Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

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 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 330 to 400 mcg can lead to toxicity. Genetics may affect the body's ability to effectively utilize selenium.

Availability: From food and OTC in supplements	**Dose**: Recommended dietary allowance for adults 55 mcg/day Maximum allowance 255 to 400 mcg/ day	**Chemical formula:** Se **MW**: 78.97 g/mol
Half-life: Varies with formulation	**BBB**: Penetrant	
Clinical trials: Large prevention clinical trials (n=1000s) have failed to show that selenium supplementation prevents cancer or dementia. Instead, there is evidence for a possible increased risk for diabetes.	**Observational studies**: Reduced selenium levels have been associated with increased risk for mortality, cardiovascular disease, cancer, and neurodegenerative disease in observational studies involving thousands of people.	

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 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 association may be confounded by the impact of malnutrition and disease-etiology related changes in selenium regulation.

Types of evidence:

- 5 meta-analyses or systematic reviews studies assessing selenium biomarkers in AD
- 1 meta-analysis of studies assessing selenium supplementation in AD
- 2 meta-analyses of case-controls studies of selenium biomarkers in PD
- 1 meta-analysis of studies assessing selenium biomarkers in ALS
- 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
- 1 clinical trial of selenium nanoparticles in MS
- 8 observational studies of selenium biomarkers in AD
- 3 observational studies on selenium nutritional intake and cognition
- 2 observational studies on selenium biomarkers in ALS
- 2 observational studies of selenium levels in HD
- 1 Mendelian randomization study of selenium 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). The overall incidence of selenium deficiency was quite low in this US nutritional survey. Another study including 1,681 NHANES participants ≥ 65 years old found that the association between selenium intake and CERAD scores was driven by an association between energy intake and cognition, such that those with insufficient selenium intake also had low energy consumption [7].

In contrast to the relationship between adequate dietary intake of selenium and cognition, evidence from a Mendelian randomization study suggests that chronically elevated levels of selenium are associated with a greater risk for AD [8]. The study used genetic associations derived from meta-analyses of genome-wide association studies (GWAS) based on populations with European ancestry to assess the link between eight antioxidants with cognitive function and AD. Higher genetically determined selenium levels were found to be associated with a 5% higher risk of AD (OR 1.047, 95% CI 1.005 to 1.091). This suggests that similar to other metals and trace elements, there is an optimal range of exposure for health, with the potential for toxicity at chronically high levels. This type of study assesses lifelong exposure, and thus it is not clear if there is a particular period of the lifespan in which high selenium levels would be most problematic for brain heath. Additionally, it affirms that metabolic processing of selenium in the body is influenced by genetics, such that individuals may respond to selenium exposure differently depending on their genetic makeup.

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) [9]. 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 [10]. 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 [11]. 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 [12]. The levels of selenium were correlated with levels of the selenoprotein, glutathione peroxidase (GPx), suggesting that selenium availability influences antioxidant capacity, at least peripherally. Heterogeneity across studies has been observed in other meta-analyses. A meta-analysis of population-based studies examining the link between 39 trace elements with AD including 15 studies with 588 AD patients and 558 controls found that there was no overall association between circulating (serum, plasma, and whole blood) selenium levels and AD, but decreased levels were observed when restricted to plasma (SMD −0.61, 95% CI −0.97 to −0.25) [13]. A separate meta-analysis assessing the association between selenium levels and five neurodegenerative diseases including 2,377 AD patients found selenium levels were lower in AD patients, but the finding was only significant for erythrocyte levels (SMD −1.54, 95% CI −2.97 to −0.12), with no significant association in plasma, serum, blood or CSF [14]. In a comparative study (n=40), plasma selenium levels were lower in individuals with AD (76.07±18.45 µg/L) and 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 MMSE [15]. 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 [16]. 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).

