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BRIEF REPORT

Association between selenium intake and cognitive function among older adults in the US: National Health and Nutrition Examination Surveys 2011–2014

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Abstract

Cognitive decline occurs commonly as people age. Despite the complexity of cellular mechanisms, oxidative stress is a critical contributor to age-associated cognitive impairment. Selenium plays an important role in antioxidant defense systems. The purpose of the present study was to assess the correlation between selenium intake and cognitive function among older adults. The participants were individuals ≥65 years old (n=1681) who participated in the 2011–2014 National Health and Nutrition Examination Survey (NHANES), a country-wide cross-sectional survey. Dietary selenium intake and adequacy were evaluated with 2 d of 24-h recalls and the estimated average requirement (EAR) cut-point method, respectively. Cognitive function was assessed with the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score, which was significantly higher when selenium intake was adequate. After adjusting for energy intake, the association was no longer significant. Inadequate intake of selenium is rare in the US and dependent on caloric intake in older adults.

Key words: **Age: CERAD: Cognition: NHANES: Selenium**

Introduction

Cognitive impairment is characterised by progressive structural and functional degradation of the brain that leads to changes in learning, remembering and reasoning, and affects people's quality of life adversely[1]. Aging is a risk factor that enhances the susceptibility to cognitive decline. As the life expectancy has increased worldwide, the number of older adults and the frequency of cognitive impairment are increasing. According to the Centers for Disease Control and Prevention (CDC), approximately 7 million people in the United States (US) are living with dementia, and one in nine adults 65 years or older were diagnosed with Alzheimer's disease in 2021[2]. Furthermore, older adults with cognitive impairment have a lower household income, as they require medical care and nursing services, and their caregivers also have a poor quality of life[3]. The US spent $321 billion in healthcare on Alzheimer's disease and dementia in 2022[2].

One potential cause of cognitive impairment is the increase in oxidative stress levels with age[4]. Excessive free radical production damages the brain cells and decreases cognitive function. Selenium is associated with decreased oxidative stress, as it is a component of the selenoproteins, such as glutathione peroxidase, an endogenous antioxidant enzyme that helps scavenge reactive oxygen species and prevent oxidative damage[5,6]. Adequate selenium intake may have a protective effect against cognitive impairment by preventing aging-associated oxidative stress in the brain. Although selenium's neuroprotective roles have been reported in various cellular and molecular studies, there is a lack of epidemiological studies that have explored the relation between selenium intake and cognitive

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function. We hypothesised that adequate selenium intake is associated with a higher Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score, a measure of cognitive impairment. The goal of the present study was to investigate the association between selenium intake and the CERAD scores among community-dwelling adults 65 years or older in the US.

Methods

Study design and participants

The present study is a secondary analysis of data from the National Health and Nutrition Examination Survey (NHANES) 2011–2014. NHANES is a country-wide, cross-sectional survey designed to assess the US population's health and nutritional status. Details of the study design are publicly available at https://www.cdc.gov/nchs/nhanes/about_nhanes.htm. The survey collects data on health and nutritional parameters, such as dietary intake, anthropometrics, disease status, cognitive function and demographic/socioeconomic factors. NHANES uses a multistage, probability sampling method of non-institutionalized civilians living in the US. The sample extracted for these analyses included only adults 65 years or older with data available for all variables used in the analyses[7,8]. All survey participants provided written informed consent, and the National Center for Health Statistics Institutional Ethics Board approved the NHANES survey protocol. Our study was based upon secondary analysis, and therefore, did not require additional ethics review[7,8].

Dependent variables of interest

The primary outcome of interest was cognitive function, which was assessed by the score that CERAD established. It is a brief standardised test used to assess cognitive function in the memory sub-domain[9], and is used frequently in large epidemiological studies with diverse racial and cultural populations. The participants underwent three consecutive learning trials with a delayed recall trial. In each learning trial, they were asked to read ten unrelated words aloud and recall them later. The participants received one point for each correct answer. The total CERAD score ranged from 0 to 40, which was the sum of the scores from four trials. A higher score indicates better cognitive function. The CERAD score was distributed normally among the sample, and therefore, it was used as a continuous variable in this analysis. Other domains of cognition include attention, motor control, language, executive function and social cognition. Cognitive tests are available for assessment of these domains. However, we only included the CERAD score due to the limited scope of the study.

