Selenium

Evidence Summary
Selenium dietary intake at levels that allow for optimal expression of selenoproteins can maximize health outcomes, but additional supplementation is not associated with benefit, and excessive levels are toxic.

Neuroprotective Benefit: Prevention of selenium deficiency may mitigate dementia risk, but the association may be confounded by the impact of malnutrition and disease etiology-related changes in selenium regulation.

Aging and related health concerns: Maintenance of selenium levels within the range to maximally activate antioxidant selenoproteins is associated with reduced mortality and age-related disease risk, but further supplementation doesn’t add further benefit.

Safety: Selenium intake at the recommended dietary allowance is safe and associated with better health outcomes, but levels in excess of 400 mcg can lead to toxicity. Genetics may affect the body’s ability to effectively utilize selenium.
What is it?

Selenium is an essential trace element. It is typically obtained through the diet, and selenium intake needs to be within a relatively narrow range for health benefits \[1\]. Selenium deficiency is associated with higher risk for age-related diseases, such as cardiovascular disease and neurodegenerative diseases, coupled with an increased risk for mortality. However, excess levels of selenium are toxic. Selenium occurs in both organic and inorganic forms, which have different bioavailability and may be differentially utilized in the body. Selenium gets incorporated into proteins, called selenoproteins, which have a variety of functions, though the best characterized are involved in redox reactions \[2\]. These include the glutathione peroxidases. In this way selenium is important for the body to combat oxidative stress. Selenium can get incorporated into amino acids in place of sulfur to produce selenocysteine or selenomethionine. Selenocysteine is the 21st amino acid, and it is genetically encoded into selenoproteins via the codon UGA, which is ordinarily a stop codon. There are 25 known genetically encoded selenoproteins in humans. These genes are regulated such that they can only be formed when there are adequate levels of selenium, such that if there is an inadequate supply of selenocysteine then the UGA will instead be read as a stop codon, ultimately leading to degradation. In the redox selenoproteins, the selenocysteine sits at the catalytic center, and is essential for the redox activity of these enzymes. There is a hierarchy of the selenoproteins such that under limited selenium levels, certain proteins will be made at the expense of others \[3\]. There is also a hierarchy of tissue distribution, in that some tissues, such as the brain and testes, will preferentially retain selenium when levels are limiting, while levels get depleted in other tissues, such as the liver. Due to its antioxidant functions,
selenium supplementation has been proposed as a potential preventative measure against a variety of age-related diseases, such as cancer. The totality of the studies conducted thus far indicate that beyond the recommended dietary levels, further supplementation of selenium does not appear to offer additional benefit for the prevention or treatment of age-related diseases.

**Neuroprotective Benefit:** Prevention of selenium deficiency may mitigate dementia risk, but the association may be confounded by the impact of malnutrition and disease- etiology related changes in selenium regulation.

*Types of evidence:*
- 3 meta-analyses or systematic reviews studies assessing selenium biomarkers in AD
- 1 meta-analysis of case-controls studies of selenium biomarkers in PD
- 1 systematic review of selenium clinical trials in AD
- 2 clinical trials for selenium supplementation in AD
- 1 clinical trial for selenium supplementation in prevention of AD
- 6 observational studies of selenium biomarkers in AD
- 2 observational studies on selenium nutritional intake and cognition
- 1 case-control study of selenium biomarkers in PD
- 1 observational study on selenium nutritional intake and association with AD risk
- Numerous laboratory studies

*Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:*

The conclusions regarding the effect of selenium on cognitive function and dementia risk vary depending on the type of study conducted. Taken as a whole, the studies suggest that selenium deficiency is a risk factor for dementia, but that supplementation with selenium in the context of selenium sufficiency does not confer additional benefit. The ability of the brain to take up and effectively utilize selenium appears to be disrupted within the context of dementia, which can lead to an issue of reverse causation interpretations in some studies. Additionally, the effects of low selenium intake are influenced by the relative levels of other trace minerals, as well as genetic factors. Some studies suggest that selenium contributes to neurodegeneration through its neurotoxic effects at high levels, however, most studies do not differentiate the various forms of selenium. The toxic effects tend to stem from the inorganic forms, while an increase in some organic forms may be associated with a
compensatory protective effect of elevated selenium-containing antioxidant proteins in the context of increased oxidative stress.

