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Selenium exposure and depressive symptoms: the Coronary Artery Risk Development in Young Adults Trace Element Study

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Abstract

Selenium is an essential trace element important to neurotransmission, but toxic at high levels. Some studies suggest beneficial effects on mood. We assessed the association of selenium exposure with presence of depressive symptoms. Selenium exposure was measured in toenail samples collected in 1987 from 3,735 US participants (age 20–32 years) and depressive symptoms assessed in 1990, 1995, 2000, 2005, and 2010 using the Center for Epidemiologic Studies Depression Scale (CES-D). Binary and polytomous logistic regression models were used to assess the relation of $\log_2$(selenium) and selenium quintiles with presence of depressive symptoms (CES-D score ≥ 27 or on antidepressant medication). Relative to selenium quintile 1, the adjusted odds ratio (OR) for having depressive symptoms in 1990 for quintile 5 was 1.59 (95% CI: 1.01, 2.51) and a unit increase in $\log_2$(selenium), which represents a doubling of the selenium level, was associated with an OR=2.03 (95% CI: 1.12, 3.70). When examining 1, 2 or 3+ exams vs no exams with symptoms, the OR for quintile 5 was 1.73 (1.04, 2.89) for 3+ exams and for one exam and two exams, there were no associations. In a generalized estimating equations longitudinal model, a doubling of the selenium level was associated with a 56% higher odds of having depressive symptoms at an exam. Contrary to previously reported findings related to mood, higher level of selenium exposure was associated with presence of elevated depressive symptoms. More research is needed to elucidate the role of selenium in depressive disorders.

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Keywords

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1. INTRODUCTION

Selenium is an essential trace element with a role in protecting against oxidative damage. As such, it has been investigated in observational studies and in clinical trials as a preventive agent for cardiovascular disease, diabetes, and prostate and colorectal cancer (Rayman, 2012). Since the 1990s, selenium's reputation as an antioxidant has grown, with the consequence that selenium supplements and selenium enriched foods have become more common (Rayman, 2008, Stranges et al., 2010), However, recently, as a consequence of some reported adverse cardiometabolic findings (Bleys et al., 2007; Bleys et al., 2009; Stranges et al., 2010) a recognition of the narrow physiological range between selenium benefit and toxicity has emerged. Thus, a need for caution in overemphasizing the benefits and neglecting the potential toxicity has been expressed, as part of what is currently established to be in the nutritional range of selenium might actually more properly belong in the toxicological range (Vinceti et al., 2009).

In addition to having cardiometabolic effects, there has been suggestion in review articles that selenium has potentially mood modulating effects (Bodnar & Wisner, 2005; Kaplan et al., 2007; Leung & Kaplan, 2009) as a few small studies (Benton & Cook, 1991; Finley & Penland, 1998; Gosney et al., 2008) do suggest a beneficial effect on mood. Recently, lower selenium levels were associated with higher depressive symptoms in an elderly, rural Chinese cohort (Gao et al., 2012) after adjusting for demographic and medical conditions. However, there are no large population-based studies from the US that have examined the association of selenium status with depressive symptoms. Because the differing background selenium status across countries (Combs Jr, 2001) prevents generalization of findings from studies conducted in other countries to the US, it is important to examine the relation of selenium levels to depressive symptoms in a U.S. population. Moreover, in view of recent awareness of selenium's narrow physiological range between benefit and toxicity, the direction of any association is of vital interest. The Coronary Artery Risk Development in (Young) Adults (CARDIA) Trace Elements study is a population-based, longitudinal study of young black and white men and women with data collected on selenium exposure at the Year 2 examination and on depressive symptoms measured subsequently at the Year 5, 10, 15, 20 and 25 examinations. Based on prior studies (Benton & Cook, 1991; Finley & Penland, 1998) we initially hypothesized that selenium levels measured in toenails collected at Year 2 would be associated with reduced odds of presence of depressive symptoms assessed at the Year 5 and subsequent examinations. However, as will be shown, this hypothesis was not supported.

2. MATERIALS AND METHODS

2.1 Study population

In the CARDIA study, a total of 5,115 African-American and Caucasian men and women, 18 to 30 years of age, were recruited in 1985–1986 from four geographic areas:

Birmingham, Alabama; Chicago, Illinois: Minneapolis, Minnesota; and Oakland, California. Seven follow-up examinations were completed in 1987–1988 (Year 2), 1990–1991 (Year 5), 1992–1993 (Year 7), 1995–1996 (Year 10), 2000–2001 (Year 15), 2005–2006 (Year 20), and 2010–2011 (Year 25). Centrally trained and certified technicians collected data using standardized protocols. Quality of the data collection was monitored by the CARDIA coordinating center and the CARDIA quality control committee. The institutional review boards of each local center approved the study. Informed consent was obtained from each participant at each examination.