A prospective case-control study including 54 patients with MCI, 36 of whom progressed to dementia, found that higher serum concentrations of selenoprotein P were associated with increased risk of

progression to dementia at levels above their reference point, 10,999 and 6952 ng/mL, on the AA3 and BD1 assays, respectively [17]. The association was stronger for non-AD forms of dementia, such as frontotemporal dementia and Lewy body dementia. It is unclear if the increase is biologically meaningful or related to a compensatory response to disease-related oxidative stress.
An observational study including 469 adults over the age of 60 in China assessed the relationship between blood selenium levels with AD biomarkers. There was an inverse association between selenium and serum Aβ42 and Aβ40, along with an inverse association between selenium with the Aβ42/40 ratio, such that higher selenium levels were associated with lower Aβ, which is suggestive of a protective effect. There was also a positive association between the selenium-containing antioxidant enzyme GPX with Aβ levels, which could be a compensatory response to Aβ-related oxidative stress [18].
Overall, circulating levels of selenium appear to be generally lower in AD patients, but it is unclear whether this relates to changes in dietary habits, altered metabolism, compensatory responses, disease etiology, or a combination of factors.

CSF: SELENENIUM 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 CSF selenium levels [19]. This likely stems from 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 [12].
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 [20]. 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 [21]. Elevated CSF levels of the inorganic selenium form, selenate (Se(VI)), was associated with AD risk (adjusted 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 [22]. 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 [23]. 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 [24]. The study was scheduled to run for ten years and was terminated early after six years. 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. A meta-analysis of six studies assessing the impact of selenium supplementation in patients with MCI and AD found that while supplementation led to increases in selenium levels and GPX activity, it was also associated with increased levels of the oxidative stress marker, malondialdehyde (MDA) [25]. Trends toward improvements were observed on some cognitive tests, but the effects were generally not clinically meaningful. 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 [19]. 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 [26]. 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 [27]. 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.
Several preclinical studies have been conducted showing that selenoproteins confer neuroprotection in the context of AD models, though it is not clear the degree to which these selenoproteins are affected or contribute to pathology in AD patients.
Brain levels of selenoprotein W (SELENOW) are the last to be affected in the context of selenium deficiency, suggesting that it plays an important role in the brain [28]. Low levels of SELENOW were shown to be associated with tau pathology, such that overexpression of SELENOW in the hippocampus mitigated tau pathology and cognitive deficits in the 3xTg mouse model [28]. SELENOW competes with Hsp70 for tau binding, such that the interaction between SELENOW and tau promotes tau clearance through the ubiquitin-proteosome pathway.
Selenoprotein K (SELENOK) may help maintain microglial homeostasis and influence the phagocytosis of Aβ [29]. In cell culture, SELENOK was shown to promote CD36 palmitoylation, influencing the localization of this scavenger receptor to the plasma membrane, which affects the capacity of microglia

to phagocytose Aβ. Loss of SELENOK exacerbated deficits in the 5XFAD model, while supplementation with selenium (i.p.) increased levels of SELENOK and enhanced microglial uptake of Aβ in this model.

Selenium nanoparticles: To circumvent potential toxicity issues with systemic administration of inorganic or organic forms of selenium, efforts are underway to develop and test selenium nanoparticles [30]. The tissue localization, clearance rate, and biological activities of the nanoparticles can be modulated based on the size and composition of the nanoparticles. Modulation of these parameters can determine whether the particles have the capacity to enter the CNS. To date they have generally been tested in preclinical models, and further work is needed to optimize the particles for potential clinical use.

Parkinson's disease: EVIDENCE FOR SELENIUM DYSREGULATION
A meta-analysis of case-control studies (n=588 cases, 721controls) 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 [31]. Similarly, a meta-analysis of 12 studies including 597 PD cases and 733 controls found a significant increase in selenium levels in PD patients only in CSF (SMD 1.21, 95% CI 0.04 to 2.39) and not in serum or blood [32]. High levels of exposure to the inorganic hexavalent form of selenium have also been associated with excess PD mortality. Although 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 [33]. The high level of serum albumin-bound selenium is suggestive of blood-brain-barrier 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.