Nutritional selenium intake levels vary geographically based on the level of selenium content in the soil where the food is grown. The selenium content of the soil in North America is generally higher than in Europe and parts of Asia. In a U.S. geological survey (4,856 sites) within the 48 contiguous states examining the levels of 41 trace elements, soil selenium levels were most significantly associated with Alzheimer’s disease (AD) mortality rates [4]. The effect was influenced by levels of both selenium and sulfur, such that the six states in which the lowest soil selenium and sulfur concentrations had a 53% higher AD mortality rate compared with the six states with the highest soil selenium and sulfur levels (Rate ratio [RR] 1.53, 95% Confidence Interval [CI] 1.51 to 1.54). In a cross-sectional study from the National Health and Nutrition Examination Survey (NHANES) including 2,332 adults ≥ age 60, those in the highest quartile of total selenium intake were at lower risk for low cognitive performance on the Digit Symbol Substitution Test (DSST) relative to the lowest quartile of total selenium intake (weighted multivariate adjusted odds ratio [OR] 0.48, 95% CI 0.25 to 0.92) [5]. A separate analysis from the NHANES study (n=2,016) found that blood selenium concentration was positively associated with performance on the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) recall (β: 0.015, 95% CI 0.007 to 0.022) and animal fluency (β: 0.017, 95% CI 0.003 to 0.030) tests in a sex-specific manner [6]. The associations between selenium and cognitive performance were only seen in males. The sexually dimorphic effect may be related to known differences in tissue selenium distribution and prioritization between males and females. It should be noted that all participants in this study had adequate blood levels of selenium (mean 196.7 μg/L; 95% CI 193.5 to 200.0 μg/L).

**Biomarkers:** It is evident from biomarker studies that circulating, and tissue levels of selenium can vary across individuals with similar levels of selenium intake. Biomarkers tend to be best associated with intake in the context of low selenium intake, as the incorporation of selenium into selenoproteins becomes saturated with selenium sufficiency. Different biomarkers reflect different durations of selenium exposure. Serum and plasma levels reflect short-term exposure, and are highly influenced by changes in dietary selenium levels. Whole blood and erythrocytes reflect longer-term selenium exposure due to the 120-day half-life of erythrocytes. Hair and nails are also reflective of long-term selenium exposure, but may be less reliable. Circulating and peripheral levels may not accurately reflect selenium levels in tissues, such as the brain, which are prioritized for selenium uptake and retention. Within the brain itself there can be wide variation in the levels across different regions. Selenium can be found in both inorganic and organic forms, such that both estimates, and conclusions can vary depending on
which forms are measured in a given assay. Furthermore, the expression and activity levels of selenoproteins can be influenced by genetic variation.

**Brain: SELENIUM LEVELS LOWER IN AD**

A meta-analysis of 13 studies found that brain levels of selenium were decreased in AD patients relative to controls (standardized mean difference [SMD] 0.42, 95% CI −0.71 to −0.13), with significantly lower levels found in the hippocampus (SMD = −0.46; Z = 2.44; p = 0.01) and cortex (SMD = −1.03; Z = 3.58; p = 0.0003) [7]. A study of postmortem temporal cortex tissue (n=71) found that selenium content in the soluble and insoluble brain tissue fractions were inversely associated with AD, while total selenium levels were not significantly associated with AD [8]. This suggests that levels of the selenium carrier protein selenoprotein P are normal or elevated, but that the selenium is not being delivered to neurons in sufficient quantities to allow for the synthesis of other selenoproteins.

**Plasma and blood: SELENIUM LEVELS GENERALLY REDUCED IN AD**

A systematic review containing four studies (141 control subjects and 129 AD) assessing plasma selenium levels found a lack of consensus across the studies, as two reported lower selenium levels, one reported no significant difference, and one reported higher selenium levels in AD patients [9]. The discrepancies could be a feature of differences in nutritional status of the participants, as plasma selenium levels are influenced by short-term changes in nutrition, and dementia patients are prone to malnutrition. A meta-analysis of 12 case-control and observational studies (594 AD cases and 472 controls) found a decrease in circulating levels of selenium in AD (SMD = −0.44, 95% CI −0.71 to −0.17), however, there was considerable variability, with only half the studies showing a significant decrease in selenium [10]. The levels of selenium were correlated with levels of the selenoprotein, glutathione peroxidase (GPx), suggesting that selenium availability influences antioxidant capacity, at least peripherally. In a comparative study (n=40), plasma selenium levels were lower in individuals with AD (76.07±18.45 μg/L) and mild cognitive impairment (MCI) (69.63±14.71 μg/L) relative to controls (90.72±17.56 μg/L), though were not associated with cognitive scores on the Mini-Mental State Exam (MMSE) [11]. Although all the means were within the normal physiological range, levels in the range of 90.01 to 94.75 μg/L are needed to get full activation of GPx in the plasma. Correspondingly, selenium levels were inversely associated with plasma oxidative stress markers in this cohort. In a cross-sectional study (n=102), AD patients had lower plasma (mean 45.29±14.51 μg/dL vs. 55.14±14.01 μg/dL; p=0.004) and erythrocyte selenium levels relative to controls [12]. There was a higher percentage of AD cases in the lowest quartile of erythrocyte selenium levels such that for each 1 μg/L increase in intracellular
selenium, there was an approximately 2.5% reduction in the incidence of AD in this elderly cohort (OR 0.975, 95% CI 0.953 to 0.997).

**CSF: SELENIUM LEVELS ARE DYSREGULATED WITH DISEASE COURSE**

A pilot clinical trial (n=40), found that nutritional supplementation of selenium (0.32 mg sodium selenate 3X/day) had only modest effects on cerebrospinal fluid (CSF) selenium levels [13]. This likely stems from the CNS compartment specific regulation of selenium levels, which suggests that genetic and physiological-related factors may be more important for controlling CNS selenium levels relative to overall selenium intake. CSF levels of selenium were non-significantly decreased in AD patients relative to controls (SMD −0.14, 95% CI −0.40 to 0.12) based on a meta-analysis of three studies, though there was heterogeneity across studies [10].

