Selenium status in elderly people : longevity and age-related diseases

Review article (for Current Pharmaceutical Design)

Selenium status in elderly people: longevity and age-related diseases.

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Abstract

Selenium (Se) concentration in biological samples, primarily serum or plasma, is discussed as a function of age and its relation with longevity. Highest values were observed in healthy adults, while in an elderly population significantly lower concentrations were reported.
The elemental level in various age-related diseases is reviewed and variables responsible for contradictory findings are mentioned.
Risk and benefits of Se-supplementation are still under debate.

Keywords: selenium, biological materials, longevity, age-related diseases

List with abbreviations:

-AD: Alzheimer's disease

-CSF: cerebrospinal fluid

-CI: cognitive impairment

-CVD: cardiovascular diseases

-GPx: glutathione peroxidase

IGF-1: insulin-like growth factor-1

-MCI: mild cognitive impairment

-MetS: metabolic syndrome

-P: plasma

-PD: Parkinson's disease

-S: serum

-SMC: subjective memory complaint

-WB: whole blood

Introduction

Aging is an inevitable biological process with gradual and spontaneous biochemical and physiological changes and increased susceptibility to diseases.

Epidemiological studies suggest that extension of human lifespan or the reduction of age-associated diseases may be achieved by physical exercise, caloric restriction, and by consumption of certain substances. Although intriguing, these studies only show correlative (not always causative) effects between the application of the particular substances and longevity [1].

Some nutritional factors may remodel these age-related changes leading to a possible escape of diseases, with the consequence of healthy aging. They are involved in improving immune function [2], metabolic homeostasis and antioxidant defence [3]. Moreover, micronutrients (zinc, copper, selenium) can play a pivotal role in affecting the complex network of the genes (nutrigenomics) with anti- and pro-inflammatory action [4].

In the case of selenium, 25 human genes encode for selenoproteins [5,6], such as glutathione peroxidases (GPx), the plasma Se-transport protein (SePP) and thioredoxin reductases (TrxR) [7-9]. These selenoproteins regulate oxidative stress by maintaining the redox balance of the cells through high thiol levels, and participating in the reduction of hydrogen peroxide and lipoperoxide [10,11]. SNPs (single nucleotide polymorphisms) in the selenoprotein genes can modulate the function of these proteins and hence affect both the cellular response to oxidative stress [12] and immune responses.

GPX is a selenium-dependent enzyme with elimination of peroxides as main function and is also expressed in neurons and glia cells [13]. Therefore, the lack of selenium might increase oxidative stress, destruction of neurons and increase risk of dementia [14].
Overall, selenium status is generally perceived as an important factor for maintaining health in the elderly [15,16]. Since ageing is generally characterized by selenium deficiency due to a reduced intake of protein dense food, such as red meat [17] selenium supplementation is sometimes claimed to be useful in preventing cellular senescence [18].

With this review we intended to screen literature data (PubMed and Web of Science) on the relationship of Se levels in biological samples (primarily serum or plasma) and age, longevity and the risk of various diseases, including cognitive impairment. Focus is on literature data from 2000 onwards are taken; nevertheless, unless some important older reports, mentioned in recent reviews, are considered as well.

After finishing this review a special 200-year anniversary issue on “Selenium and selenoproteins in (redox) signalling, diseases, and animal models” was published. Four review papers out of this could be recommended to consult, since these are related to the topic of our article [19-22].

1. Selenium concentration in biological samples as a function of age

Se-levels are very low during the first months of life, with a gradual increase with age. Highest values are observed in healthy adults, while the elderly revealed significantly lower concentrations [23].

However, the age-definition of “elderly people” may vary from over 55 years, over 65 years or ranges like 60-75 years.

For elderly, besides lower intake and bioavailability, influences of emerging disease and increasing intake of pharmaceuticals will jeopardize definite conclusions [23]. We have reviewed older literature data on Se serum (plasma) levels in elderly and found ranges from 66 µg/l (Brazil, Turkey) to 126 µg/l (Japan, USA). Recent publications on elderly people and Se concentrations in biological material are summarized in Table 1.