Of 5,115 participants enrolled in Year 0, 4,624 attended the Year 2 exam, considered the baseline for this study. Then 481 who did not attend the Year 5 exam were excluded as this was when the first Center for Epidemiologic Studies Depression Scale (CES-D) score was measured; additionally, participants were excluded for missing data on selenium (n=205), Year 5 CES-D score (n=50) or Year 2 covariates (n=130). Because extremely high levels of toenail selenium may indicate external contamination, participants with selenium ≥2 μg/g (n=23) were also excluded. Thus, these analyses are based on 3,735 participants (45% men, 55% women).

We compared the 3,735 participants included in the analysis to the 1380 who were excluded on baseline characteristics. Compared to the included those excluded were younger (mean age 24.2 years vs 25.1 years, $p<0.0001$), less educated (13.4 years vs 13.9 years, $p < 0.0001$), smoked more (4.5 cigarettes/d vs 3.8 cigarettes/d, $p=0.01$), were slightly less lean (BMI=24.8 kg/m^2 vs 24.4 kg/m^2, $p=0.01$), and were more likely to be Black (65.15 vs 46.5%, $p<0.0001$). Despite these differences, the full range of each covariate was represented.

2.2 Assessment of selenium exposure

When year 2 appointments were scheduled, participants were asked not to trim their toenails until their clinic appointment, during which the participants were provided a stainless steel clipper to clip their nails. The toenail clippings from the great toes and the rest of the toes were stored separately in two 1.5″×3″ bags and stored at room temperature in the driest condition possible in a pre-designated area in the local clinics. Participants completed a questionnaire providing information on nail polish, medication on toes and the frequency of using stainless steel cooking wares. Toenail clippings were processed with a washing procedure in a sonicator with deionized water. Details regarding nail collection and storage and the merits of using nail measurements have been reviewed elsewhere (He, 2011). Toenail selenium levels were assessed using neutron-activation analysis at the University of Missouri Research Reactor Laboratory. Personnel were blinded to clinical measures and treated toenail specimens in random order. The average coefficient of variation in duplicate subsamples for the toenail selenium measurement was 2.45%.

2.3 Outcome variable assessment

Depressive symptoms were assessed at the years 5, 10, 15, 20 and 25 examinations using the 20-item CES-D scale (Radloff, 1977), which has a maximum score of 60. Participants were asked to indicate how often they experienced each symptom in the past week with scores for

the responses ranging from 0 to 3 points (0, rarely or none of the time; 1, some of the time; 2, much of the time; 3, most or all of the time). Examples of symptoms included are poor appetite, trouble concentrating, restless sleep, depressed mood, crying spells, feeling disliked, talking less than usual, and inability to "get going." A cutoff score of ≥16 is suggested in epidemiologic studies to indicate a high level of depressive symptoms (Radloff, 1977; Radloff & Locke, 1986). For a cutpoint of 16, reported sensitivities for detecting clinically diagnosed depression ranged from 73% to 99% in various patient groups (McDowell, 1996), and in primary medical care centers, sensitivity and specificity of 96.3% and 38.6%, respectively, were reported (Schulberg et al., 1985). Although this cutoff is widely used, the specificity is low and a higher cutoff of 27 has been recommended to achieve higher specificity (70.4%) with a small reduction in sensitivity (88.9%) (Schulberg et al., 1985). Thus, analyses were performed utilizing the higher cutoff of 27 and repeated using the standard cutoff of 16 in sensitivity analyses. In either case, participants who were taking antidepressant medication were classified as having elevated depressive symptoms, referred to hereafter as "depressive symptoms." At Years 5 and 10, antidepressant medications were identified from the participant's self-reported list of prescription medication, and at Year 15, 20 and 25 participants were asked specifically, "Are you taking medications for depression?" At Years 5, 10, 15, 20 and 25, the prevalence of depressive symptoms was, respectively, 232/3735 (6.2%), 231/3210 (7.2%), 304/3021 (10.1%), 359/2838 (12.7%), and 407/2816 (14.5%). The numbers of participants taking antidepressant medication without having CES-D ≥27 were, respectively, 39, 72, 193, 249, and 296.

2.4 Assessment of covariates

Demographic, anthropometric, and lifestyle measures obtained at the years 2, 5, 10, 15, 20, and 25 examinations were used in these analyses. Height and weight were measured with the participant wearing light clothing with no shoes, and body mass index (BMI) was computed. Age, race, years of education, income (reported at all years except year 2), ability to pay for basics (as a surrogate for income, which was not recorded at Year 2), marital and employment status, and cigarettes smoked per day, were self-reported. Alcohol intake (ml/d) was computed from self-reported frequency of consumption of beer, wine, and liquor per week (Dyer et al., 1990). A physical activity score was obtained from the CARDIA Physical Activity History, a modified version of the Minnesota Leisure Time Physical Activity Questionnaire (Jacobs Jr et al., 1989). Because data on selenium intake from dietary sources or supplements were not recorded at the year 0 CARDIA exam, we created a dichotomous variable representing intake of a supplement containing magnesium, vitamin E, or beta carotene as a proxy for selenium supplementation.