A case-control study (n=89) found that progression from MCI to AD modifies the levels of selenium species in CSF, which can lead to incorrect assessments regarding selenium-related dementia risk [14]. Some of the conflicting results seen across studies may stem from a lack of speciation analysis. In this study, MCI subjects had higher levels of overall selenium, inorganic selenium, and selenium bound to the carrier protein selenoprotein P, relative to AD cases. The increase in organo-selenium species in AD cases is thought to reflect a compensatory increase in antioxidant enzymes in response to disease progression-related oxidative stress, suggesting that it is part of a disease response rather than being a causal factor. An observational study in which 21/56 participants developed AD over a 42-month follow-up period assessed the association between different selenium species in the CSF and AD conversion [15]. Elevated CSF levels of the inorganic selenium form, selenate (Se(VI)), was associated with AD risk (adjusted Hazard ratio [HR] 3.1, 95% CI 1.0 to 9.5). These studies suggest that elevated levels of certain inorganic selenium species in the CNS may be associated with increased dementia risk. However, disease-related processes may influence the distribution, processing, and utilization of selenium in the body, especially within the CNS, which could confound association studies between selenium levels and AD risk.

**Hair and nail: SELENIUM LEVELS ELEVATED/DYSREGULATED**

In a case-control study (n=80), the levels of selenium were elevated in hair (3.01 μg/g dry tissue, 95% CI 0.34 to 7.02 vs 0.73 μg/g, 95% CI 0.06 to 2.95) and nail (1.55 μg/g, 95% CI 0.37 to 4.61 vs 0.51 μg/g, 95% CI 0.02 to 1.09) in AD cases relative to controls [16]. Levels of arsenic were also elevated, and there was a positive association between selenium and arsenic levels in AD cases. This provides further evidence to
suggest that there is a dysregulation of trace element accumulation and distribution in the context of AD, which may be related to genetic and/or metabolic factors.

**Clinical trials: NO BENEFIT IN ABSENCE OF SELENIUM DEFICIENCY**

A systematic review of nine placebo-controlled clinical trials determined that there was no conclusive evidence from these trials that selenium supplementation is effective for the prevention of AD [17]. The largest study to date was the PREADViSE RCT which included 3,786 men over age 60, who were treated with vitamin E, selenium (200 μg/day), a combination of the two, or placebo [18]. The study ran for six years, but was scheduled to run for ten years and was terminated early. The incidence of dementia did not differ across the four study arms (3.95%, 4.15%, 4.96%, and 4.62%, respectively). The hazard ratio for selenium relative to placebo was 0.83 (95% CI 0.60 to 1.13).

**Human research to suggest benefits to patients with dementia:**

**Alzheimer's disease: NO CLEAR BENEFIT FOR SUPPLEMENTATION**

Despite biomarker evidence indicating that selenium levels are altered in the context of dementia, supplementation with nutritional levels of selenium does not appear to offer significant benefit for dementia patients. The form of selenium used for supplementation may be important, as AD patients may not be able to utilize all forms equally. Based on the rationale that AD patients are inefficient at utilizing selenium, a pilot study (n=40) tested whether supplementation with supranutritional levels of selenium, in the form of sodium selenate (10 mg 3X/day) was needed for a clinical effect [13]. In this 24-week study, supranutritional selenium supplementation increased selenium CSF levels, though there was variability across subjects. A stabilization of MMSE score was seen only in the subset of participants who showed a significant increase in CSF selenium. There was also radiological evidence suggestive of reduced white matter atrophy in this subgroup.

Bacteria in the gut microbiome can metabolize inorganic and organic forms of selenium into selenomethionine, which increases its bioavailability [19]. However, the utilization of selenium by the gut bacteria can also limit host levels under conditions of selenium deficiency. Thus, the microbiome may play an important role in the regulation of selenium bioavailability and utilization. In an RCT (n=79), the combination of probiotics with selenium (200 μg/day) for 12 weeks led to an improvement in MMSE score (+1.5 ± 1.3) not seen with selenium supplementation alone [20]. The combination was also associated with reductions in oxidative stress markers and improvement on metabolic markers.
Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Antioxidant capacity: SELENOPROTEINS ACT AS ANTIOXIDANTS

The primary mechanism by which selenium is thought to exert neuroprotection is through its role in antioxidant enzymes. Selenium plays a role in catalyzing redox reactions through its position at the active site of these enzymes as part of the amino acid selenocysteine [1]. The best characterized of these are the glutathione peroxidases and the thioredoxin reductases. Limited selenium levels restrict the levels of selenoproteins that can be made. As a result, chronic selenium deficiency may also lead to insufficient levels of antioxidant enzymes, which increases the susceptibility to oxidative stress damage. The functions of all of the selenoproteins have not yet been determined, thus there may be additional mechanisms by which the selenoproteins confer neuroprotection.