Amyotrophic lateral sclerosis: EXPOSURE TO HIGH LEVELS OF METALS, INCLUDING INORGANIC SELENIUM, MAY INCREASE RISK
Toxicity with various metals has been associated with increased risk for ALS.
A meta-analysis assessing the relationship between concentrations of 23 different metals in CSF, blood, serum, plasma, hair, and nails found that selenium levels in serum/plasma were significantly elevated in

ALS patients (n=206) by 4.26 µg/L (95% CI 0.73 to 7.79, based on 4 studies), relative to controls (n=115) [34]. CSF levels of lead were also elevated in ALS patients, along with trends toward higher levels of aluminum, manganese, and lead in serum/plasma and higher levels of copper, magnesium, manganese, and iron in CSF. Consistent with these findings, a case-control study including 454 ALS and 294 control participants, found that elevated levels of the metals copper, selenium, and zinc were associated with higher ALS risk and worse survival [35].
The prevalence of ALS was found to be elevated in a region of Northern Italy that had high levels of inorganic hexavalent selenium in their drinking water from 1974 to 1985, relative to those in an unexposed cohort (14 vs. 5 cases per 100,000 person-years) [36]. The incidence rate ratio for ALS was higher in the ten years (1986-1994) following the exposure (8.2, 95% CI 2.7 to 24.7) than in the following decade (1995-2015) (1.5, 95% CI 0.5 to 4.7). Selenium neurotoxicity may stem from oxidative damage due to the depletion of glutathione reserves because the selenium species need to be reduced so they can merge into selenoproteins [34].

A Mendelian randomization study using ALS and selenium associated variants derived from GWAS using European populations found that there was no evidence to support a causal role for genetically related selenium levels with the development of ALS (OR 1.02, 95% CI 0.96 to 1.08) [37]. This further supports the notion that toxicity stemming from environmental exposure to toxic forms of selenium may be relevant for ALS risk, as opposed to a dysregulation of selenium biology.

Huntington's disease: EVIDENCE FOR SELENIUM DYSREGULATION
Levels of several potentially toxic metals were found to be increased in the blood of HD patients, including iron, chromium, selenium, zinc, and arsenic [38]. Relative to controls (101±16 µg/L), selenium levels were increased by nearly 40% in HD patients (138±12 µg/L).
A case-control study including nine genetically confirmed HD cases, and nine controls examined the concentrations of eight essential metals across 11 brain regions, and found that selenium levels were decreased in all examined regions, though decreases were most pronounced in the putamen and entorhinal cortex [39]. Selenium levels were also found to be reduced in several brain regions, including the putamen, in postmortem brain tissue from HD patients, in a separate study.
A similar pattern has been observed in the N171-82Q HD mouse model with an increase in plasma selenium levels, but decrease in the brain [40]. Supplementation with sodium selenite (0.25 or 1.00 ppm in the drinking water) starting at six weeks of age enhanced the expression of selenoproteins in the brain without further elevating plasma levels, but did not increase survival.

Multiple Sclerosis: LINK WITH SELENIUM IS UNCLEAR

Some studies have indicated that low selenium levels may contribute to pathology in MS, however, the evidence to date is inconclusive. A meta-analysis of 32 studies including 1,567 MS cases and 1,328 controls examining the relationship between trace element concentrations in the blood and MS status found there was no significant difference in selenium levels (WMD − 0.19 mcg/dL, 95% CI − 1.69 to 1.31, based on eight studies), though there was considerable heterogeneity across the studies [41]. The declines in selenium seen in some cases may be related to inflammatory status. Based on the notion that selenium could be neuroprotective, a meta-analysis of nine studies including 2381 participants, found that over 10% of MS patients used selenium supplements, despite the lack of clinical evidence for benefit [42].

A clinical trial testing crocin-selenium nanoparticles (Cor@SeNs) capsules, containing 5.74 mg crocin and 55 mcg selenium in 51 MS patients for 12 weeks, had mixed results on biomarkers of oxidative stress. Treatment with the nanoparticles resulted in an increase in serum total antioxidant capacity (TAC), but had no significant effects on the oxidative stress marker MDA, or on cognitive test performance, relative to placebo [43].