2.5 Statistical analysis

Logistic regression was used to relate quintiles of selenium levels to presence of depressive symptoms at the year 5 exam. A polytomous logistic regression model was used to relate quintiles of selenium to the four categories: (1) never having depressive symptoms; (2) having depressive symptoms at 1 exam; (3) having depressive symptoms at 2 exams; and (4) having depressive symptoms at 3 or more exams. We modeled presence of depressive symptoms at years 5, 10, 15, 20 and 25 using a generalized estimating equation (GEE)

model. In addition to categorizing selenium levels into quintiles, we analyzed the base 2 log transformed selenium levels as a continuous variable and categorized selenium into four equal distance categories: 0.5150 to 0.8808 μg/g, 0.8809 to 1.2465 μg/g, 1.2466 to 1.6122 μg/g, and 1.6123 to 1.9780 μg/g. The logistic regression, polytomous logistic regression and GEE models were then analyzed using $\log_2$(selenium) and the equal distance categories.

Important potential confounders of the association between selenium and presence of depressive symptoms include BMI, cigarette smoking, and alcohol intake (Lloyd et al., 1983). There is evidence that vitamin and mineral supplementation may have some effect on mood and mild psychiatric symptoms (Long & Benton, 2013) and that supplement usage is associated with healthy lifestyle factors (Radimer et al. 2004; Millen et al., 2004), implying supplement usage may be a confounder, whether or not it contains selenium. Factors known to be related to depression, but with unknown relation to selenium status include education, employment status, income, marital status, and physical activity. Thus three models were considered for each of the statistical approaches: Model 1 adjusted for age, race, gender, and study center; Model 2 adjusted for all variables in Model 1 with additional adjustment for BMI, cigarettes/d, alcohol consumption, toenail mass, and intake of supplement containing magnesium, vitamin E, or beta carotene at examination 1 (yes/no); and Model 3 adjusted for all variables in Model 2 with additional adjustment for education, employment status, ability to pay for basics at year 2 or income at other years, marital status, and total physical activity. Only the GEE model adjusted for exam visit as well. In exploratory analyses, interactions of $\log_2$(selenium) and selenium quintiles with center, race, gender, cigarettes/d, and use of a supplement containing magnesium, vitamin E, or beta carotene were tested using the Wald Chi-Square test provided under the type 3 analysis of effects for model 3. The GEE model also tested the interaction of selenium with visit year as a continuous variable. It was not significant and, subsequently, the interaction term was dropped and a main effects model was utilized. The logistic and polytomous logistic models utilized covariates measured at year 2 and the GEE model used covariates measured contemporaneously with the CES-D outcomes.

Three additional sensitivity analyses were done. First, because depressive symptoms were not measured at year 2, we excluded participants with depressive symptoms (using the lower cutpoint of CES-D ≥16 or taking antidepressants) at year 5 as a proxy for depression at the year 2 visit. A time to first depressive symptoms (CES-D ≥27 or taking antidepressant) event analysis was done using the PHREG procedure from SAS software specifying the “Exact” option for the treatment of tied event times. Second, we modeled the CES-D score at year 5 as a continuous variable by using a censored normal regression model and also by using ordinary linear regression with a constant added to the CES-D scores of individuals taking an antidepressant (Tobin et al., 2005). Additionally, we used GEE to model the Y5, Y10, Y15, Y20, and Y25 CES-D scores as continuous outcome measures, adding a constant to the scores of individuals taking an antidepressant. Third, to assess whether high CES-D scores persist after 5 or 10 years and, if so, whether accounting for this persistence attenuates the association of selenium with depressive symptoms, we modified the GEE model by including 2 indicator variables representing high CES-D score at each of the two most recent visits. Statistical analyses were conducted using SAS for Windows, release 9.3

(SAS Institute Inc., Cary, NC). P-values less than 0.05 were considered statistically significant and were not adjusted for multiple comparisons.

3. RESULTS

The mean±SD selenium levels among 1,679 men and 2056 women were 0.83±0.15 and 0.89±0.15, respectively. These means are slightly lower and moderately higher, respectively, than those reported in the Health Professionals Follow-Up Study (0.84±0.15) and the Nurses' Health Study (0.77±0.13) (Park et al., 2012). Table 1 shows participants with higher levels of selenium exposure were less likely to be African American, smoked fewer cigarettes and consumed less alcohol, had higher level of education and less unemployment, were more likely to be taking a supplement and were most likely to be from the Minneapolis center and least likely to be from the Birmingham center.