Parkinson’s disease: EVIDENCE FOR SELENIUM DYSREGULATION

A meta-analysis of case-control studies (n=588 cases, 721 controls) found that CSF levels of selenium were elevated by 51.6% in Parkinson’s disease (PD) cases (Weighted mean difference [WMD] 5.49, 95% CI 2.82 to 8.15; based on 3 studies), but serum levels were not significantly different from controls [21]. High levels of exposure to the inorganic hexavalent form of selenium have also been associated with excess PD mortality. Although the many organic selenoproteins have antioxidant functions, some inorganic forms of selenium have pro-oxidant capacity, and may exacerbate oxidative stress. Dopaminergic neurons may be especially vulnerable to inorganic selenium-induced oxidative stress. A speciation analysis (n=75 cases, 68 controls) found that PD cases showed a higher ratio of human serum albumin-bound selenium to selenomethionine in the CSF [22]. The high level of serum albumin-bound selenium is suggestive of blood-brain-barrier (BBB) dysfunction, while the lower levels of selenomethionine suggest that there is less incorporation of selenium into selenoproteins within the body, which may lead to a compromised response toward oxidative stress. Potentially neurotoxic inorganic forms were largely under the limit of detection in this study, but this does not address the potential accumulation of the inorganic forms within the brain tissue itself.

APOE4 interactions: There is evidence indicating that ApoE4 carriers have lower selenium levels [17]. In temporal cortex brain tissue, ApoE4 carriers had the lowest total selenium levels as well as the lowest levels in the membrane fraction, where it is typically found in highest abundance [8]. This suggests that selenium was not effectively being incorporated into membrane-bound selenoproteins in ApoE4 carriers. Observational biomarker studies indicate a dysregulation of selenium in the AD brain, and the presence of the E4 allele may contribute to this dysregulation. The ApoER2 receptor is responsible for
the uptake of selenium into neurons [23]. Selenoprotein P serves as a carrier, and interactions between selenoprotein P and ApoER2 facilitate the uptake of selenium across the BBB. These interactions are critical for allowing the preservation of brain selenium levels in the context of selenium deficiency. Dysregulation or loss of either of these components prevents selenium uptake at required levels, resulting in a neurodegeneration phenotype in mice. Overall, this suggests that the brains of ApoE4 carriers may be more sensitive to the negative effects of mild to moderate selenium deficiency, which may contribute to the acceleration of neurodegenerative processes. It is unclear whether E4 carriers would benefit from supplementation above nutritionally recommended levels.

**Aging and related health concerns:** Maintenance of selenium levels within the range to maximally activate antioxidant selenoproteins is associated with reduced mortality and age-related disease risk, but further supplementation doesn’t add further benefit.

**Types of evidence:**
- 7 meta-analyses on cancer risk in relation to selenium levels or supplementation
- 3 meta-analyses on cardiovascular disease risk in relation to selenium
- 2 meta-analyses or systematic reviews of studies assessing selenium with mortality risk
- 2 meta-analyses or systematic reviews on selenium supplementation for diabetes
- 1 meta-analysis on diabetes risk in relation to selenium
- 1 systematic review of studies assessing effect of selenium on athletic performance
- 2 observational studies on relationship between selenium and diabetes risk
- 2 observational studies assessing relationship between selenium and longevity
- 2 observational studies assessing relationship between selenium and frailty measures
- Numerous laboratory studies

**Longevity and mortality:** HIGHER PHYSIOLOGICAL RANGE SELENIUM LEVELS ASSOCIATED WITH LOWER RISK OF MORTALITY AND INCREASED HEALTHSPAN

Observational biomarker studies consistently find that selenium levels decrease with age, and higher selenium levels are associated with a longer lifespan and lower risk of mortality. In a meta-analysis of 12 observational studies (n= 25,667), each standard deviation increase in selenium significantly reduced all-cause mortality risk by 20% [24]. Although higher selenium levels were associated with reduced risk of all-cause mortality (RR 1.36, 95% CI 1.18 to 1.58), very high levels (> 150 μg/L) may also be associated with increased mortality risk, suggesting that having blood levels around 90 μg/L, the level needed to
get full activation of selenium-containing antioxidant enzymes, is optimal for health. In Hezhou, a region of China known for its high percentage of centenarians, the mean level of selenium in hair (444.31 ng/g) was near the highest levels seen throughout China (250–500 ng/g) \[25\]. In a prospective cohort study (iISIRENTE) of community dwelling older adults in Italy (n=347), higher serum levels of selenium (>105.3 μg/L) were associated with reduced risk of mortality (HR 0.71, 95% CI 0.54 to 0.92) after adjusting for confounders \[26\]. A meta-analysis of RCTs found that the combination of selenium with other antioxidants was associated with a decreased risk for all-cause mortality (RR: 0.90, 95% CI 0.82 to 0.98) \[27\]. There was no significant effect of selenium supplementation itself, and in the absence of selenium, supplementation with other antioxidants was associated with an increased risk for all-cause mortality, but only in countries with low soil selenium content. This suggests that adequate selenium levels, whether through diet or supplementation, are needed to get benefit from antioxidant supplementation, likely due to the critical role of selenium in endogenous antioxidant enzymes.