Independent variables of interest

Dietary and supplemental intake of selenium was assessed with two non-consecutive 24-h dietary recalls. A two-day average of both dietary selenium and dietary selenium plus supplemental selenium were computed. Using the estimated average requirement (EAR) cut-point method[10], the participants were categorised into inadequate selenium and adequate selenium intake groups based upon the EAR of selenium, which is 45 μg/d[11].

Covariates

Factors that may influence cognitive function were chosen as covariates based upon previous research[12,13]. Socio-demographic variables such as gender (male and female), race/ethnicity (Hispanic, other Hispanic, non-Hispanic White, non-Hispanic Black and other races), marital status (married/living with a partner, widowed/separated/divorced and never married) and education level (<high school, high school and >high school) were included. Anthropometric and behavioural variables such as body mass index (BMI) were used to classify the participants as underweight, normal, overweight, obese and morbidly obese. Smoking status and alcohol intake were also included in the analysis, as were such health conditions as diabetes, hypertension and stroke, because previous studies have demonstrated their association with cognition[12].

Statistical analysis

Statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA) and SUDAAN 11.04 (Research Triangle Institute, Research Triangle Park, NC, USA). SAS was used to recode the data, and SUDAAN was used to calculate inferential statistics while adjusting for study design and sampling weights. Descriptive statistics were used to describe the distribution of participants for each variable. Means and standard errors of the mean were calculated and then the differences between the means in each variable sub-group were analysed with a *t*-test or ANOVA. In Model 1, multiple linear regression was used to assess the association between dietary selenium intake and cognitive outcomes while controlling for the selected covariates. In Model 2, dietary plus supplemental intake was assessed. Both models were run without and with energy adjustment. An *a priori* $\alpha < 0{\cdot}05$ was defined as statistically significant.

Results and discussion

The final analytical sample (n=1681) included non-institutionalized individuals 65 years or older living in the US (Table 1). The participants were largely non-Hispanic White (81·1 %), married or living with a partner (64·4 %), and had more than a high school education (59·8 %). A large proportion of them were overweight or obese (68·3 %) and had hypertension (62·6 %) or diabetes (23·2 %). With respect to selenium intake, only 5·0 % had inadequate selenium intake, and this percentage dropped to 3·7 % with supplementation.

The univariate tests showed that the CERAD scores were significantly higher among people with adequate selenium intake compared to their counterparts (25·14, SE = 0·34 *v.* 22·58, SE = 0·78, $P < 0{\cdot}01$). In Model 1, those with adequate

Table 1. The association between adequacy of selenium intake and cognitive function, measured as CERAD[a] score among older adults in the US (*n* 1681)