APOE4 interactions: There is evidence indicating that ApoE4 carriers have lower selenium levels [23]. 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 [10]. 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 [44]. 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
- 3 meta-analyses of trials testing selenium in cardiac surgery patients
- 2 meta-analyses or systematic reviews of studies assessing selenium with mortality risk
- 2 meta-analyses or systematic reviews on selenium supplementation for diabetes
- 4 meta-analyses of studies assessing selenium on glycemic parameters
- 3 meta-analyses of studies assessing selenium on inflammatory markers
- 1 meta-analyses on diabetes risk in relation to selenium
- 1 meta-analysis of studies assessing relationship between selenium and osteoporosis
- 1 systematic review of studies assessing effect of selenium on athletic performance
- 2 clinical trials testing selenium for measures of bone health
- 1 clinical trial of selenium and CoQ10 supplementation on health outcomes
- 1 clinical trial assessing selenium on immune function
- 1 clinical trial testing selenium for migraine
- 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
- 1 Mendelian randomization study of selenium and ischemic stroke
- 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% [45]. 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) [46]. In a prospective cohort study (ilSIRENTE) 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 [47]. 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) [48]. 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 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=1733) and Seniors-ENRICA-2 (n=4289) 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 for disability (OR 0.34 95% CI 0.12 to 0.56) [49]. 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 [50]. 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 ug/day) did not have significant effects on athletic performance or exercise training-induced adaptations [51]. 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 [52]. 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 [53]. 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 [52]. These mice were protected against high-fat diet induced obesity, which was accompanied by a reduction in plasma 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 [54]. 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 [55].

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.

Selenoprotein P is an important selenoprotein involved in selenium transport. It is often used as a biomarker of selenium status. An RCT (NCT01443780) tested the impact of a combined intervention of selenium yeast (200 µg/day) and coenzyme Q10 (200 mg/day) for four years in a cohort of 403 elderly individuals with low selenium levels living in a rural region of Sweden [56]. A sub-analysis of the study assessed the relationship between selenoproteins and mortality. Baseline serum selenium levels were 67 µg/L, which is below the level required for adequate levels of the selenoproteins GPX and selenoprotein P, which are saturated at serum selenium levels of 99 µg/L and 146 µg/L (95 % CI 140 to 171 µg/L), respectively. Selenoprotein P reached concentrations of 6.4 mg/L at the saturable level, and adverse health outcomes were more apparent in those with levels below the median of 4 mg/L. Low levels of selenoprotein P were associated with shorter leukocyte telomere length and higher levels of the inflammatory marker CRP. Those in the lowest quartiles of selenoprotein P also had higher risks of all-cause mortality and cardiovascular mortality (HR 1.79). Supplementation resulted in increases in

levels of selenoprotein P and mitigated differences in 10-year mortality between those with high and low levels of selenoprotein P at baseline. A 10-year follow-up sub-study of this trial found that selenium may have an effect on health outcomes through modulation of sirtuins [57]. Supplementation for four years was associated with an increase in levels of SIRT1 (from 252± 162 to 469± 436 ng/mL), while those in the placebo group experienced a decline in SIRT1 (from 269± 172 to 190± 186 ng/mL). Furthermore, those with the lowest levels of SIRT1 at baseline were more likely to experience cardiovascular-related mortality.

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 [58]. The risk related to low selenium varies with cancer type. Additionally, studies indicating reduced selenium levels in cancer patients suggest 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 [59]. 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) [60].

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 [61]. 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) [62]. 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) [59].

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) [63]. 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) [59].

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 [64].

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) [65]. 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) [59]. 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) [66].

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) [67].

Colorectal cancer: A meta-analysis of 24 studies, including 18 serum and 6 tissue studies, with a total of 2,640 participants found that levels of selenium were higher in cancerous colorectal tissue compared with matched healthy colon tissue, with an increase that was equal to 0.07 µg/g wet tissue weight (95% CI 0.06 to 0.09). In contrast, selenium levels in the pooled serum/plasma/whole blood estimate were 3.73 µg/dL (95% CI -6.85 to −0.61) lower in patients with colorectal cancer relative to controls [68].

Cardiovascular disease: HIGHER SELENIUM ASSOICATED WITH REDUCED CARDIOVASCULAR MORTALITY; NO CLEAR BENEFIT OF PERIOPERATIVE SELENIUM SUPPLEMENTATION IN THE CONTEXT OF CARDIAC SURGERY

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) [69]. 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 [70]. 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) [60]. 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) [48]. 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.