The evidence is weak regarding whether selenium is beneficial for the prevention of frailty. In a meta-analysis of the NHANES (n=1,733) and Seniors-ENRICA-2 (n=4,289) studies, each log2 increase in whole blood selenium was associated with reduced odds for weakness (OR 0.54, 95% CI 0.32 to 0.76), impaired lower-extremity performance (OR 0.59, 95% CI 0.34 to 0.83), mobility limitations (OR 0.48, 95% CI 0.31 to 0.68), agility limitations (OR 0.71, 95% CI 0.45 to 0.97), and disability (OR 0.34 95% CI 0.12 to 0.56) \[28\]. In the Newcastle 85+ Study, a longitudinal cohort of elderly adults over age 85 (n=791), individuals with selenium intake levels classified as low had 2.80 kg lower handgrip strength and were 2.30 seconds slower performing the timed-up-and-go test \[29\]. These effects are likely not due to low selenium, but due to the lower overall macronutrient intake, particularly protein, in this group. Similarly, a systematic review of six studies found that selenium supplementation (180–240 μg/day) did not have significant effects on athletic performance or exercise training-induced adaptations \[30\]. It may prevent selenium deficiencies, which could impact exercise-related oxidative stress and mitochondrial function, in the context of high-volume training. Overall, adequate selenium levels appear to play a role in optimal function of the musculoskeletal system, likely through the mitigation of oxidative stress damage, but in the absence of nutritional deficiencies, selenium supplementation may have limited value.

There is conflicting preclinical evidence regarding whether low or high selenium levels are associated with increased lifespan in different models. In yeast, selenium supplementation extends lifespan \[31\]. In humanized telomere mice, selenium deficiency appears to have opposing effects on healthspan and lifespan \[3\]. The increased lifespan is thought to stem from stress-response hormesis. The selenoproteins are made to different degrees in the context of selenium deficiency in accordance with a hierarchy, such that levels of low-hierarchy selenoproteins will be reduced to ensure adequate levels of
high-hierarchy selenoproteins when selenium levels are limiting [3]. In the context of a moderately selenium deficient diet, decreased levels of some low-hierarchy selenoproteins with antioxidant functions may lead to a modest increase in oxidative stress which has the protective hormesis effect [3]. Additionally, when selenoprotein expression is saturated, excess selenomethionine can nonspecifically replace methionine in other proteins, which may not be optimal for the function of those proteins. However, selenoproteins also have important roles in genome maintenance, such that whether low selenium can increase lifespan may be context dependent. Selenoproteins play a protective role against replicative senescence, such that selenium deficiency results in accelerated senescence entry in cultured fibroblasts [32]. Notably, while these mice show increased lifespan, they show a marked deterioration in healthspan with age, suggesting the potential importance of these low-hierarchy selenoproteins for the maintenance of healthspan [3]. Wild type (C57bl/6j) mice receiving a selenium supplemented diet showed evidence of an increased healthspan, resembling the effects seen with a methionine-restricted diet [31]. These mice were protected against high-fat diet induced obesity, which was accompanied by a reduction in plasma insulin-like growth factor-1 (IGF-1), without affecting levels of growth hormone. Metabolic profiling of wild type mice on a selenium deficient diet revealed significant effects on free fatty acids, bile acids, and lipid mediators in the liver, with a lesser effect on the brain [33]. The regulation of redox homeostasis and methionine metabolism were among the most highly affected pathways. Similarly, naturally aged (55-week-old) male mice fed a selenium-rich diet that was within recommended dietary levels, had increased liver antioxidant capacity [34].

Overall, the evidence that the maintenance of adequate levels of selenium throughout life is associated with a prolonged healthspan is compelling, and there is no human evidence to support the mouse studies suggesting that selenium deficiency increases lifespan.

**Cancer: NO BENEFIT FOR SELENIUM SUPPLEMENTATION UNLESS DEFICIENT**

The utility of selenium supplementation has been most extensively studied in the context of cancer. The totality of evidence suggests that selenium supplementation is unlikely to reduce cancer risk in individuals who obtain adequate levels of selenium from the diet. Since observational studies tend to show an increased incidence of cancer in populations with lower selenium levels, any protective value in supplementation would stem from avoiding a selenium deficiency. Genetic polymorphisms in selenoprotein genes have also been associated with differential risk for some cancers, such as prostate cancer [35]. The risk related to low selenium varies with cancer type. Additionally, studies indicating reduced selenium levels in cancer patients suggests that cancer-related processes may affect selenium levels.
A Cochrane systematic review of 83 studies, including 27,232 RCT participants and over 2,360,000 observational study participants, found that there was no association with selenium supplementation for cancer incidence (RR 1.01, 95% CI 0.93 to 1.10; 3 studies, 19,475 participants) or cancer mortality (RR 1.02, 95% CI 0.80 to 1.30; 1 study, 17,448 participants) in RCTs with low risk of bias, providing high-certainty evidence [36]. Meanwhile, the analysis of observational studies showed an association for higher selenium exposure with lower cancer incidence (OR 0.72, 95% CI 0.55 to 0.93; 7 studies, 76,239 participants) and lower cancer mortality (OR 0.76, 95% CI 0.59 to 0.97; 7 studies, 183,863 participants), with the effect being stronger in men. A meta-analysis of 37 population-based prospective studies found that selenium intake at the recommended level of 55 ug/day was associated with decreased cancer risk (RR 0.94, 95% CI 0.90 to 0.98) [37].