When utilizing a CES-D cutpoint of 27, positive associations of toenail selenium levels with presence of depressive symptoms were observed in both the binary and the polytomous logistic regression analyses. Table 2 shows odds ratios (ORs) for presence of depressive symptoms at Year 5 across toenail selenium quintiles. In analyses adjusted for age, gender, race, and study site (Model 1) non-significant, positive associations of selenium exposure were observed with presence of depressive symptoms at Year 5. A doubling in the toenail selenium levels was associated with an OR=1.7 (*P-value*=0.08). After additional adjustment for BMI, cigarettes, alcohol consumption, toenail mass, and supplement use (model 2), the positive association became stronger (OR=2.0) and statistically significant (*P-value*=0.02). With further adjustment for education, employment status, ability to pay for basics, marital status, and total physical activity (model 3), the positive associations persisted. Table 3 shows ORs for the associations of selenium quintiles with presence of depressive symptoms at any one, two, or at 3 or more exams. Associations for the presence of depressive symptoms at 3 or more exams were significant in all three models treating selenium as a continuous variable (*P-values* = 0.01, 0.002, and 0.003, respectively) with OR=2.7 in model 3. For participants with the highest compared to the lowest quintile of selenium levels, the odds of having depressive symptoms at 3 or more exams were higher by 50 to 75% across different multivariable adjustment models.

In the GEE fully adjusted analysis (model 3) modeling quintiles of selenium, the highest OR, for the highest quintile, was 1.24 (p=0.10) and in the analysis of $\log_2$(selenium), a doubling of the selenium levels was associated with a significant 56% higher risk (p=0.02) OR = 1.56 (95% Confidence Interval (CI): 1.07, 2.26).

When the fully adjusted models (model 3) were run using the four equal distance selenium categories, the ORs increased in a graded manner over the intervals for both the binary and the GEE regressions. The polytomous model resulted with some unstable parameter estimates and is not reported. The ORs (95% CI)) for depressive symptoms at Year 5 were respectively, 1, 1.39 (1.03, 1.88), 1.89 (0.71, 5.02), and 3.20 (0.66, 15.54). In the GEE model, the ORs were respectively, 1, 1.09 (0.93, 1.29), 1.44 (0.80, 2.62), and 4.25 (1.79, 10.14). Tests of interaction of toenail selenium levels both as a continuous variable and as quintiles, with center, sex, race, smoking, and use of a supplement containing magnesium,

vitamin E, or beta carotene revealed significant or marginally significant interactions for center (p=0.02) and sex (p=0.02) under the polytomous model and for supplement usage under each of the approaches (p-values ranging from 0.01 to 0.28). In further analysis stratifying the polytomous model by center, the ORs for $\log_2$(selenium) for having 3 or more exams with depressive symptoms were highest for the Birmingham center (OR=4.31) and Oakland (OR=3.99), lower for Minnesota (OR=2.70), and lowest for Chicago (OR=1.49), When stratified by sex, the OR for women was 3.09 and for men was 2.06). Table 4 shows the ORs for the fully adjusted logistic, polytomous, and GEE models stratified by supplement use. In each case the associations were more strongly adverse for supplement users.

In sensitivity analyses using the cut-point of CES-D score ≥16 or taking an antidepressant medication, no associations of selenium with depressive symptoms were observed in any of the analytic approaches (data not shown). In a time to first depressive symptoms (CES-D ≥27 or taking antidepressant) event analysis excluding prevalent cases at Year 5, using $\log_2$(Selenium) as the exposure yielded a hazard ratio=1.20 (95%CI: 0.77, 1.88) with p=0.42. Interestingly, a quadratic term for $\log_2$(Selenium) added to the model was statistically significant (p=0.045). When we modeled selenium using the equal distance intervals, the highest interval, relative to the lowest, had a marginally significant hazard ratio=2.76 (95%CI: 0.88, 8.70), p=0.08. In the sensitivity analyses treating the CES-D score as a continuous outcome, there were only marginally significant positive associations for selenium when it was modeled as a continuous variable or when it was categorized into equal distance intervals (data not shown). In the sensitivity analysis assessment of whether high CES-D scores persist after 5 or 10 years and, if so, whether accounting for this persistence attenuates the association of selenium with depressive symptoms, we found in the modified GEE models (whether using equal distance categories, quintiles, or $\log_2$(Se)), the ORs of the indicators for first and second previous visits were high (~9.2 and ~4.1, respectively) and significant (both p<0.0001). The associations for $\log_2$(selenium) and for the highest interval of equal distance interval categorization were significant and not attenuated.

4. DISCUSSION

To our knowledge, this is the first study to demonstrate that higher selenium status is associated with greater odds of having depressive symptoms. This was apparent in three different statistical models, although we caution that the cohort was not free of prevalent cases of depressive symptoms at Year 2. One model related selenium exposure to prevalence of depressive symptoms at the examination closest in time to the measurement of the exposure. A second model which assumed four nominal outcome categories had OR=1.7 for the highest quintile of selenium exposure for having three or more exams with depressive symptoms. Finally, a GEE longitudinal model indicated that a doubling of the selenium level is associated with an OR=1.56 for presence of depressive symptoms. When this GEE model was rerun using 4 equal distance categories of selenium, the highest category had OR=4.25 for presence of depressive symptoms.