A meta-analysis of 21 studies including 1,192 cardiac surgery patients assessed alterations to serum concentrations of zinc, copper, and selenium in response to surgery. The concentrations of all of these trace elements, including selenium (WMD 0.1,95% CI 0.03 to 0.16, based on 8 studies) decreased within a day of surgery, likely related to postsurgical inflammation, and generally rebounded within a week [71].

Based on these associations, selenium supplementation has been tested in cardiac surgery patients, however, the trials to date have failed to show that it improves outcomes. Furthermore, analyses highlight that selenium supplementation may be associated with greater risk of some adverse outcomes in this population.

A meta-analysis of 7 RCTs testing perioperative selenium on postoperative complications in 2,521 patients found that there were no significant effects on rates of postoperative acute kidney injury, mortality, length of stay in the hospital and intensive care unit (ICU), troponin I, and CK-MB levels [72]. However, there were trends toward those supplemented with selenium having higher rates of acute

kidney injury (based on 4 RCTs), higher rates of mortality (based on 4 RCTs), longer ICU stays (based on 3 RCTs), and mild elevations of troponin 1 (based on 3 RCTs).
A meta-analysis of 7 RCTs including 2,276 middle-aged patients undergoing cardiac surgery found that selenium interventions had no significant effects on days spent in the ICU, mortality, or the incidence of hospital acquired infections, but did reduce the duration of hospital stay (MD -1.33; 95% CI -2.51 to -0.16) and postoperative levels of the inflammatory marker CRP (SMD -0.18; 95% CI -0.34 to -0.02) [73].

The most extensive of these studies was the SUSTAIN CSX trial (NCT02002247), which assessed the impact of high dose selenium on patient outcomes in patients undergoing cardiac surgery at high risk for organ dysfunction and death [74]. The randomized, double-blind, placebo-controlled trial was conducted at multiple sites in Germany and Canada and included 1,416 cardiac surgery patients with a median predicted 30-day mortality risk based on the European System for Cardiac Operative Risk Evaluation II score of 8.7% (interquartile range 5.6% to 14.9%). Participants were randomized to placebo or intravenous 2,000 µg/L of sodium selenite prior to cardiopulmonary bypass, 2,000 µg/L immediately postoperatively, and 1,000 µg/L during each day in intensive care for a maximum of 10 days. The trial did not meet its primary endpoint, a composite of the numbers of days alive and free from organ dysfunction during the first 30 days after cardiac surgery. Subgroup analyses indicated that selenium treatment also had no significant effect on functional recovery (n=174) as assessed by the six-minute walk distance, as well as the Short Form-36 and Barthel Index questionnaires [75]. Selenium also did not impact the duration of mechanical circulating support (tMCS) therapy, organ dysfunction, or mortality in the subset of patients (n=39) with post-cardiotomy cardiogenic shock. The median number of days on renal replacement therapy was higher in the selenium group, but this could be related to baseline differences in kidney function between the groups and/or a potential adverse effect of high-dose selenium on the kidneys [76].
A possible explanation for the lack of benefit may be related to the timing of selenium administration. The purpose of the selenium treatment was to modify the cardiac surgery–related inflammatory response to oxidative stress, however, systemic inflammatory responses reduce the expression of selenoproteins, thus selenium may need to be regularly administered several weeks prior to surgery to ensure sufficient levels of these antioxidant proteins at the time of surgery [74].

Ischemic stroke: NO CLEAR LINK WITH SELENIUM
A bidirectional Mendelian randomization study assessing the potential relationship between selenium levels and stroke identified four SNPs (rs921943, rs6859667, rs6586282, and rs1789953) that were significantly associated with selenium levels [77]. However, the analysis, using the inverse variance

weighted method, did not find evidence to support a causal effect of selenium levels on ischemic stroke (OR 0.968, 95% CI 0.914 to 1.026) generally or within any subtypes of ischemic stroke. The analysis also did not find evidence of a causal effect of ischemic stroke on selenium levels.