**Prostate Cancer:** A meta-analysis of 38 studies found that overall selenium levels were inversely associated with prostate cancer risk (RR 0.86, 95% CI 0.78 to 0.94), but the effect was driven by case-control studies, as the association was not significant in the cohort or RCT subgroups [38]. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was a major study testing the ability of selenium to protect against prostate cancer. The study was ultimately terminated early for futility. No effect on prostate cancer incidence was seen with selenium supplementation (HR 1.03, 95% CI 0.90 to 1.18) or selenium in combination with vitamin E (HR 1.05, 95% CI 0.91 to 1.20) [39]. A similar lack of benefit was seen in most other trials such that a meta-analysis of five RCTs (n=19,869) found no association between selenium supplementation and prostate cancer risk (RR 0.91, 95% CI 0.75 to 1.12) [36].

**Breast Cancer:** A meta-analysis of 18 case-control studies (n=3,374 cases, 3,582 controls) found that selenium levels were reduced in breast cancer patients relative to controls (−0.53 μg/l, 95%CI −0.72 to −0.34) [40]. However, a pooled analysis of three RCTs (n=2,260) found that there was no significant association between selenium supplementation and breast cancer risk (1.44, 95% CI 0.96 to 2.17) [36].

**Hepatocellular carcinoma:** A meta-analysis of 13 studies found that selenium levels were inversely associated with the risk of hepatocellular carcinoma (SMD -1.02, 95% CI -1.34 to -0.70), with the strongest associations seen in geographical regions with low selenium [41].

**Cervical cancer:** In a meta-analysis of five case-control studies (n=353 cases, 853 controls), serum selenium levels were significantly lower in cervical cancer patients (OR 0.55, 95% CI 0.42 to 0.73) [42]. The levels decreased with stage of disease, and selenium levels significantly increased with treatment (SMD 2.59, 95% CI 0.50 to 4.69). This suggests that the decrease in selenium seen in many cancer
patients may be related to cancer-related biological processes rather than serving as a causal risk factor, per se.

**Non-melanoma skin cancer:** The Nutritional Prevention of Cancer Trial (NPCT) (n=1,250) primarily assessed whether selenium had a protective effect against non-melanoma skin cancer. Contrary to expectation, selenium supplementation was associated with increased risk for non-melanoma skin cancer in this study (adjusted HR 1.17, 95% CI 1.02 to 1.34) \[36\]. Other trials showed similar trends, but with greater variability, such that a pooled analysis of four RCTs (n=3461) indicated a statistically unstable increased risk (RR 1.23, 95% CI 0.73 to 2.08) \[43\].

**Lung cancer:** A meta-analysis of two studies (n=19,009) with a low risk of bias found that selenium supplementation had no significant effect on lung cancer risk (RR 1.16, 95% CI 0.89 to 1.50). Similarly, high-certainty evidence from one RCT with 17,448 participants found that selenium supplementation had no significant effect on lung cancer incidence (RR 1.11, 95% CI 0.80 to 1.54) or lung cancer mortality (RR 1.09, 95% CI 0.72 to 1.66) \[44\].

**Cardiovascular disease:** HIGHER SELENIUM ASSOCIATED WITH REDUCED CARDIOVASCULAR MORTALITY

Higher circulating levels of selenium within the normal range have generally been associated with decreased incidence of cardiovascular diseases and mortality. A meta-analysis of 12 observational studies found an inverse association between circulating selenium levels, particularly in whole blood, with stroke (RR 0.48, 95% CI 0.24 to 0.94) \[45\]. In a meta-analysis of 13 studies, a high level of selenium within the physiological range was associated with a reduced risk of cardiovascular disease incidence (RR 0.66, 95% CI 0.40 to 1.09) and mortality (RR 0.69, 95% CI 0.57 to 0.84) relative to low selenium status \[46\]. Each 10 µg increase in blood selenium levels was associated with a 15% decrease in cardiovascular disease incidence (RR 0.85, 95% CI 0.76 to 0.94). Similarly, a meta-analysis of 12 observational studies found that relative to participants with the highest circulating selenium levels, those with the lowest had higher risk for cardiovascular mortality (RR 1.35, 95% CI 1.13 to 1.62), though the effect on coronary mortality was not significant (RR 1.43, 95% CI 0.93 to 2.19) \[46\]. A meta-analysis of 43 RCTs testing antioxidants found that the use of selenium or other antioxidants alone did not significantly impact mortality, but the combination of the selenium with other antioxidants was associated with a reduced risk for cardiovascular mortality (RR 0.77, 95% CI 0.62 to 0.97) \[27\]. Based on regional analyses, the protective effect of selenium supplementation appears to stem from the prevention of selenium deficiencies in regions where soil selenium levels are lower, such that residents of those regions are at higher risk for obtaining adequate selenium levels through diet alone.
**Diabetes: HIGH SELENIUM IS ASSOCIATED WITH INSULIN RESISTANCE**