Influence of sex and age on Se levels are hard to isolate, since there are a lot of confounding factors: intake, hormonal status and probably a higher intention to consume vegetarian food by women [46], leading to lower Se levels
Also education can confound conclusions. Some authors [47] claimed to observe higher Se levels in the more educated elderly population in France. Maybe this group is taking care of a more adequate food intake or uses multivitamin and/or multi-mineral preparations [48].
Observed trends in Se levels in elderly people are summarized in Table 2.
In general, a negative correlation was found between age and blood Se levels, for whole blood [31], as well as serum [36]. In the latter study poor Se-status was also observed for α-tocopherol, even among younger, well-educated female seniors. Quite remarkably, serum selenium was positively associated with alcohol intake [36]. Either it increases Se bioavailability or influences hepatic biotransformation.

In the second part (Se and longevity) various elderly subgroups are discussed in more detail.

Since there are several publications dealing with low selenium level as a predictor of disease and mortality among older adults [15,47,56,57] we review the relation of Se with various diseases of old-age in the third part of the article.

2. Selenium concentration in biological samples and longevity

An older publication already suggested that human lifespan was shortened by severe selenium deficiency [58]. A Chinese study mentioned that Se could be an important environmental geochemical factor influencing the longevity of humans [59]. In this country higher Se distribution in the soil [60], greater fish consumption [60], food and drinking water [61,62], and rice [63] were related to longevity townships. In France also increased Se intake in elderly high fish consumers may account for health benefits previously ascribed to omega-3 fatty acids [64].
Table 3 summarizes publications on Se concentration levels in biological samples of nonagenarians and centenarians. Quite contradictory results were obtained in Italy with lower values [67,68], compared to China with higher values [65,66] for centenarians compared to nonagenarians.
Part of the contradictory findings could be ascribed to the characteristics of group sampled and characteristics of this. Even the description “centenarians” can be used for a heterogeneous group of subjects, who can delay (“delayers”), survive (“survivors”) or even escape common age-related diseases (“dodgers”) [70].
Quite recently, beneficial and paradoxical roles of Se at nutritional levels of intake in healthspan and longevity are summarized [22].
Se-enzyme activity [55] and Se-proteins [71] might be more important predictors of the Se-status than the Se-elemental concentrations as such. Two studies (Poland, Italy) found that GPx activity in

centenarians appeared to be similar [72] or very close to the values found in young subjects [69], although selenium in whole blood was lower in the aged group [69]. However, whole blood Se levels for health young females, as well as for the centenarians are unrealistic low (55 ug/l and 37 µg/l, respectively). Even for serum or plasma these values are far too low, although these are considered to be about 20 % lower than the whole blood level [23,73].

Insulin-like growth factor (IGF-1) stimulates cell proliferation, inhibits cell apoptosis and may enhance longevity. The positive and significant association between Se and IGF-1 serum levels in community-dwelling older adults in Italy offers some indication on the positive role of Se playing in longevity [39].

3. Selenium concentration in biological samples and age-related diseases

3.1. Neurological disorders

The role of selenium and selenoproteins in neurotransmission might not only be limited to their antioxidant properties but also to the role in inflammation and ion channel function, the influence on protein phosphorylation, and the alteration of calcium homeostasis and brain cholesterol metabolism could be important [74].

Decreased expression of several selenoproteins is associated with the etiology of age-related neurodisorders and cognitive decline, including Alzheimer's disease, Parkinson's disease and epilepsy [75].

A neuroprotective role has been suggested for selenoprotein P [76,77]. This selenoprotein is a secreted heparin-binding glycoprotein which serves as the main Se transport protein in mammals. Therefore it delivers Se to neurons, acts as an antioxidant, functions in cytoskeleton assembly, and interacts with redox-active metals (copper, iron, and mercury) and with misfolded proteins (amyloid-beta and hyperphosphorylated tau-protein) [78].

Alzheimer's disease is sometimes included in "cognitive decline" reports and a lot of variants are considered under the term "dementia". Some researchers divide cognitive impairment into two groups: non-dementia and manifest dementia. In the latter group the vascular dementia and the Alzheimer type of the disease are considered. This group is further subdivided into very mild, mild and fully developed. It is very hard to make a clear-cut distinction however, but we prefer to differentiate literature data into three groups: Alzheimer's disease and related dementias (ADRD), cognitive impairment (with specific term mentioned) and Parkinson's disease (PD).