Group	Overall *n* (weighted %) *n*=1681	CERAD score Mean (SE)	Univariate test *P*-value[b]	Multiple regression (Model 1)		Multiple regression (Model 2)	
				β (SE)[c]	*P*-value[c]	β (SE)[d]	*P*-value[d]
Gender							
Male	826 (46·6 %)	23·96 (0·44)	–	–	–	–	–
Female	855 (53·4 %)	25·93 (0·37)	<0·001	2·84 (0·47)	<0·001	2·84 (0·47)	<0·001
Race/ethnicity							
Hispanic-Mexican	113 (3·1 %)	22·11 (0·84)	<0·01	−1·26 (0·76)	0·11	−1·25 (0·76)	0·11
Other Hispanic	140 (3·8 %)	23·15 (0·93)	0·04	−0·86 (0·80)	0·29	−0·89 (0·81)	0·28
Non-Hispanic White	959 (81·1 %)	25·28 (0·42)	–	–	–	–	–
Non-Hispanic Black	351 (8·0 %)	23·79 (0·59)	0·05	−0·36 (0·76)	0·64	−0·35 (0·76)	0·65
Other races	118 (4·0 %)	25·92 (0·85)	0·52	1·22 (0·90)	0·18	1·20 (0·90)	0·19
Marital status							
Married or living with a partner	973 (64·4 %)	25·33 (0·41)	–	–	–	–	–
Widowed/separated/divorced	643 (32·8 %)	24·42 (0·49)	0·11	−1·31 (0·51)	0·01	−1·30 (0·50)	0·02
Never married	65 (2·8 %)	24·44 (0·95)	0·43	−0·17 (1·09)	0·88	−0·14 (1·09)	0·90
Education							
<High school	432 (17·3 %)	21·91 (0·55)	–	–	–	–	–
High school	391 (22·9 %)	24·23 (0·63)	0·01	1·78 (0·84)	0·04	1·78 (0·83)	0·04
>High school	858 (59·8 %)	26·20 (0·39)	<0·001	3·58 (0·67)	<0·001	3·60 (0·66)	<0·001
Body mass index (BMI)							
Underweight	56 (3·8 %)	24·68 (2·30)	–	–	–	–	–
Normal	456 (27·9 %)	25·22 (0·50)	0·81	−0·35 (2·07)	0·87	−0·34 (2·08)	0·87
Overweight	616 (36·7 %)	24·37 (0·39)	0·89	−0·48 (2·18)	0·83	−0·47 (2·19)	0·83
Obese	400 (22·1 %)	25·85 (0·48)	0·61	1·29 (2·18)	0·56	1·30 (2·19)	0·56
Morbidly obese	153 (9·5 %)	25·02 (0·68)	0·88	0·51 (2·16)	0·82	0·49 (2·18)	0·82
Smoking status							
Current	152 (7·2 %)	24·80 (0·80)	–	–	–	–	–
Former	699 (43·5 %)	24·86 (0·36)	0·93	−0·71 (0·73)	0·34	−0·68 (0·73)	0·36
Never	830 (49·3 %)	25·17 (0·50)	0·67	−0·86 (0·87)	0·33	−0·83 (0·86)	0·34
Alcohol drinking							
Current	282 (13·5 %)	23·50 (0·49)	–	–	–	–	–
Former	261 (14·8 %)	24·90 (0·62)	0·11	0·88 (0·72)	0·23	0·84 (0·72)	0·25
Never	1138 (71·7 %)	25·31 (0·36)	0·002	1·61 (0·54)	<0·01	1·61 (0·54)	0·01
Diabetes							
Diabetic	480 (23·2 %)	23·82 (0·47)	–	–	–	–	–
Non-diabetic	1201 (76·8 %)	25·37 (0·38)	0·006	0·78 (0·45)	0·09	0·78 (0·45)	0·09
Hypertension							
Hypertensive	1099 (62·6 %)	24·56 (0·42)	–	–	–	–	–
Non-hypertensive	582 (37·4 %)	25·76 (0·39)	0·01	0·83 (0·45)	0·07	0·84 (0·45)	0·07
Stroke							
Had stroke	141 (7·4 %)	23·37 (0·67)	–	–	–	–	–
Never had stroke	1540 (92·6 %)	25·14 (0·35)	0·02	0·89 (0·70)	0·21	0·90 (0·71)	0·21
Dietary Se intake[e]							
Inadequate (<45 μg/d)	111 (5·0 %)	22·58 (0·78)	–	–	–		
Adequate (≥45 μg/d)	1570 (95·0 %)	25·14 (0·34)	0·01	2·02 (0·90)	0·03		
Dietary + supplemental Se intake[e]							
Inadequate (<45 μg/d)	75 (3·7 %)	22·49 (0·97)	–	–	–	–	–
Adequate (≥45 μg/d)	1606 (96·3 %)	25·10 (0·34)	0.01	–	–	2·15 (1·08)	0·06

[a] CERAD score is the Consortium to Establish a Registry for Alzheimer's Disease.
[b] ANOVA and *t*-tests were completed in SUDAAN to determine significant differences in CERAD scores between groups with an *a priori* alpha set at <0·05.
[c] Multiple regression was used to assess for significant differences in CERAD scores by dietary Se adequacy while controlling for socio-demographic, behavioural and health conditions that are typically associated with cognition.
[d] Multiple regression was used to assess for significant differences in CERAD scores by dietary and supplemental Se adequacy while controlling for socio-demographic, behavioural and health conditions that are typically associated with cognition.
[e] Selenium Intake: Estimated Average Requirement (EAR), or 45 μg/d for the age group was used to determine adequacy.