Several studies have found evidence to suggest that elevated selenium may be associated with increased risk for type 2 diabetes, which suggests that supplementation is not recommended in those with adequate dietary intake of selenium with risk factors for diabetes. A meta-analysis of 34 studies assessing the relationship between environmental selenium exposure and diabetes risk found that relative to individuals with the reference blood selenium levels of 90 μg/L, which corresponds to a daily selenium intake of approximately 60 μg, blood selenium levels of 120 μg/L and 160 μg/L were associated with increased diabetes risk, with risk ratios of 1.27 (95% CI 1.10 to 1.47) and 1.96 (95% CI 1.27 to 3.03), respectively [43]. Case-control studies suggest that there is a U-shaped dose-response-related risk, with increased risk both when selenium levels are less than 60 μg/L and greater than 100 μg/L. In the NHANES study (n=4,339), selenium was positively associated with insulin, glucose and the homeostatic model for insulin resistance (HOMA-IR) [47]. There was an association of a 1.5% (95% CI 0.4 to 2.6%) increase in insulin and 1.7% (95% CI 0.5 to 2.9%) increase in HOMA-IR with each 10 μg/L increase in blood selenium levels. Although there was no evidence of an increase in diabetes prevalence with higher selenium levels (1.00, 95% CI 1.00 to 1.01). Gene association studies provide additional evidence for a causal link between high selenium levels and altered glycemic indices. Several single nucleotide polymorphisms (SNPs) have been shown to affect selenium levels and selenoprotein expression, and a study including 9,639 individuals of European ancestry found that those with genetically higher selenium had elevated insulin and glycated hemoglobin (HbA1c) [48]. Each standard deviation increase in selenium was associated with an 0.023 mmol/L (95% CI 0.001 to 0.045) increase of insulin and a 0.013 mmol/L (95% CI 0.003 to 0.023) increase of HbA1c.

Additionally, there is limited evidence regarding whether selenium supplementation offers benefit to individuals with metabolic diseases. A meta-analysis of seven RCTs (n=372) found that selenium supplementation did not have a significant impact on inflammatory markers overall, but was associated with a significant decrease in high-sensitivity C-reactive protein (hs-CRP) (SMD -0.44, 95% CI -0.67 to -0.21) in subgroup analysis [49]. A systematic review of four RCTs (n=241) found no clear evidence to support the effectiveness of selenium supplementation in patients with type 2 diabetes [50]. Two studies found a significant decrease in fasting insulin levels and a slight decrease in insulin resistance (HOMA-IR), however, there were no significant effects on body weight, HbA1c, insulin sensitivity, total cholesterol, triglycerides, or low-density lipoproteins (LDL). None of the studies examined diabetes-related complications or mortality.
Safety: Selenium intake at the recommended dietary allowance is safe and associated with better health outcomes, but levels in excess of 400 mcg can lead to toxicity. Genetics may affect the body’s ability to effectively utilize selenium.

Types of evidence:
- 13 meta-analyses or systematic reviews on selenium and disease risk
- 1 systematic review of RCTs for selenium supplementation and cancer
- 3 clinical trials selenium supplementation in elderly
- 3 gene association studies
- 2 reviews on selenium dietary sources

Selenium is an essential trace mineral, and intake through diet or supplements within the recommended nutritional range is generally not associated with adverse health risks [1]. However, selenium may become toxic when levels exceed the maximum tolerated level of 400 mcg per day. Selenium-induced toxicity, called selenosis, can lead to fatigue, hair loss, nail damage, nausea, muscle weakness, dizziness, burning or tingling feeling, and heart problems (Drugs.com). The effects are often reversible if selenium exposure is reduced. There is some evidence that high selenium levels may negatively impact glycemic indices [47], thus selenium supplementation may not be recommended in those at risk for diabetes and/or with a genetic makeup that induces higher than average levels of selenoproteins.

A clinical trial testing supranutritional levels of selenium (sodium selenate 10 mg/3X daily) found that this level of selenium supplementation was well tolerated, and adverse events were mild. The most common treatment-emergent adverse events were fatigue, headache, lethargy, nausea, muscle spasms, and dizziness [13]. A systematic review of RCTs testing selenium supplementation for cancer prevention indicated that selenium overexposure was associated with increases risks for diabetes, hair loss, dermatitis, nail damage, and bad breath [36].

