with intakes higher than 86 mg/day in the lowest quintiles [2]. Studies reporting significantly lower cancer risk found these associations in individuals with vitamin C intakes of at least 80–110 mg/day, a range associated with close to vitamin C tissue saturation [2,24,34].

Evidence from most randomized clinical trials suggests that vitamin C supplementation, usually in combination with other micronutrients, does not affect cancer risk. In the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study, a randomized, double-blind, placebo-controlled clinical trial,13,017 healthy French adults received antioxidant supplementation with 120 mg ascorbic acid, 30 mg vitamin E, 6 mg beta-carotene, 100 mcg selenium, and 20 mg zinc, or placebo [35]. After a median follow-up time of 7.5 years, antioxidant supplementation lowered total cancer incidence in men, but not in women. In addition, baseline antioxidant status was related to

cancer risk in men, but not in women [36]. Supplements of 500 mg/day vitamin C plus 400 IU vitamin E every other day for a mean follow-up period of 8 years failed to reduce the risk of prostate or total cancer compared with placebo in middle-aged and older men participating in the Physicians' Health Study II [37]. Similar findings were reported in women participating in the Women's Antioxidant Cardiovascular Study [38]. Compared with placebo, supplementation with vitamin C (500 mg/day) for an average of 9.4 years had no significant effect on total cancer incidence or cancer mortality. In a large intervention trial conducted in Linxian, China, daily supplements of vitamin C (120 mg) plus molybdenum (30 mcg) for 5–6 years did not significantly affect the risk of developing esophageal or gastric cancer [39]. Moreover, during 10 years of follow-up, this supplementation regimen failed to significantly affect total morbidity or mortality from esophageal, gastric, or other cancers [40]. A 2008 review of vitamin C and other antioxidant supplements for the prevention of gastrointestinal cancers found no convincing evidence that vitamin C (or beta-carotene, vitamin A, or vitamin E) prevents gastrointestinal cancers [41]. A similar review by Coulter and colleagues found that vitamin C supplementation, in combination with vitamin E, had no significant effect on death risk due to cancer in healthy individuals [42].

At this time, the evidence is inconsistent on whether dietary vitamin C intake affects cancer risk. Results from most clinical trials suggest that modest vitamin C *supplementation* alone or with other nutrients offers no benefit in the prevention of cancer.

A substantial limitation in interpreting many of these studies is that investigators did not measure vitamin C concentrations before or after supplementation. Plasma and tissue concentrations of vitamin C are tightly controlled in humans. At daily intakes of 100 mg or higher, cells appear to be saturated and at intakes of at least 200 mg, plasma concentrations increase only marginally [2,10,24,33,39]. If subjects' vitamin C levels were already close to saturation at study entry, supplementation would be expected to have made little or no difference on measured outcomes [24,25,43,44].

Cancer treatment

During the 1970s, studies by Cameron, Campbell, and Pauling suggested that high-dose vitamin C has beneficial effects on quality of life and survival time in patients with terminal cancer [45,46]. However, some subsequent studies—including a randomized, double-blind, placebo-controlled clinical trial by Moertel and colleagues at the Mayo Clinic [47]—did not support these findings. In the Moertel study, patients with advanced colorectal cancer who received 10 g/day vitamin C fared no better than those receiving a placebo. The authors of a 2003 review assessing the effects of vitamin C in patients with advanced cancer concluded that vitamin C confers no significant mortality benefit [42].

Emerging research suggests that the route of vitamin C administration (intravenous vs. oral) could explain the conflicting findings [1,48,49]. Most intervention trials, including the one conducted by Moertel and colleagues, used only oral administration, whereas Cameron and colleagues used a combination of oral and intravenous (IV) administration. Oral administration of vitamin C, even of very large doses, can raise plasma vitamin C concentrations to a maximum of only 220 micromol/L, whereas IV administration can produce plasma concentrations as high as 26,000 micromol/L [49,50]. Concentrations of this magnitude are selectively cytotoxic to tumor cells in vitro [1,69]. Research in mice suggests that pharmacologic doses of IV vitamin C might show promise in treating

otherwise difficult-to-treat tumors [51]. A high concentration of vitamin C may act as a pro-oxidant and generate hydrogen peroxide that has selective toxicity toward cancer cells [51-53]. Based on these findings and a few case reports of patients with advanced cancers who had remarkably long survival times following administration of high-dose IV vitamin C, some researchers support reassessment of the use of high-dose IV vitamin C as a drug to treat cancer [3,49,51,54].