The ORs in many of the models presented were not trivial in magnitude equaling or exceeding 2 for $\log_2$(selenium) models.. It is interesting that the selenium-depressive symptoms association was very strong for repeated episodes of depressive symptoms over the course of 20 years. This finding raises additional questions about the temporal relation of selenium exposure with occurrence of depressive symptoms which can only be addressed with repeated measures of selenium exposure (Willett, 1998). For instance, it is possible that the selenium status measured at exam 2 has a moderate or even a strong tracking over the subsequent 23 years. A more recent measure of selenium status could then correlate with the exam 2 measure and this could account for a short latency. Alternatively, with moderate tracking over 23 years, cumulative exposure to selenium may account for an association over the long term. However, this study did not have the opportunity to collect repeated measures of selenium status.

A few small studies conducted in the UK and the US have suggested that selenium might have a beneficial effect on mood, but it must be emphasized that this benefit might be limited to persons with selenium deficiency. Collectively, the studies by Benton & Cook (1991), Hawkes & Hornbostel (1996), Finley & Penland (1998), Rayman et al. (2005), and Gosney et al. (2008) support this concept: improvements in mood or depression scores with supplementation were noted when the participants' baseline selenium status was low, and no improvements were observed when the baseline selenium status was judged higher (Hawkes & Hornbostel (1996), Rayman et al. (2005)).

Moreover, evidence of global variation in the biologically available selenium from soils (Combs, 2001) precludes generalizing results of selenium studies from one country to another. The selenium status of the UK has in general been judged to be lower than that of the US. The INTERMAP study (Zhou et al. 2003) estimated mean±SD selenium intakes were higher among US (153±78) mcg/day in men and 109±37 mcg/day in women) than among UK participants (110±41 mcg/day in men and 77±25 mcg/day in women). Combs (2001) reported the per capita dietary selenium intakes for different countries with estimates of 12–43 and 60–220 μg/person per day for England and the US, respectively. Thus, findings from studies conducted in the UK may not apply to the US. As noted, the UK Benton and Cook (1991) study concluded that selenium supplementation may benefit those who are in a state of deficiency. Since the selenium status of the US is in general deemed adequate (Combs, 2001), most CARDIA participants should be selenium replete.

Despite the replete status of the US, biogeochemical mapping (Subcommittee on Selenium, p. 24) demonstrates that selenium status in forages and grains varies by region of the US. This mapping (p. 24), published in 1983 – a few years prior to CARDIA examination 2 - indicates the presence of adequate selenium levels for the proximity of Birmingham, Alabama, low levels for Chicago, levels bordering between variable and adequate for Minneapolis, and variable levels for Oakland, California. Therefore, we tested for effect modification by center but only found it in the analysis of $\log_2$(selenium) under the polytomous regression model with Birmingham having the highest OR (4.31) and Chicago the lowest (1.49). It is likely that the food distribution system of the US prevents the low-selenium regions from having low selenium intake (National Academy of Sciences, p. 309), hence we did not observe a protective association for Chicago.

On the other hand, we observed more consistent effect modification by vitamin supplement use. Because we used supplementation with magnesium, vitamin E, or beta carotene as a proxy for selenium supplementation, our finding of a stronger association for supplement users should be interpreted with caution. Provided the association is not due to an unmeasured confounder, it raises questions about the chemical form and quality of the supplement. In the mid-1980s, while selenomethionine (SeMet), the preferred organic form, was available, sodium selenite and sodium selenate were also used and as late as 2001, the quality of some marketed supplements was deemed questionable (Schrauzer, 2001). Even today, the physical and chemical form, or speciation, of selenium supplements may not be identified by manufacturers, but only the total selenium content stated. As a result, chemical methods have been developed to identify and quantify speciation forms in selenium supplements (Güler et al., 2011; Zembrzuska et al., 2014). It is well recognized in the field of food chemistry that different species of selenium differ in bioavailability and bioactivity, and consequently, speciation as opposed to total selenium content, may influence the preventative, therapeutic, or toxic health effects of selenium (Thiry et al. (2012); Weekley & Harris (2013).

While the present study shows no protective association for depressive symptoms with selenium exposure, we hypothesize that this may be due to an excess of exposure in a selenium replete population. Nevertheless, findings from mouse models studied during the 1990's and in the last decade affirm the value of research evaluating selenium's potential antidepressant effect. The mouse studies during the 1990's suggested that selenium may have an effect on neurotransmission. Castano and colleagues compared the effect of a selenium-deficient diet to a control diet in rats and reported an increase in dopamine turnover in the substantia nigra (Castano et al., 1993), the hippocampus (Castano et al, 1995), and the prefrontal cortex (Castano et al. 1997) in the experimental rats. In the last decade, several organic selenium compounds, initially examined for antioxidant activities as they were known to be glutathione peroxidase mimetic agents (Savegnago et al. 2006), have been investigated for antidepressant-like effects in mouse models (Nogueira & Rocha, 2011). Ebselen (Posser et al., 2009), diphenyl diselenide (Savegnago et al., 2007), and bis selenide (Jesse et al., 2010) are toxic to mice and rats in large doses, but non-toxic at pharmacological doses (Nogueira & Rocha, 2011). The antidepressant-like activity of these compounds involves the serotonergic, noradrenergic and dopaminergic systems at various receptor sites. Specific sites of action have been summarized elsewhere (Nogueira & Rocha, 2011).