Genetic background is likely to play an important role in determining which individuals will preferentially benefit or be harmed by selenium supplementation or a selenium-enriched diet. A gene association study of 9,639 individuals of European descent showed associations between basal selenium levels and seven SNPs (rs921943, rs567754, rs3797535, rs11951068, rs705415, rs6586282, and rs1789953) [48]. A genome wide association study including 428 participants of the Selenium and Celecoxib Trial, who received 200 ug of selenized yeast per day for one year found several SNPs that were associated with changes in plasma selenium levels following supplementation [51]. rs11960388 and rs6887869, which are located in the dimethylglycine dehydrogenase (DMGDH)/betaine-homocysteine S-methyltransferase (BHMT) region were associated with higher basal selenium levels as well as greater increases in
selenium after supplementation. rs56856693, which is located upstream of the NEK6, also showed a nominal association with supplementation-related selenium changes. However, examining changes to overall selenium levels may not be particularly informative of whether the selenium supplementation is having a biological effect, as organic forms, such as selenomethionine can nonspecifically incorporate into proteins without necessarily impacting the function of biologically active selenoproteins [1]. In an open-label study of 32 statin-using patients treated with one unit of selenium-rich Brazil nuts per day for three months, SNPs in selenoprotein P (SENELOP) influenced the ability of the intervention to alter erythrocyte glutathione peroxidase (GPx) activity, creatine kinase activity, triacylglycerol level, and LDL level [52]. GPx1 expression was increased in those with the rs1050450 CC genotype. Those with the rs7579 GG genotype had reduced levels of SELENOP both before and after Brazil nut (selenium) supplementation.

**Drug interactions:** According to Drugs.com, there are 28 known drug interactions with selenium. This includes chemotherapy drugs, drugs for heavy-metal poisoning/metal ion chelation, and quinolone antibiotics.

**Sources and dosing:**

Selenium is primarily obtained through the diet. Due to similar chemical properties between sulfur and selenium, selenium-containing amino acids contain the backbone of the sulfur containing amino acids, cysteine and methionine, to instead create selenocysteine and selenomethionine [53]. Therefore, selenium contents tend to be higher in protein-rich foods such as meat, chicken, fish, eggs, and cereals. Fruits and vegetables generally have very low selenium levels. Although fish/shellfish tend to have some of the highest levels of selenium, much of it is mixed up with heavy metals, such that it is in an insoluble inorganic form which has low bioavailability [1]. Globally, the primary dietary sources of selenium are cereals and legumes. However, the selenium content in these crops, such as wheat, is highly dependent on the selenium content of the soil, which varies regionally [53]. The cereals grown in North America are generally grown in relatively selenium-rich soil, thus direct consumption of these grains along with the animal products from livestock fed crops grown in this soil is generally associated with dietary selenium sufficiency. Due to the lower selenium content in the soil of other areas, such as some parts of Europe and Asia, crops grown and animals raised in these regions may contain significantly lower selenium levels, which could lead to a state of chronic selenium insufficiency in some individuals or populations. Only under conditions where adequate selenium levels cannot be obtained through diet, or in the context of certain conditions which deplete selenium, is selenium supplementation through non-dietary means recommended. Selenium can be taken in organic or inorganic forms, and there is a lack of consensus over whether there is an optimal form for supplementation. The organic form,
selenomethionine, is more readily absorbed and bioavailable in the sense that a rise in selenium levels is more readily detectable after selenomethionine supplementation [1]. However, selenomethionine itself will simply be nonspecifically incorporated into proteins, such as albumin, in place of methionine. Extensive metabolism is required to convert it to selenocysteine, which is the form that is used in redox enzymes. Inorganic forms, such as selenite, are less bioavailable, but more readily converted to selenocysteine. It is unclear whether there is greater risk for potential toxicity with use of inorganic forms, which are known to exhibit toxicity at high levels, or from excess nonspecific incorporation and retention of selenomethionine in proteins.

Due in part to the high selenium content where they are grown, Brazil nuts have the highest selenium content of any food (3800 µg/kg). At 70-90 mcg, a single Brazil nut contains greater than the recommended dietary intake of selenium, thus they should be eaten in moderation (NIH). According to the WHO, the recommended dietary allowance for selenium is 55 mcg per day for adults, with slightly higher levels (60-70 mcg) for women who are pregnant or lactating, and lower levels (15- 40 mcg) for children (NIH). The maximum daily limit for adults is 400 mcg per day, above which there is an increased risk for selenium-induced toxicity.

**Research underway:**

There are currently 78 active trials testing selenium as an intervention and/or using it as a biomarker readout on Clinicaltrials.gov. It is being tested in a variety of conditions including cancer, prevention of chemotherapy-related adverse effects, thyroid disease, covid-19, and fertility. A variety of different forms of selenium are being tested: organic forms, inorganic forms, as supplements, through dietary intervention, and in combination with other interventions.

**Search terms:**

Pubmed, Google: Selenium

- Alzheimer’s disease, Parkinson’s disease, neurodegeneration, aging, lifespan, healthspan, cancer, cardiovascular, diabetes, clinical trials, meta-analysis, systematic review, safety

**Websites visited for Selenium:**

- Clinicaltrials.gov
- Examine.com
- DrugAge
References:


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*If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF’s Aging and Alzheimer’s Prevention Program, please contact [INFO@alzdiscovery.org](mailto:INFO@alzdiscovery.org). To view our official ratings, visit [Cognitive Vitality’s Rating page](#).*