As discussed below, it is uncertain whether supplemental vitamin C and other antioxidants might interact with chemotherapy and/or radiation [55]. Therefore, individuals undergoing these procedures should consult with their oncologist prior to taking vitamin C or other antioxidant supplements, especially in high doses [56].

Cardiovascular disease

Evidence from many epidemiological studies suggests that high intakes of fruits and vegetables are associated with a reduced risk of cardiovascular disease [1,57,58]. This association might be partly attributable to the antioxidant content of these foods because oxidative damage, including oxidative modification of low-density lipoproteins, is a major cause of cardiovascular disease [1,4,58]. In addition to its antioxidant properties, vitamin C has been shown to reduce monocyte adherence to the endothelium, improve endothelium-dependent nitric oxide production and vasodilation, and reduce vascular smooth-muscle-cell apoptosis, which prevents plaque instability in atherosclerosis [2,59].

Results from prospective studies examining associations between vitamin C intake and cardiovascular disease risk are conflicting [58]. In the Nurses' Health Study, a 16-year prospective study involving 85,118 female nurses, total intake of vitamin C from both dietary and supplemental sources was inversely associated with coronary heart disease risk [60]. However, intake of vitamin C from diet alone showed no significant associations, suggesting that vitamin C supplement users might be at lower risk of coronary heart disease. A much smaller study indicated that postmenopausal women with diabetes who took at least 300 mg/day vitamin C supplements had increased cardiovascular disease mortality [61].

A prospective study in 20,649 British adults found that those in the top quartile of baseline plasma vitamin C concentrations had a 42% lower risk of stroke than those in the bottom quartile [62]. In male physicians participating in the Physicians' Health Study, use of vitamin C supplements for a mean of 5.5 years was not associated with a significant decrease in total cardiovascular disease mortality or coronary heart disease mortality [63]. A pooled analysis of nine prospective studies that included 293,172 subjects free of coronary heart disease at baseline found that people who took ≥700 mg/day of supplemental vitamin C had a 25% lower risk of coronary heart disease incidence than those who took no supplemental vitamin C [64]. The authors of a 2008 meta-analysis of prospective cohort studies, including 14 studies reporting on vitamin C for a median follow-up of 10 years, concluded that dietary, but not supplemental, intake of vitamin C is inversely associated with coronary heart disease risk [57].

Results from most clinical intervention trials have failed to show a beneficial effect of vitamin C supplementation on the primary or secondary prevention of cardiovascular disease. In the Women's Antioxidant Cardiovascular Study, a secondary prevention trial involving 8,171 women aged 40 years or older with a history of cardiovascular disease, supplementation with 500 mg/day vitamin C

for a mean of 9.4 years showed no overall effect on cardiovascular events [65]. Similarly, vitamin C supplementation (500 mg/day) for a mean follow-up of 8 years had no effect on major cardiovascular events in male physicians enrolled in the Physicians' Health Study II [66].

Other clinical trials have generally examined the effects on cardiovascular disease of supplements combining vitamin C with other antioxidants, such as vitamin E and beta-carotene, making it more difficult to isolate the potential contribution of vitamin C. The SU.VI.MAX study examined the effects of a combination of vitamin C (120 mg/day), vitamin E (30 mg/day), beta-carotene (6 mg/day), selenium (100 mcg/day), and zinc (20 mg/day) in 13,017 French adults from the general population [35]. After a median follow-up time of 7.5 years, the combined supplements had no effect on ischemic cardiovascular disease in either men or women. In the Women's Angiographic Vitamin and Estrogen (WAVE) study, involving 423 postmenopausal women with at least one coronary stenosis of 15%–75%, supplements of 500 mg vitamin C plus 400 IU vitamin E twice per day not only provided no cardiovascular benefit, but significantly increased all-cause mortality compared with placebo [67].