Inflammation: SELENIUM STATUS IMPACTS INFLAMMATORY RESPONSES

Selenoprotein-mediated regulation of cellular redox status impacts immune function and inflammatory processes [78]. Many selenoproteins, such as GPX, have antioxidant activity. Selenium levels can also influence the oxidative burst induced during the activation of immune cells, which plays a role in cellular signaling, and drives effector cell functions, such as phagocytic activity. Higher selenium levels lead to a stronger oxidative burst. Therefore, selenium can have both pro-oxidant and antioxidant effects. Additionally, chronic inflammation is associated with a reduction in circulating selenium levels through various mechanisms [78].

Selenium supplementation has been proposed and tested as a mechanism to mitigate deleterious inflammation. The studies to date suggest that it may be best suited to those with moderately elevated systemic inflammation and disease processes that may predispose one to selenium deficiency. There is no clear evidence to indicate that selenium supplementation would offer additional benefit to those with adequate selenium levels in the absence of chronic inflammation, particularly due to the potential pro-oxidant effects of supranutritional levels of selenium.

A meta-analysis of 13 studies including 1,169 participants examining the effect of selenium supplementation on CRP found that selenium was associated with a significant reduction in serum CRP levels relative to controls (WMD -0.22 mg/L, 95 % CI - 0.39 to - 0.04), with a high level of heterogeneity across studies [79]. Subgroup analysis indicated that the effects on CRP were strongest in studies longer than 70 days, including participants with baseline CRP levels ≥ 2.19 mg/L with underlying disease. A meta-analysis including 24 studies testing oral or intravenous selenium supplementation (60–2,000 µg/day) found that oral administration did not have a significant effect on CRP levels while i.v. administration was associated with a reduction in CRP (WMD -2.24; 95 % CI -4.24 to -0.24) in pooled analysis [80]. Subgroup analysis indicated that a reduction in CRP was more likely in trials using doses of 100 mcg or 200 mcg, lasting 10–12 weeks. Selenium supplementation was also associated with reductions in plasma levels of IL-6 with both routes of administration.

A meta-analysis of 8 RCTs assessing the effect of parenteral selenium (from 60 to 4,000 µg/day) on inflammatory markers found that it was associated with decreased serum levels of IL-6 (WMD -3.85 pg/mL; 95% CI -7.37 to -0.34 pg/mL, based on 3 RCTs), but not serum CRP levels (WMD 4.58 mg/L, 95% CI -6.11 to 15.27 mg/L, based on 6 RCTs) [81]. Subgroup analysis indicated that an effect on CRP was

more apparent in studies including participants with baseline CRP levels <141 mg/L, younger than age 60, and using selenium doses ≥ 600 µg/day.
A meta-analysis of nine trials assessing the impact of inorganic (doses 50 to 200 µg/day) or organic (doses 50 to 400 µg/day) selenium (ranging from 8 to 48 weeks) on immune function including 370 healthy participants found that supplementation had no significant effects on immunoglobulins, white blood cell concentrations, or cytokine levels [82]. Baseline mean plasma selenium levels were generally within the normal range (mean 103-110 µg/L), and supplementation raised them higher (range 92–228 µg/L). Increases in IgA occurred with increasing selenium levels up to 110 µg/L, at which point there was no further increase in IgA. A similar trend was observed for T cells. A dose-response relationship emerged between selenium and NK cells, in which levels of NK cells increased up to selenium concentrations of 140 µg/L, after which higher selenium levels were associated with lower levels of NK cells. These studies further support the notion that in an otherwise healthy population with adequate selenium levels, further supplementation is unlikely to enhance immune function, and at high levels may hinder it.

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 to1.47) and 1.96 (95% CI 1.27 to 3.03), respectively [66]. 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 HOMA-IR [83]. 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 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 HbA1c [84]. 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.
A meta-analysis assessing the impact of selenium supplementation on blood lipids and blood pressure found that supplementation was associated with reductions in levels of total cholesterol (WMD −2.11 mg/dL, 95 % CI −4.09 to −0.13) and VLDL-c (WMD −1.35 mg/dL, 95 % CI −2.33 to −0.37), but had no significant effects on triglycerides, LDL-c, or HDL-c [85]. However, subgroup analysis indicated that selenium was associated with an increase in LDL-c levels (WMD 2.89 mg/dL, 95 % CI 0.26 to 5.51) in individuals with baseline levels <130 mg/dL, which represents those with levels in the normal range. Additionally, selenium supplementation was associated with a modest increase in systolic blood pressure (WMD 2.02 mmHg, 95 % CI 0.50 to 3.55).