Limitations of this study include, most notably, a structured clinical interview was not used to assess depressive status of participants and neither CES-D scores nor any other measure of depressive symptoms were assessed at the Year 2 exam, so we could not exclude prevalent cases of depressive symptoms. Thus, causality cannot be inferred from this study. It is possible that prevalent depressive symptoms may have led to dietary changes that included higher intake of selenium. Additionally, similar to other observational studies, residual confounding and confounding from unknown and unmeasured factors cannot be completely excluded. Finally, some misclassification of depressive symptoms cases may have occurred if a participant did not fully understand for what condition he or she was

prescribed an antidepressant. However, the toenail biomarkers and study population make this study unique.

5.CONCLUSIONS

In a selenium replete population, higher toenail selenium levels were associated with higher odds of having a high level of depressive symptoms. Given the limitations of the current study, these findings need to be replicated in an independent cohort that has baseline information on depression or depressive symptoms. The beneficial and toxic roles of selenium and its narrow therapeutic range have been emphasized by others (Bleys et al., 2007; Nogueira & Rocha, 2011; Vinceti et al., 2009), as has the importance of selenium speciation (Thiry et al. (2012), Weekley & Harris (2013)). With this in mind, findings from animal models suggest the need for more research on the potential antidepressant role of organic selenium, particularly among those with severe selenium deficiency. In completed or ongoing clinical trials of selenium supplementation, secondary analyses with depression or depressive symptoms as an endpoint may be informative towards identifying neurotoxicity in a population. Future researchers investigating selenium exposure or selenium supplementation in relation to depressive symptoms as well as other chronic diseases should be cognizant that the narrow physiological range between toxicity and benefit is not yet well demarcated (Vinceti et al., 2009).

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Highlights

- Selenium (Se) exposure was assessed for associations with depressive symptoms.
- Depressive symptoms were assessed 5 times from 1990 to 2010 in 3,735 participants.
- A unit increase in log2(Se) had an odds ratio=2 for depressive symptoms in 1990.
- Longitudinally, the odds ratio was 1.6 per unit increase in log2(Se).
- Higher Se levels are associated with higher odds of having depressive symptoms.

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Table 1

Year 2 (1987) Characteristics of 3735 CARDIA Participants by Quintile of Toenail Selenium Levels,[a] CARDIA Trace Elements Study.

Characteristic	Q1	Q2	Q3	Q4	Q5	*P-value*
Se range (μg/g), men	0.52–0.72	0.72–0.78	0.78–0.84	0.84–0.92	0.92–1.98	
Se range (μg/g), women	0.52–0.77	0.77–0.83	0.83–0.90	0.90–0.99	0.99–1.85	
Age (years)	27.5 (3.6)	27.4 (3.6)	27.6 (3.6)	27.7 (3.7)	27.9 (3.6)	0.17
African American (%)	60.5	47.9	47.3	42.2	34.8	<0.001
Male (%)	44.9	45.0	44.9	45.0	45.0	>0.99
Body mass index (kg/m^2)	25.4 (5.5)	25.2 (5.1)	25.2 (5.4)	25.2 (5.4)	24.7 (5.1)	0.12
Cigarettes (no./day)	6.2 (9.9)	4.6 (8.8)	3.4 (7.2)	2.6 (6.5)	2.3 (6.5)	<0.001
Alcohol (ml/day)	16.3 (28.2)	12.1(21.8)	9.9 (17.1)	10.9 (21.9)	10.5(22.0)	<0.001
Total physical activity	381.2 (314.7)	375.9(276.5)	379.3(288.0)	387.3 (270.3)	386.5(270.6)	0.93
Education (years)	13.8 (2.3)	14.1 (2.3)	14.3 (2.3)	14.3 (2.4)	14.7 (2.4)	<0.001
Marital status:						0.91
Unmarried (%)	59.2	57.0	57.1	58.5	60.9	
Married (%)	31.2	32.9	33.3	31.7	30.1	
Separated, widowed, or divorced (%)	9.5	10.0	9.6	9.8	9.0	
Unemployed (%)	26.0	21.2	20.1	19.9	22.4	0.03
Difficulty paying for basics (%)	30.8	29.7	26.3	28.8	30.3	0.34
Center:						<0.001
Birmingham (%)	45.6	29.0	19.8	12.3	7.1	
Chicago (%)	21.0	21.2	19.3	20.5	16.2	
Minneapolis (%)	13.0	22.4	29.7	36.9	47.4	
Oakland (%)	20.4	27.4	31.3	30.3	29.3	
Toenail mass (mg)	23.4 (7.0)	23.5(42.4)	23.7 (6.5)	24.2 (6.0)	24.3 (6.1)	0.04
Taking supplement (%)	20.5	23.4	29.8	29.2	29.7	<0.001

CARDIA, Coronary Artery Risk Development in Young Adults

[a]Unless noted otherwise, data are expressed as mean (SD).