The authors of a 2006 meta-analysis of randomized controlled trials concluded that antioxidant supplements (vitamins C and E and beta-carotene or selenium) do not affect the progression of atherosclerosis [68]. Similarly, a systematic review of vitamin C's effects on the prevention and treatment of cardiovascular disease found that vitamin C did not have favorable effects on cardiovascular disease prevention [69]. Since then, researchers have published follow-up data from the Linxian trial, a population nutrition intervention trial conducted in China [40]. In this trial, daily vitamin C supplements (120 mg) plus molybdenum (30 mcg) for 5–6 years significantly reduced the risk of cerebrovascular deaths by 8% during 10 years of follow-up after the end of the active intervention.

Although the Linxian trial data suggest a possible benefit, overall, the findings from most intervention trials do not provide convincing evidence that vitamin C supplements provide protection against cardiovascular disease or reduce its morbidity or mortality. However, as discussed in the cancer prevention section, clinical trial data for vitamin C are limited by the fact that plasma and tissue concentrations of vitamin C are tightly controlled in humans. If subjects' vitamin C levels were already close to saturation at study entry, supplementation would be expected to have made little or no difference on measured outcomes [24,25,43,44].

Age-related macular degeneration (AMD) and cataracts

AMD and cataracts are two of the leading causes of vision loss in older individuals. Oxidative stress might contribute to the etiology of both conditions. Thus, researchers have hypothesized that vitamin C and other antioxidants play a role in the development and/or treatment of these diseases.

A population-based cohort study in the Netherlands found that adults aged 55 years or older who had high dietary intakes of vitamin C as well as beta-carotene, zinc, and vitamin E had a reduced risk of AMD [70]. However, most prospective studies do not support these findings [71]. The authors of a 2007 systematic review and meta-analysis of prospective cohort studies and randomized clinical trials concluded that the current evidence does not support a role for vitamin C and other antioxidants, including antioxidant supplements, in the primary prevention of early AMD [72].

Although research has not shown that antioxidants play a role in AMD development, some evidence suggests that they might help slow AMD progression [73]. The Age-Related Eye Disease Study (AREDS), a large, randomized, placebo-controlled clinical trial, evaluated the effect of high doses of selected antioxidants (500 mg vitamin C, 400 IU vitamin E, 15 mg beta-carotene, 80 mg zinc, and 2 mg copper) on the development of advanced AMD in 3,597 older individuals with varying degrees of AMD [74]. After an average follow-up period of 6.3 years, participants at high risk of developing advanced AMD (i.e., those with intermediate AMD or those with advanced AMD in one eye) who received the antioxidant supplements had a 28% lower risk of progression to advanced AMD than participants who received a placebo. A follow-up AREDS2 study confirmed the value of this and similar supplement formulations in reducing the progression of AMD over a median follow-up period of 5 years [75].

High dietary intakes of vitamin C and higher plasma ascorbate concentrations have been associated with a lower risk of cataract formation in some studies [2,4]. In a 5-year prospective cohort study conducted in Japan, higher dietary vitamin C intake was associated with a reduced risk of developing cataracts in a cohort of more than 30,000 adults aged 45–64 years [76]. Results from two case-control studies indicate that vitamin C intakes greater than 300 mg/day reduce the risk of cataract formation by 70%–75% [2,4]. Use of vitamin C supplements, on the other hand, was associated with a 25% higher risk of age-related cataract extraction among a cohort of 24,593 Swedish women aged 49–83 years [77]. These findings applied to study participants who took relatively high-dose vitamin C supplements (approximately 1,000 mg/day) and not to those who took multivitamins containing substantially less vitamin C (approximately 60 mg/day).