The impact on glycemic parameters appears to depend on the glycemic status of the supplemented population leading to heterogeneity on these measures in meta-analyses. Although inconsistent across individual glycemic measures and studies, there is some evidence to suggest that selenium may offer modest 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 [86]. 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 [87]. 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 LDL. None of the studies examined diabetes-related complications or mortality.
A meta-analysis of 20 trials assessing the effect of selenium supplementation (doses of 100–960 (µg/day) on glycemic control found that selenium intake was associated with reductions in fasting insulin (WMD -3.02 µIu/mL, 95% CI -5.13 to -0.90) and increased insulin sensitivity based on the quantitative insulin sensitivity check index (QUICKI) (WMD 0.01, 95% CI 0.01 to 0.02), but had no significant effects on fasting blood sugar, HbA1c, or HOMA-IR. Effects on blood sugar were most prominent in studies using doses ≤ 200 µg/day in populations with type 2 diabetes or gestational diabetes [88].
A meta-analysis of ten studies conducted in Iran including 526 participants with cardiometabolic diseases assessing the impact of selenium supplementation (for 2 to 24 weeks) on insulin resistance found that selenium supplementation was associated with a reduction in serum insulin levels (SMD −0.53, 95% CI −0.84 to −0.21) and HOMA-IR (SMD −0.50, 95% CI −0.86 to −0.14), along with an increase

in HDL-c levels (SMD 0.97, 95% CI 0.26 to 1.68), but had no significant effects on fasting plasma glucose, total cholesterol, triglycerides, LDL-c, or VLDL-c [89].

There is some evidence to suggest that the combination of selenium with probiotics may enhance the benefits of selenium supplementation. A meta-analysis of five studies including 282 participants testing selenium supplementation (dose ranging from 50 to 200 µg/day) in combination with a probiotic assessed the impact of the combination on glycemic parameters [90]. The co-supplementation of selenium with a probiotic was associated with a reduction in fasting plasma glucose (WMD −4.02 mg/dL, 95% CI −5.87 to −2.18), serum insulin (WMD −2.50 mIU/mL, 95% CI −3.11 to −1.90), and HOMA-IR (WMD −0.59; 95% CI: −0.74 to −0.43), as well as an increase on QUICKI (WMD 0.01, 95% CI 0.01 to 0.02). The combination was also associated with a reduction in serum levels of total cholesterol (WMD −12.75 mg/dL, 95% CI−19.44 to −6.07), LDL-c (WMD −7.09 mg/dL, 95% CI −13.45 to −0.73), and serum triglycerides (WMD −14.38 mg/dL, 95% CI −23.13 to −5.62).

Migraine: ASSOCIATION WITH LOW SELENIUM

Low levels of selenium have been implicated in migraine in some observational studies. Data from the NHANES survey (1999-2004) including 12,964 participants found a non-linear relationship between selenium intake and migraine, such that the odds of migraine decreased with increasing selenium intake up to the inflection point of 93.1mcg/day, but had no significant association at higher levels [91]. A case-control study including 61 participants found that migraine patients had lower levels of serum selenium (81.06 ± 8.66 vs. 88.94 ± 10.23 µg/L) and higher levels of the oxidative stress marker MDA (3.04 ± 1.74 vs. 2.06 ± 0.59 nmol/ml) relative to controls, such that those in the lowest quartile of selenium levels were 11 times more likely to experience migraines [92].

The ability of selenium supplementation to mitigate migraines was assessed in a placebo controlled clinical trial including 72 migraine patients [93]. Participants supplemented with 200 µg/day selenium for 12 weeks showed reductions in serum markers of oxidative stress including MDA levels (0.34 ± 2.36 vs. 1.82 ± 3.85 nmol/mL), nitric oxide (−1.68 ± 3.55 vs. 0.59 ± 3.11 nmol/mL), and increased total antioxidant capacity (9.68 ± 15.07 vs. 0.04 ± 13.63 nmol of trolox equivalent/mL). This was accompanied by reductions in headache frequency (-8.15 ± 0.77 vs. -4.12 ± 0.77 days/month), severity (-2.89 ± 0.42 vs. -1.16 ± 0.42 VAS score) and Headache Impact Test-6 (HIT-6) scores (-9.22 ± 2.00 vs. -2.08 ± 2.00).