It is hard to trace in the studies quoted if AD is autopsy or imaging confirmed. Therefore the current tendency is to realize that most elderly people with dementia have some form of dementia rather than pure AD and we prefer to use the term ADRD (Alzheimer's disease and related dementias).

a. Alzheimer's disease and related dementias (ADRD)

Selenium can act as a potent inhibitor of tau hyperphosphorylation, presumably by optimizing the functions of anti-oxidative seleno-enzymes, that protect the neuronal cytoskeleton [76,77].

Table 4 summarizes literature data on the relation of selenium level in biological materials and ADRD. As can be seen from this table most of the time no difference or lower selenium levels were observed in the ADRD patients. Only one publication mentioned higher values [85]. Besides this older publication, a recent one also claimed that higher Se levels predict the conversion to AD [83]. Definition flaws (subjective memory complaint, very mild or mild cognitive impairment, early stage AD, late stage AD), as well as some genetic polymorphisms (glutathione peroxidase 1Pro198Leu: 27 and apo E ε4: 87,88) could jeopardize definite conclusions.

Four recent systematic reviews and meta-analyses [21,89-91] confirm observations found and suggest that circulatory Se is directly correlated with GPX, an important antioxidant Se-enzyme, in AD [91].

Neutrophil granulocytes uniquely express the selenoenzyme methionine sulfoxide reductase B1 (MsrB1). Achilli and co-workers [92] very recently found that there was a significant decline in activity of this enzyme in patients affected by AD, compared to normal subjects.

Due to the lower selenium concentration in the blood of AD patients supplementation trials with doses of 200 µg/day have started [93]. Investigations on the long-term effect of anti-oxidant supplementation (400 IU/day of vitamin E and 200 µg Se/day did not prove any prevention of dementia incidence among asymptomatic men [94].

Earlier, Loef and co-workers [95] also claimed that there is an absence of consistent clinical evidence as to whether supplementation of Se is beneficial in the treatment of AD.

b. Cognitive impairment (CI)

Dementia is one of the major health problems. In manifest dementia there are two groups: Alzheimer type and vascular dementia. The form called “cognitive impairment non-dementia” represents a subclinical phase of dementia. Since a sharp-cut division cannot be made since psychiatric disorders show a broad spectrum with inter-individual differences, together with the interpretation of “subjective” memory complaint (SMC), this can explain divergent results found in literature. Data are summarized in table 5.

In Italy a group claimed to find a trend in increase of Se level in SMC patients and a decrease in AD patients [38]. However, no statistically different values were found for mild cognitive impairment (MCI) in Brazil [81], while in the Czech Republic lower values were found [32]. Moreover, the authors claimed to find a negative correlation between Se concentrations and lipid peroxidation end-products of oxidative stress in plasma of MCI, as well as in patients with AD.

Lower Se levels measured in nail samples were significantly associated with lower cognitive scores in rural elderly in China [30]. Low Se exposure was claimed to be associated with lower cognitive function in this rural population [96]. Also Se deficient preschool children from rural Ethiopia had lower scores on all cognitive tests than normal children [97].

The EVA study in France, which included volunteers with better educational level, higher income, and better cognitive function, proved that subjects with low levels of Se have an increased risk of cognitive decline [14,98], in a 9-year longitudinal study [99]. In another study no difference was observed in mean dietary Se intake levels between persons whose global cognitive performance improved over time or not, over a follow-up of 8.5 months [100]. A cohort study in Italy [101], was

also not included in a review paper on antioxidant nutrients and age-related cognitive decline [102]. Numbers of patients were too small and also serum Se levels were unrealistic high for that country and age of the patients [23].

There is preliminary evidence that consumption of one Brazil nut/day for 6 months can have positive effects on some cognitive functions of older adults with a mild form of impairment [28].

c. Parkinson's disease (PD)

Parkinson's disease is a progressive neurodegenerative disorder. The aetiology of this disease is still not fully clear, but free radicals have been proposed to cause neural injury [103]. Due to its function in antioxidative enzymes, selenium may possibly exert a role in the prevention and management of this disease.

Table 6 summarizes contradictory results of studies found in the literature. Higher [29,105,106], as well as equal [43,107] concentration levels compared to controls are found. This proves that the antioxidant role of Se in the onset of PD is not clearly established, although in the USA a high soil Se is related to a reduced PD mortality [108].