Data from clinical trials are limited. In one study, Chinese adults who took daily supplements of 120 mg vitamin C plus 30 mcg molybdenum for 5 years did not have a significantly lower cataract risk [78]. However, adults aged 65–74 years who received 180 mg vitamin C plus 30 mcg molybdenum combined with other nutrients in a multivitamin/mineral supplement had a 43% significantly lower risk of developing nuclear cataracts than those who received a placebo [78]. In the AREDS study, older individuals who received supplements of 500 mg vitamin C, 400 IU vitamin E, and 15 mg beta-carotene for an average of 6.3 years did not have a significantly lower risk of developing cataracts or of cataract progression than those who received a placebo [79]. The AREDS2 study, which also tested formulations containing 500 mg vitamin C, confirmed these findings [80].

Overall, the currently available evidence does not indicate that vitamin C, taken alone or with other antioxidants, affects the risk of developing AMD, although some evidence indicates that the AREDS formulations might slow AMD progression in people at high risk of developing advanced AMD.

The common cold

In the 1970s Linus Pauling suggested that vitamin C could successfully treat and/or prevent the common cold [81]. Results of subsequent controlled studies have been inconsistent, resulting in confusion and controversy, although public interest in the subject remains high [82,83].

A 2007 Cochrane review examined placebo-controlled trials involving the use of at least 200 mg/day vitamin C taken either continuously as a prophylactic treatment or after the onset of cold symptoms [83]. Prophylactic use of vitamin C did not significantly reduce the risk of developing a cold in the general population. However, in trials involving marathon runners, skiers, and soldiers exposed to

extreme physical exercise and/or cold environments, prophylactic use of vitamin C in doses ranging from 250 mg/day to 1 g/day reduced cold incidence by 50%. In the general population, use of prophylactic vitamin C modestly reduced cold duration by 8% in adults and 14% in children. When taken after the onset of cold symptoms, vitamin C did not affect cold duration or symptom severity.

Overall, the evidence to date suggests that regular intakes of vitamin C at doses of at least 200 mg/day do not reduce the incidence of the common cold in the general population, but such intakes might be helpful in people exposed to extreme physical exercise or cold environments and those with marginal vitamin C status, such as the elderly and chronic smokers [83-85]. The use of vitamin C supplements might shorten the duration of the common cold and ameliorate symptom severity in the general population [82,85], possibly due to the anti-histamine effect of high-dose vitamin C [86]. However, taking vitamin C after the onset of cold symptoms does not appear to be beneficial [83].

Health Risks from Excessive Vitamin C

Vitamin C has low toxicity and is not believed to cause serious adverse effects at high intakes [8]. The most common complaints are diarrhea, nausea, abdominal cramps, and other gastrointestinal disturbances due to the osmotic effect of unabsorbed vitamin C in the gastrointestinal tract [4,8].

In postmenopausal women with diabetes who participated in the Iowa Women's Health Study, supplemental (but not dietary) vitamin C intake (at least 300 mg/day) was significantly associated with an increased risk of cardiovascular disease mortality [61]. The mechanism for this effect, if real, is not clear and this finding is from a subgroup of patients in an epidemiological study. No such association has been observed in any other epidemiological study, so the significance of this finding is uncertain. High vitamin C intakes also have the potential to increase urinary oxalate and uric acid excretion, which could contribute to the formation of kidney stones, especially in individuals with renal disorders [8]. However, studies evaluating the effects on urinary oxalate excretion of vitamin C intakes ranging from 30 mg to 10 g/day have had conflicting results, so it is not clear whether vitamin C actually plays a role in the development of kidney stones [8,87-89]. The best evidence that vitamin C contributes to kidney stone formation is in patients with pre-existing hyperoxaluria [25].

Due to the enhancement of nonheme iron absorption by vitamin C, a theoretical concern is that high vitamin C intakes might cause excess iron absorption. In healthy individuals, this does not appear to be a concern [8]. However, in individuals with hereditary hemochromatosis, chronic consumption of high doses of vitamin C could exacerbate iron overload and result in tissue damage [4,8].

Under certain conditions, vitamin C can act as a pro-oxidant, potentially contributing to oxidative damage [8]. A few studies in vitro have suggested that by acting as a pro-oxidant, supplemental oral vitamin C could cause chromosomal and/or DNA damage and possibly contribute to the development of cancer [8,90,91]. However, other studies have not shown increased oxidative damage or increased cancer risk with high intakes of vitamin C [8,92].