Table 2

Odds Ratios (95% CI) for Elevated Depressive Symptoms at Year 5 (1990) (CES-D ≥ 27 or Taking Antidepressant Medication) by Quintile of Toenail Selenium Levels, CARDIA Trace Element Study.

	Model 1[a]			Model 2[b]			Model 3[c]		
	Odds ratio	**95% CI**	**P-value**	**Odds ratio**	**95% CI**	**P-value**	**Odds ratio**	**95% CI**	**P-value**
Q1	1			1			1		
Q2	0.86	(0.54, 1.35)	0.50	0.91	(0.57, 1.44)	0.68	0.91	(0.57, 1.44)	0.68
Q3	1.04	(0.67, 1.62)	0.86	1.14	(0.73, 1.79)	0.56	1.21	(0.76, 1.90)	0.42
Q4	1.02	(0.65, 1.61)	0.93	1.13	(0.71, 1.80)	0.60	1.14	(0.71, 1.82)	0.58
Q5	1.37	(0.88, 2.13)	0.16	1.56	(1.00, 2.45)	0.05	1.59	(1.01, 2.51)	0.05
$Log_2(Se)$[d]	1.70	(0.94, 3.08)	0.08	1.99	(1.09, 3.61)	0.02	2.03	(1.12, 3.70)	0.02

CARDIA, Coronary Artery Risk Development in Young Adults; CI, confidence interval; CES-D, Center for Epidemiologic Studies Depression Scale.

[a] Adjusted for age, race, gender, and study center

[b] Adjusted for model 1 variables and body mass index, cigarettes per day, alcohol intake (milliliters per day), toenail mass (mg), and taking a supplement (yes/no)

[c] Adjusted for model 2 variables and education (years), employment status (2 categories: unemployed, employed), ability to pay for basics (2 categories: somewhat hard, hard, or very hard vs not very hard), marital status (3 categories: married, never married, and widowed, separated or divorced), total physical activity.

[d] A unit increase in $\log_2$(selenium) represents a doubling of the selenium level.

Table 3

Association of Quintiles of Selenium and $\log_2$(selenium) With No Exams With Elevated Depressive Symptoms (reference group), 1 Exam With Elevated Depressive Symptoms, 2 Exams with Elevated Depressive Symptoms, and 3 or More Exams With Elevated Depressive Symptoms, CARDIA Trace Elements Study, 1987–2010. (Elevated depressive symptoms: CES-D ≥ 27 or taking antidepressant medication)

	1 exam with elevated depressive symptoms						2 exams with elevated depressive symptoms						3 or more exams with elevated depressive symptoms					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	***Log2(Se)*** [a]	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***Log2(Se)*** [a]	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***Log2(Se)*** [a]
N [b]	92	99	97	91	99		47	37	29	41	46		32	30	37	35	52	
Model 1 [c]	1.00	1.06 (0.77, 1.44) 0.74	1.00 (0.73, 1.38) 0.98	0.93 (0.67, 1.30) 0.68	1.05 (0.75, 1.46) 0.78	0.95 (0.60, 1.49) 0.81	1.00	0.75 (0.47, 1.17) 0.20	0.57 (0.35, 0.93) 0.02	0.80 (0.50, 1.26) 0.33	0.92 (0.58, 1.46) 0.73	1.19 (0.62. 3.30) 0.60	1.00	0.97 (0.54, 1.52) 0.70	1.08 (0.65, 1.80) 0.76	1.00 (0.60, 1.69) 0.99	1.50 (0.91, 2.48) 0.11	2.27 (1.18, 4.36) 0.01
Model 2 [d]	1.00	1.12 (0.82, 1.54) 0.48	1.11 (0.80, 1.54) 0.53	1.06 (0.76, 1.49) 0.72	1.23 (0.87, 1.72) 0.24	1.17 (0.74, 1.85) 0.50	1.00	0.75 (0.48, 1.19) 0.22	0.58 (0.35, 0.95) 0.03	0.81 (0.51, 1.29) 0.38	0.96 (0.60, 1.54) 0.87	1.28 (0.66, 2.50) 0.59	1.00	0.96 (0.57, 1.63) 0.89	1.19 (0.71, 1.99) 0.50	1.15 (0.67, 1.95) 0.62	1.75 (1.05, 2.92) 0.03	2.76 (1.43, 5.33) 0.002
Model 3 [e]	1.00	1.13 (0.82, 1.55) 0.46	1.15 (0.83, 1.60) 0.39	1.08 (0.77, 1.51) 0.67	1.26 (0.89, 1.77) 0.19	1.21 (0.76, 1.91) 0.42	1.00	0.75 (0.48, 1.19) 0.22	0.59 (0.36, 0.97) 0.04	0.81 (0.51, 1.29) 0.37	0.97 (0.61, 1.55) 0.90	1.30 (0.67, 2.54) 0.44	1.00	0.97 (0.57, 1.65) 0.92	1.25 (0.75, 2.10) 0.39	1.16 (0.68, 1.98) 0.59	1.73 (1.04, 2.89) 0.04	2.70 (1.39, 5.22) 0.003

CARDIA, Coronary Artery Risk Development in Young Adults; CES-D, Center for Epidemiologic Studies Depression Scale.