3.2. Cancer

Besides the fact that cancer is a multifactorial and a multistational process there are a lot of biases. Changes in selenium levels can be as well a cause as a consequence of the disease and even pre-diagnostic levels have to be considered with some precautions.
An inverse association between Se exposure and the risk of some types of cancer was found in observational studies, but this cannot be taken as evidence of a causal relation [24].
The studies have many limitations: assessment of Se-exposure, heterogeneity, age of the studied population [109] and deplete or replete status [25,34,36,110-112].
The conflicting results include inverse, null and direct associations for some cancer types [113]. Since prostate cancer is related to elderly men we paid more attention to this type of cancer. Also here contradictory findings were published for benign [114], as well as for malign hyperplasia [115,116].

Also randomized controlled trials assessing the effects of Se supplementation on cancer risk have yielded inconsistent results, with primarily no beneficial effect on cancer risk, as well as little evidence of any influence of baseline Se status [113,117-119].
To gather evidence for the aetiological relationship between Se exposure and cancer risk in humans and offer some proofs for the efficacy of Se supplementation for cancer prevention in humans Vinceti and co-workers [120] published an extensive and systematic review in the Cochrane Systematic Reviews.
Some trials even suggested harmful effects of Se exposure, therefore, there is no convincing evidence that Se supplements can prevent cancer in humans [110,113].

The SELECT trial on effect of Se and vitamin E on risk of prostate cancer in a population of relatively healthy men revealed prevention of both compounds, alone or in combination [121]. The trial was terminated early because of both safety concerns and negative data for the formulations and doses given [122].

After submitting this paper an 200 years anniversary issue appeared in Free Radical Biology and Medicine on selenium research in redox biology, health and disease [123]. Here an excellent review

article explained how U-shaped thinking weaves together dogs, men, selenium, and prostate cancer risk [124].

3.3. Cardiovascular diseases (CVD)

The EVA study in France postulated that obesity and occurrence of cardiovascular events are the main factors associated with plasma Se decrease during aging [17]. Also in Germany, low Se concentrations were associated with future cardiovascular deaths in patients with acute coronary syndrome [125]. A similar decline in Se status with CVD was published for an Australian population [49].
A recent meta-analysis on prospective studies demonstrated a significant inverse association between Se status and CVD risk within a narrow Se range [126].
Elderly Swedish subjects with a low selenium status were followed for 6.8 years and those in the lowest quartile revealed an increased risk for cardiovascular mortality [127].
Moreover, a group of healthy elderly participants in south-east of Sweden, supplemented for 4 years with Se (200 µg as selenized yeast) and 200 mg coenzyme Q10 revealed a significantly reduced cardiovascular mortality [127]. The protective action was not only confined to the intervention period, but persisted during a follow-up period of 10 years [128] and even of 12 years [129]. No mechanistic basis for this observation was given.

3.4. Inflammation

Mocchegiani and co-workers [4] reviewed selenium-gene interactions in ageing and inflammation. Nearly all publications mentioned an inverse association between serum selenium and the inflammatory cytokine interleukin-6 (IL-6) among elderly people [130-132].
Therefore MacDonell and co-workers [40] argued that adjustment for inflammation should be considered when evaluating selenium status in aging population, particularly for IL-6.

3.5. Metabolic syndrome (MetS)

Metabolic syndrome is characterized by abdominal obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-c) level, increased blood pressure, and elevated fasting glucose level. Biomarkers of this syndrome are divided in various subgroups [133].

Publications on MetS and selenium level in biological material are scarce and even contradictory. Higher serum Se level may intensify MetS [134] and are associated with a higher body mass index (BMI). Total cholesterol, triglycerides, and LDL-cholesterol concentrations increased significantly with serum Se concentrations in Taiwanese elderly [135]. The latter study has some limitations: it was a cross-sectional design and causal interferences could not be established, the participants were volunteers rather than randomly selected, there were no data available on food intake and selenium supplementation and multivariate analysis adjusted for lipid-lowering medications might have biased the results.
Another longitudinal study claimed that higher Se concentration in nails has modest beneficial effects on blood lipid levels [136]. Here in a rural elderly Chinese cohort higher Se levels in nails were related to a greater decrease in total cholesterol and greater increase in HDL-cholesterol from baseline to

follow-up compared to those with the lowest Se levels. These observations were contradictory to those for a similar population in rural China [137].

3.6. Anaemia

Anaemia is common in older adults [138] and is associated with a decreased quality of life [139], decreased mobility [140], increased disability [141], decreased muscle strength [142], depression [143], and increased mortality [144]. Anaemia is also linked to congestive heart failure [145] and a higher risk of Alzheimer's disease [146]. The decrease of oxygen-carrying capacity of the blood can contribute to the mentioned complications without being its actual cause.