Other reported effects of high intakes of vitamin C include reduced vitamin B12 and copper levels, accelerated metabolism or excretion of ascorbic acid, erosion of dental enamel, and allergic responses [8]. However, at least some of these conclusions were a consequence of assay artifact, and additional studies have not confirmed these observations [8].

The FNB has established ULs for vitamin C that apply to both food and supplement intakes (Table 3) [8]. Long-term intakes of vitamin C above the UL may increase the risk of adverse health effects. The ULs do not apply to individuals receiving vitamin C for medical treatment, but such individuals should be under the care of a physician [8].

Table 3: Tolerable Upper Intake Levels (ULs) for Vitamin C [8]

Age	Male	Female	Pregnancy	Lactation
0–12 months	Not possible to establish*	Not possible to establish*		
1–3 years	400 mg	400 mg		
4–8 years	650 mg	650 mg		
9–13 years	1,200 mg	1,200 mg		
14–18 years	1,800 mg	1,800 mg	1,800 mg	1,800 mg
19+ years	2,000 mg	2,000 mg	2,000 mg	2,000 mg

*Formula and food should be the only sources of vitamin C for infants.

Interactions with Medications

Vitamin C supplements have the potential to interact with several types of medications. A few examples are provided below. Individuals taking these medications on a regular basis should discuss their vitamin C intakes with their healthcare providers.

Chemotherapy and radiation

The safety and efficacy of the use of vitamin C and other antioxidants during cancer treatment is controversial [55,93,94]. Some data indicate that antioxidants might protect tumor cells from the action of radiation therapy and chemotherapeutic agents, such as cyclophosphamide, chlorambucil, carmustine, busulfan, thiotepa, and doxorubicin [56,93,95,96]. At least some of these data have been criticized because of poor study design [54]. Other data suggest that antioxidants might protect normal tissues from chemotherapy- and radiation-induced damage [93,95] and/or enhance the effectiveness of conventional cancer treatment [97]. However, due to the physiologically tight control of vitamin C, it is unclear whether oral vitamin C supplements could alter vitamin C concentrations enough to produce the suggested effects. Individuals undergoing chemotherapy or radiation should consult with their oncologist prior to taking vitamin C or other antioxidant supplements, especially in high doses [56].

3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins)

Vitamin C, in combination with other antioxidants, may attenuate the increase in high-density lipoprotein levels resulting from combination niacin–simvastatin (Zocor®) therapy [98,99]. It is not known whether this interaction occurs with other lipid-altering regimens [56]. Healthcare providers should monitor lipid levels in individuals taking both statins and antioxidant supplements [56].

Vitamin C and Healthful Diets

The federal government's 2015-2020 *Dietary Guidelines for Americans* notes that "Nutritional needs should be met primarily from foods. … Foods in nutrient-dense forms contain essential vitamins and minerals and also dietary fiber and other naturally occurring substances that may have positive

health effects. In some cases, fortified foods and dietary supplements may be useful in providing one or more nutrients that otherwise may be consumed in less-than-recommended amounts."

For more information about building a healthy diet, refer to the *Dietary Guidelines for Americans* (http://health.gov/dietaryguidelines/2015/guidelines/) and the U.S. Department of Agriculture's MyPlate (http://www.choosemyplate.gov/).

The *Dietary Guidelines for Americans* describes a healthy eating pattern as one that:

- Includes a variety of vegetables, fruits, whole grains, fat-free or low-fat milk and milk products, and oils.

    Fruits, particularly citrus fruits, fruit juices, and many vegetables are excellent sources of vitamin C. Some ready-to-eat breakfast cereals are fortified with vitamin C.

- Includes a variety of protein foods, including seafood, lean meats and poultry, eggs, legumes (beans and peas), nuts, seeds, and soy products.
- Limits saturated and *trans* fats, added sugars, and sodium.
- Stays within your daily calorie needs.

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Updated: February 27, 2020 History of changes to this fact sheet