dietary selenium intake scored significantly higher on the CERAD test compared to people with low intake ($25{\cdot}14 \pm 0{\cdot}34$ *v.* $22{\cdot}58 \pm 0{\cdot}78$; $\beta = 2{\cdot}02$, $P = 0{\cdot}03$) after gender, race, education status, marital status, alcohol intake, smoking status, diabetes, hypertension and stroke were controlled. However, when the model was adjusted for energy, the CERAD scores were no longer significant ($\beta = 1{\cdot}45$, $P = 0{\cdot}13$). Average energy intake was significantly lower in the selenium-deficient group ($851{\cdot}82 \pm 25{\cdot}28$ *v.* $1899{\cdot}10 \pm 26{\cdot}91$, $P < 0{\cdot}001$). The CERAD scores continued to differ depending upon the adequacy of selenium intake after supplemental selenium was added ($22{\cdot}49 \pm 0{\cdot}97$ *v.* $25{\cdot}10 \pm 0{\cdot}34$, $P = 0{\cdot}01$). When the association between adequacy of selenium intake plus supplemental intake was assessed, older adults with adequate intake continued to have higher CERAD scores; however, these differences were insignificant, both with and without energy adjustment ($\beta = 2{\cdot}15$, $P = 0{\cdot}06$ and $\beta = 1{\cdot}56$, $P = 0{\cdot}16$). Furthermore, energy intake was significantly related to

CERAD scores ($P = 0{\cdot}005$). The results suggested that the prevalence of inadequate selenium intake is low among US older adults. Inadequate selenium intake is associated with a vegetarian diet, low consumption of meat and seafood intake, or consumption of food grown in soil with poor selenium levels[14]. Selenium is an essential micronutrient in our diet that is involved in the production of selenoproteins, which are necessary for antioxidant defense system, metabolism, growth and development. Although there is a scarcity of epidemiological evidence of the relation between selenium status and cognitive function, some studies have suggested that selenium may play a protective role in maintaining cognitive function. A 4-year follow-up study conducted in France with adults 62–72 years of age observed reduced cognitive function after 4 years among individuals with lower glutathione peroxidase and superoxide dismutase levels in the red blood cells at baseline[15]. Another 9-year longitudinal study observed better cognitive performance among older adults with increased plasma levels of selenium[16]. However, short-term changes in plasma selenium levels were not associated with cognitive performance. A cross-sectional study conducted in China with rural adults over 65 years of age reported lower cognitive scores among individuals with low selenium levels in nail samples[17]. A case-control study demonstrated that, compared to healthy controls, Alzheimer's patients who lacked selenium in their diet had low levels of selenium in plasma, erythrocyte and nail samples[18]. In addition, a cross-sectional association was observed between low plasma selenium and motor function in older adults[19].

A recent study using the NHANES data also assessed the relationship between selenium intake and cognitive function among older people using multiple cognitive tests including CERAD, the Digit Symbol Substitution Test (DSST) and Animal Fluency test[20]. The DSST test evaluates processing speed, attention and working memory, while the Animal Fluency test evaluates executive function. Selenium intake was divided into quartiles. The results showed that low selenium intake was associated with low cognitive performance on the DSST and the Animal Fluency test but not the CERAD test[20]. Meeting the Recommended Dietary Allowance (RDA) of selenium was also not associated with cognitive function in any of the tests in the multivariate model. In the present study, we used the EAR as the preferred method to assess inadequate selenium intake. The results of the study above are consistent with our results which suggest an inverse relationship between dietary selenium intake and CERAD scores. However, the addition of supplemental selenium intake, and adjusting for total energy intake weakened the strength of the association. In these older adults, selenium intake was dependent on energy intake. A larger dataset with a greater number of participants with selenium deficiency may help to identify the true association between selenium intake and cognition. In addition, the CERAD score only assesses cognition in the memory sub-domain which limits our understanding of the full scope of cognitive function and its association with selenium intake.

The strengths of the present study are a large sample size representative of the US population. Therefore, the results from the present study can be generalised to the population overall. In addition, the study included healthy older adults who had not been diagnosed with any neurodegenerative disease. However, the present study has some limitations. First, it was a cross-sectional study design which can only identify associations between two factors, not causation. Understanding the causal relation between long-term selenium intake and cognitive status requires longitudinal studies that assess selenium intake and cognition at multiple points over many years. In addition, dietary and supplemental selenium intake was assessed with 2 d of self-reported 24-h recalls, which can be subject to recall bias and may not reflect long-term intake. However, NHANES uses the multiple pass method to collect dietary intake data which helps reduce recall bias. In addition, cognitive tests are subjective assessments. Although we used the CERAD test scores to evaluate cognition in this study, CERAD only tests the memory sub-domain of cognition. Therefore, investigating other domains such as attention, executive function, fluency and motor control may be important in future studies. To make an accurate interpretation of the relationship between cognition and selenium intake, we included multiple covariates that have previously been associated with cognition. However, there may be additional important confounding variables such as other dietary components, mental health status and living conditions that we did not include.

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