Low blood Se levels are cited as long-term independent predictors of anaemia in older community-dwelling adults in Italy [147] as well as in the United States [148].

3.7. Dysglycemia

Three publications on dysglycemia and selenium status in elderly could be traced. A prospective study in France suggests a sex-specific protective effect of higher Se status at baseline on later occurrence of dysglycemia. The observation was only observed in men [149]. In Sweden on the other hand the results do not support a role of dietary Se in the development of disturbances in glucose metabolism or diabetes in older male individuals .
In an elderly Taiwanese population fasting glucose concentration increased significantly with serum Se concentration [135]. Only the serum fasting glucose without any data on insulin levels was available, so the relationship between Se and insulin resistance could not be explored.
The finding that Se supplementation can support the development of type 2 diabetes [151] was unexpected, however a meta-analysis recently concluded that the increased risk was albeit relatively low [152].

3.8. Endocrine disorders

Selenium did not seem to play a significant role in the occurrence of total testosterone deficiency in aging men [153].
In extremely aged people lower selenium levels are however associated with serum iodothyronine levels [51]. A positive association was found between Se and the T3/T4-ratio [154]. This confirms the important role of Se in the conversion of T4 into its most metabolically active form T3, as a consequence of the Se-dependency of some deiodinase enzymes [155].

3.9. Physical integrity

The maintenance of good serum Se level is important, since it may affect the self-perception of health, chewing ability, or physical activity and, consequently the quality of life in elderly people [16]. Low plasma Se is independently associated with poor skeletal strength in community-dwelling older adults in Tuscany [52], as well as with functional mobility problems [156,157]. Lower total antioxidant levels are found in physically disabled elderly [157]. Higher erythrocyte glutathione peroxidase was found in exercising elderly, compared to their sedentary counterparts [158].
In China no significant differences were found for Se levels in men [159] or women [160] with varying bone mineral density.

3.10. (Chronic) parasitic infections

Malaria, toxoplasmosis, African (sleeping sickness) and American (Chagas disease) trypanosomiasis, leishmaniasis, and schistosomiasis are (chronic) parasitic diseases due to pathogenic protozoans or helminths in human populations. The etiological agents of each disease are responsible for dramatic economic losses and the highest morbidity and mortality rates in tropical and subtropical areas worldwide. While parameters like aging and nutrition were intensively investigated to measure their impact on parasitic infection rates and their immune responses in humans, it is not sure that there is a general consensus on a link between aging and infection rates [161].

4. Selenium and supplementation in the elderly

A number of clinical trials have provided convincing evidence of the central role of selenium, either alone or in combination with other micronutrients or antioxidants, in the prevention and treatment of multiple diseases. Advances made so far in the study of mechanisms and applications of selenium compounds that could be suitable for the prevention/treatment of chronic diseases are reviewed by Sanmartin and co-workers [162]. Nevertheless the widespread use of Se supplementation or other strategies that artificially increase Se status above the level required for optimal selenoprotein activity is not justified and should not be encouraged [163].

A meta-analysis of randomized controlled trials proved a null effect of selenium supplementation on CVD [126]. This was in contrast to a recent study on supplementation with selenium and coenzyme Q10 for 4 years. Here a reduced cardiovascular mortality 12 years after supplementation was found [129].
A small study in England proved that depression was associated with low levels of Se in frail older individuals. Supplementation of Se (60 µg/twice a day)for 8 weeks reduced the Hospital Anxiety and Depression rating scale (HAD), a parameter used to assess mood in these nursing home residents [164].
The Su.Vi.Max Study in France revealed that supplementation with 100 µg Se (in combination with vitamins and other antioxidants) resulted 5 years later in a greater healthy aging probability among men, but not among women [35].
Long-term supplementation with Se-enriched yeast (300 µg/day for 6 months) did not result in significant differences in plasma cholesterol concentrations or its sub-fractions compared to placebo in elderly Danish people [33].
In the same country with a moderately-low Se status a 300 µg/day dose taken for 5 years increased all-cause mortality 10 years later. Cancer and CVD mortality similarly appeared to increase, but the effects were not statistically significant. Though the 100 and 200 µg/day doses showed a non-significant reduction in mortality during the 5-year treatment period, the effect had disappeared 10 years post-treatment [20]. Authors warned however that total Se intake over 300 µg/day should be avoided. Recently this was also claimed by Ivory and co-workers [165]. A 12-week randomised, double-blind, placebo-controlled clinical trial with varying amounts of Se in different forms in healthy subjects (50-64 years) with marginal Se status resulted in both beneficial and detrimental effects on cellular immunity to flu [165]. These effects were affected by the form of Se, supplemental dose and delivery matrix.
All these observations call for a thorough evaluation of the risks and benefits associated with Se-supplementation.