Data are OR (95% CI), p-value.

[a] A unit increase in $\log_2$(Selenium) represents a doubling of the selenium level.

[b] Ns for no exams with elevated depressive symptoms in Q1 through Q5, respectively: 575, 581, 585, 580, 550

[c] Adjusted for age, race, gender, and study center

[d] Adjusted for model 1 variables and body mass index, cigarettes per day, alcohol intake (milliliters per day), toenail mass (mg), and taking a supplement (yes/no)

[e] Adjusted for model 2 variables and education (years), employment status (2 categories: unemployed, employed), ability to pay for basics (2 categories: somewhat hard, hard, or very hard vs not very hard), marital status (3 categories: married, never married, and widowed, separated or divorced), total physical activity.

Table 4

Fully Adjusted Association of Quintiles of Selenium and Log_2(selenium) With Elevated Depressive Symptoms in Three Statistical Models Stratified by Supplement Usage. CARDIA Trace Elements Study, 1987–2010.

		Q1	Q2	Q3	Q4	Q5	Log_2(Se)
Logistic Regression[a]							
	Supplement non-users	1.00	0.83 (0.49,1.38), 0.46	1.27 (0.77, 2.08), 0.35	1.06 (0.63, 1.78), 0.84	1.31 (0.78, 2.18), 0.31	1.32 (0.66, 2.65), 0.44
	Supplement users	1.00	1.29 (0.40, 4.18), 0.68	1.03 (0.30, 3.53), 0.96	1.72 (0.54, 5.44), 0.36	3.27 (1.08, 9.96), 0.04	7.64 (2.31, 25.34), 0.0009
Polytomous logistic regression[a,b]							
	Supplement non-users						
	1 exam with depressive symptoms	1.00	1.22 (0.85, 1.75), 0.28	1.20 (0.82, 1.77), 0.34	1.20 (0.81, 1.77), 0.37	1.23 (0.83, 1.84), 0.31	1.18 (0.69, 2.01), 0.56
	2 exams with depressive symptoms	1.00	0.68 (0.40, 1.15), 0.15	0.75 (0.43, 1.30), 0.30	0.74 (0.43, 1.30), 0.29	0.95 (0.55, 1.65), 0.86	1.12 (0.51, 2.47), 0.78
	3 or more exams with depressive symptoms	1.00	0.83 (0.44, 1.57), 0.56	1.51 (0.83,2.74), 0.17	1.55 (0.84, 2.87), 0.16	1.48 (0.79, 2.77), 0.22	2.31 (1.04, 5.14), 0.04
	Supplement users						
	1 exam with depressive symptoms	1.00	0.83 (0.42, 1.64), 0.59	0.97 (0.51, 1.83), 0.92	0.77 (0.39, 1.52), 0.46	1.22 (0.63, 2.37), 0.56	1.27 (0.52, 3.11), 0.61
	2 exams with depressive symptoms	1.00	0.99 (0.37, 2.61), 0.98	0.27 (0.08, 0.96), 0.04	1.01 (0.39, 2.60), 0.99	1.06 (0.40, 2.80), 0.91	2.11 (0.60, 7.38), 0.24
	3 or more exams with depressive symptoms	1.00	1.38 (0.51, 3.74), 0.53	0.86 (0.30, 2.50), 0.79	0.56 (0.17, 1.79), 0.32	2.33 (0.89, 6.14), 0.09	3.85 (1.20,12.39), 0.02
GEE regression[c]							
	Supplement non-users	1.00	0.85 (0.64, 1.13), 0.25	1.10 (0.82, 1.47), 0.53	1.03 (0.77, 1.39), 0.82	1.10 (0.82, 1.49), 0.52	1.29 (0.85, 1.97), 0.24
	Supplement users	1.00	1.19 (0.72, 1.97), 0.50	0.83 (0.49, 1.43), 0.50	0.94 (0.57, 1.57), 0.82	1.61 (0.98, 2.67), 0.06	2.51 (1.20, 5.25), 0.01

CARDIA, Coronary Artery Risk Development in Young Adults

Data are OR (95% CI), p-value.

[a] Adjusted for age, race, gender, and study center, body mass index, cigarettes per day, alcohol intake (milliliters per day), toenail mass (mg), education (years), employment status (2 categories: unemployed, employed), ability to pay for basics (2 categories: somewhat hard, hard, or very hard vs not very hard), marital status (3 categories: married, never married, and widowed, separated or divorced), total physical activity.

[b] Reference group is participants who had no exams with elevated depressive symptoms

[c] Adjusted for age, race, gender, study center, and visit year and time dependent body mass index, cigarettes per day, alcohol intake (milliliters per day), toenail mass (mg), education (years), employment status (2 categories: unemployed, employed), income (2 categories: <$16K vs ≥$16K), marital status (3 categories: married, never married, and widowed, separated or divorced), total physical activity.