Osteoporosis: NO CLEAR BENEFIT OF SELENIUM SUPPLEMENTATION

Selenium is important for skeletal development, and bones contain the second highest proportion of the body's selenium stores, after skeletal muscle [94]. Selenium deficiency may negatively impact bone mass, however, similar to the brain, bone stores of selenium are preferentially preserved under

conditions of low selenium intake. Consequently, changes in circulating levels of selenium may not be reflective of bone levels. The degree to which selenium impacts bone health varies across studies depending on the population and degree of selenium deficiency. Overall, selenium sufficiency appears to promote bone health, but additional supplementation does not appear to offer further benefit. Selenium levels were not found to be associated with the risk of osteoporosis in a Mendelian randomization study using gene associations derived from a European population [95].
A meta-analysis of 19 studies (18 observational and 1 RCT) including 69, 672 participants examined the relationship between selenium status and bone health measures [96] . Mean selenium intake ranged from 41.2 to 154.4 µg/day. A positive association was found between dietary selenium intake and bone mineral density based on four studies including 36,270 subjects. An inverse association between selenium intake and incidence of osteoporosis was also observed (OR 0.47, 95% CI 0.31 to 0.72; based on 2 studies, n=6,391). The associations between serum selenium levels and bone health were less apparent, likely due to the preferential preservation of bone selenium stores in the context of selenium insufficiency. A positive association was observed between serum selenium levels and bone mineral density, but no significant associations were observed for rates of osteoporosis or fracture risk.
Selenium supplementation has not been shown to improve measures of bone health in individuals with adequate levels of selenium at baseline. An RCT including 120 postmenopausal women with osteopenia or osteoporosis, but normal serum selenium levels at baseline (≥70 µg/L), found that treatment with 50 µg or 200 µg/day of selenite did not result in improvement of bone mineral density relative to placebo at the six-month follow-up [97]. Furthermore, an RCT assessing the effect of supplementation with 100, 200, or 300 µg/day selenium-enriched yeast for 5 years in 354 Danish men and women, with an average plasma selenium concentration of 86.5 µg/L at baseline, found that supplementation increased circulating selenium levels, but had no significant effects on levels of the bone turnover markers, osteocalcin, procollagen type I N-terminal propeptide, collagen type I cross-linked C-telopeptide (CTX), and bone alkaline phosphatase [98]. There was a marginally significant effect on CTX only in participants that had selenium levels <70 µg/L at baseline.

Safety: Selenium intake at the recommended dietary allowance is safe and associated with better health outcomes, but levels in excess of 330 to 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
- 4 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 [83], 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 [19]. 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 [59]. An RCT testing the impact of selenium-enriched yeast at a dose of 100, 200, or 300 µg per day for five years in a cohort of generally healthy Danish men and women over age 60 reported that adverse events were mild and consisted of grooved nails, hair loss, and skin reactions [98]. There was no impact on mortality.

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) [84]. 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 [99]. 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 low-density lipoprotein (LDL) level [100]. 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 [101]. 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 [101]. 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. However, in 2022, these limits were revised downward in the recommendations by the EFSA Panel on Nutrition, Novel Foods and Food Allergens [102]. The panel concluded that based on the lowest-observed-adverse-effect-level (LOAEL) of 330 µg/day seen in the SELECT trial and an uncertainty factor of 1.3, the upper limit for selenium intake for adult men and women, including those who are pregnant or lactating, should be set at 255 µg/day.

Research underway:

According to Clinicaltrials.gov, there are currently 41 active trials involving selenium. It is being tested in a variety of conditions, including Graves ophthalmopathy, bowel polyps, cancer, type 2 diabetes, oral lichen planus, chemotherapy-induced neuropathy, heart failure, hair growth, and prenatal supplementation. 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
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- ConsumerLab.com

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