Conclusion

Selenium plays a role in health maintenance during the aging process, however the mechanism is still under debate and hence explain partly some contradictory findings. The determination of selenoproteins such as selenoprotein P, glutathione peroxidase or selenium metabolites could help to clarify this mechanism.
Multiple factors confound determination of the role of Se in aging and longevity: gender, lifestyle habits, health status, elemental intake, environmental factors and supplementation with Se and other antioxidants. Besides malnutrition, reduced digestion and absorption, and interaction with medication can contribute to a reduced intake and hence a lower Se status [12].
Several recent studies call for a thorough evaluation of the risks and benefits associated with Se-supplementation, which primarily depend on the Se-status of the population studied, the duration and the daily dose.

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Table 1: Recent literature data on selenium concentration (μg/l) in biological samples in elderly people

Country	Age (years)	N	Sample	Concentration	Ref
Belgium (Limburg)	64±10	362	S	92.3±23.7	[24]
Belgium (43 districts)	62.4±10.0	585	S	78.7±13.9	[25]
Brazil (Sao Paolo)	60-89	28	P	51.0±21.1	[26]
Brazil (Sao Paolo)	60-89	28	erythrocytes	79.2±46.4	[26]
Brazil (Sao Paolo)	71.2±6.2	21	P	54.9±23.5	[27]
Brazil (Sao Paolo)	77.6±6.6	9	P	50.0±15.5	[28]
China	65.6±12.2	302	P	105±33	[29]
China (Qionglai)	>65	200	blood	121.2±34.5	[30]
China (Gaomi)	>65	200	blood	117.4±22.5	[30]
China (Jiange)	>65	200	blood	71.9±5.5	[30]
China (Zichuan)	>65	200	blood	147.4±17.4	[30]
Czech Republic	61-100	197	WB	74.0	[31]
Czech Republic	75.3±6.7	12	P	90.7±17.6	[32]
Denmark (Odense)	60-74	491	P	86.5±16.3*	[33]
Europe (10 countries)	60.1±7.4	121	S	85.2 (55.2-117.5)	[34]
France	65.3	3756	S	88.4±15.0	[35]
Germany (Hannover)	63.2±2.7 (females)	167	S	92.4±18.2	[36]
India	65.2±9.3	40	WB	187.5±48.7	[37]
Italy	65.2±6.4	40	S	82.6±23.4	[38]
Italy (Tuscany)	>65	1270	P	75.0±11.8	[39]
New Zealand	84.6	168	S	63.2	[40]
Sweden (South-east)	70-80	668	S	67.1	[41]
The Netherlands	72±9	93	P	93.1±20.5	[42]
Tunesia	59.7±12.1	36	S	95.8±14.4	[43]

Turkey	65±7 (males)	24	P	67.8±9.7	[44]
Turkey	65±7 (females)	26	P	68.7±12.6	[44]
Turkey	73±11	33	S	65.5±31.6	[45]

*: ng/g

P: plasma

S: serum

WB: whole blood

Table 2: Observed effect of selenium concentration in elderly people

Country	Age (years)	Sample	Observed effect	Reference
Australia	>81 (males)	P	decline compared to younger ones	[49]
Finland	>65	-	not associated with increased mortality from CVD	[50]
France	-	P	low baseline S level is associated with CVD and obesity	[17]
Italy (Bologna)	65-85	S	not different from people < 65 years	[51]
Italy	>65	-	lower levels associated with higher mortality	[52]
Italy (Tuscany)	>65	P	association with IGF-1	[39]
Italy (Northern)	70-80	S	lower than centenarians	[53]
Italy (Florence)	>65	S	association with nutritional status	[54]
Italy (Florence)	>65	S	inverse association with length of institutionalisation	[54]
USA	70-90 (females)	S	lower levels associated with higher mortality risk	[15]
USA	>65	-	lower GPx activity compared to younger people	[55]

CVD: cardiovascular diseases

GPx: glutathione peroxidase

IGF-1: insulin-like growth factor-1

P: plasma

S: serum

Table 3: Selenium concentration (µg/l) in biological samples of nonagenarians/centenarians.

Country	Age (years)	N	Sample	Concentration (observation)	Reference
China	> 90	380	P	113.7±67.9	[65]
China	>100	393	P	138.2±63.2	[65]
China (longevity area)	90-99	238	P	102.6±64.7	[66]
China (longevity area)	>100	208	P	128.7±74.2	[66]
Czech Republic (Prague/Templice)	61-100	197	WB	74.0* (negative correlation with age)	[31]
Italy (Bologna)	60-90	62	S	90.0±17.4	[67]
Italy (Bologna)	91-110	90	S	62.7±22.1 (lower than 60-90 years)	[67]
Italy (Sardinia)	89±6	76	P	88.9	[68]
Italy (Sardinia)	101±1	64	P	81.9 (negative correlation with age)	[68]
Italy (North)	100-104	81	S	85.7	[53]
Poland	101-105 (females)	16	WB	37.3±15.7 (lower than young healthy)	[69]

*: geometric means

P: plasma

S: serum

WB: whole blood

Table 4: Observed effect of selenium level in biological material of Alzheimer's disease and related dementias (ADRD) patients				
Country	**Age (years)**	**Sample**	**Observed effect**	**Reference**
Australia (Perth, Melbourne)	>60	S	=	[79]
	>60	erythrocytes	↓	[79]
	>60	CSF	=	[79]
Brazil	78±9	erythrocytes	↓ (severe stage)	[80]
Brazil	60-89	WB	↓ (Pro/Pro polymorphism in GPx)	[27]
Brazil (Sao Paolo)	60-89	P	↓	[26]
Brazil (Sao Paolo)		erythrocytes	↓	[26]
Brazil (Sao Paolo)		nails	↓	[26]
Brazil (Sao Paolo)	71±6	P	↓	[81]
Czech Republic	74±5	P	↓	[32]
France (Villejuif)	82±8	P	↓	[82]
France (Villejuif)	82±8	GPx	↓	[82]
India (South)	71±8	WB	=	[37]
Italy (Modena)	-	CSF	higher levels predict conversion to AD	[83]
Italy (Molise)	72±8	S	trend to lower values	[38]
Romania (Iasi)	66±4	GPx	↓	[84]
Romania (Iasi)	66±4	P	↑	[84]
Sweden	-	P	↑	[85]
Sweden (Malmö)	-	P	=	[86]
Sweden (Malmö)	-	CSF	=	[86]
The Netherlands	73±7	P	↓ (even in early stages)	[42]
Turkey	72±7(males)	P	↓	[44]
Turkey	- (females)	P	↓	[44]
Turkey (Ankara)	78±9	S	=	[45]

Turkey (Ankara)	78±9	hair	=	[45]

↓: lower

↑: higher

=: no difference

CSF: cerebrospinal fluid

GPx: glutathione peroxidase

P: plasma

S: serum

WB: whole blood

Table 5: Observed effect of selenium level in biological material of patients with cognitive impairment (CI)

Country	Age (years)	Sample	Observed effect	Reference
Brazil (Sao Paolo)	>60 (MCI)	P	not statistically different	[81]
Brazil (Sao Paolo)	>60 (MCI)	erythrocytes	↓	[81]
China	-	WB	↓	[96]
Italy (Molise)	68±8 (SMC)	S	trend to increase	[38]
Italy (Molise)	68±8 (MCI)	S	trend to decrease	[38]

MCI: mild cognitive impairment

P: plasma

S: serum

SMC: subjective memory complaint

WB: whole blood

Table 6 : Selenium concentration in biological material of Parkinson's disease (PD) patients compared to controls

Country	Age	Material	Observation	Ref.
China	67±11	P	↑	[29]
Germay (Goettingen)	-	CSF	↑	[104]
India	40-80	S	↓	[105]
Spain (Madrid)	-	S	↓	[106]
Spain (Madrid)	66 ±9	S	no difference	[107]
Tunisia (Monistir)	66±10	S	no difference	[43]

CSF: cerebrospinal fluid
P: plasma
S: serum