Optimization of selenoprotein P and other plasma selenium biomarkers for the assessment of the selenium nutritional requirement: a placebo-controlled double-blind study of selenomethionine supplementation in selenium-deficient Chinese subjects1–4

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ABSTRACT

Background: The intake of selenium needed for optimal health has not been established. Selenoproteins perform the functions of selenium, and the selenium intake needed for their full expression is not known.

Objective: This study sought to determine the intake of selenium required to optimize plasma selenoprotein P (SEPP1) and to compare SEPP1 with other plasma selenium biomarkers.

Design: A 40-wk placebo-controlled, double-blind study of selenium repletion was carried out in 98 healthy Chinese subjects who had a daily dietary selenium intake of 14 μg. Fourteen subjects each were assigned randomly to daily dose groups of 0, 21, 35, 55, 79, 102, and 125 μg Se as L-selenomethionine. Plasma glutathione peroxidase (GPX) activity, SEPP1, and selenium were measured. A biomarker was considered to be optimized when its value was not different from the mean value of the subjects receiving larger supplements.

Results: The SEPP1 concentration was optimized at 40 wk by the 35-μg supplement, which indicated that 49 μg/d could optimize it. GPX activity was optimized by 21 μg (total ingestion: 35 μg/d). The selenium concentration showed no tendency to become optimized.

Conclusions: The present results indicate that SEPP1 concentration was the best plasma biomarker studied for assessing optimal expression of all selenoproteins, because its optimization required a larger intake of selenium than did GPX activity. On the basis of the selenium intake needed for SEPP1 optimization with adjustments for body weight and individual variation, ≈75 μg Se/d as selenomethionine is postulated to allow full expression of selenoproteins in US residents. This trial was registered at clinicaltrials.gov as NCT00428649.

INTRODUCTION

Selenium is an essential micronutrient that is toxic when ingested in excess. Severe selenium deficiency, as it occurred in parts of China until the 1980s, allowed the development of a childhood cardiomyopathy known as Keshan disease (1–3). Moderate selenium deficiency persists in some areas of China, and milder deficiency occurs in Europe and other parts of the world. The health significance of these less-than-severe deficiencies is not clear.

Despite a lack of evidence that even mild selenium deficiency occurs in the United States, there has been enthusiasm for selenium supplementation with the aim of preventing cancer and other diseases. This has led to inclusion of selenium in multivitamin products at levels higher than the Recommended Dietary Allowance (RDA) and its addition at even higher levels to nutritional supplements that are marketed directly to consumers. Outbreaks of selenium poisoning have apparently been caused by errors in the formulation of these products (4, 5). In addition, it has been suggested that long-term selenium supplementation might have adverse health effects (6, 7).

To determine the selenium intake that supports optimal health, intervention trials with health-related endpoints are needed. SELECT, a trial in which selenium-replete men received selenium supplements, was such a trial (8). Its primary endpoint was the development of prostate cancer, and selenium did not affect that endpoint. Arguments have been made, however, that men with lower plasma selenium concentrations should have been studied or that different chemical forms of selenium should have been administered (9, 10). Trials such as SELECT are complex and expensive. Therefore, knowledge of selenium biology and biomarkers is needed for their design.

Selenium exerts its biological functions through selenoproteins. In the human genome, 25 genes encode selenoproteins that have a variety of functions (11). Two selenoproteins, seleno-
protein P (SEPP1) and glutathione peroxidase-3 (GPX3), are present in plasma and can be used as biomarkers of selenium nutritional status (12, 13).

In 2001, we carried out a study in a low-selenium area of China with the aim of determining the minimum selenium intake needed to optimize selenoproteins. We used plasma SEPP1 concentration and glutathione peroxidase (GPX) activity as biomarkers for the selenoproteins in the body (14). Plasma GPX activity was optimized by the intake of 47 μg Se/d for 20 wk, supporting the results of a Chinese study in which optimization had been observed at an intake of 41 μg/d (15). That Chinese study had been used to set the present US RDA for selenium at 55 μg (16).

Despite selenium intakes as high as 71 μg/d for 20 wk, optimization of SEPP1 was not achieved in the 2001 study (14). Because one of the plasma biomarkers had not been optimized, it could not have been expected that all other selenoproteins in the body had been optimized. Thus, it was clear that a higher dose of selenium or a longer supplementation period was needed to optimize SEPP1.

Because the results of the 2001 study were compatible with the need for a higher selenium RDA but did not allow its estimation, we performed another repletion study in 2007 and report on it here. The new trial achieved optimization of SEPP1. It showed the responses of each plasma selenium biomarker to supplementation and, importantly, provided data suitable for estimating the human selenium requirement.

SUBJECTS AND METHODS

Study subjects
The subjects in this study were farmers in Mianning County (2006 population: 342,824) of Liangshan Prefecture in Sichuan Province. This county has a long history of selenium deficiency and was the site in 1974–1976 of a study showing that selenium supplementation prevents Keshan disease (17).

Village staff announced the study, and 186 volunteers contributed blood samples in November 2006. Selenium concentrations in plasma, measured at the Sichuan Center for Disease Control and Prevention in Chengdu, ranged from 18 to 130 μg/L with outliers of 300 and 335 μg/L. Subjects with plasma selenium concentrations >79 μg/L and 2 volunteers with chronic health problems, as determined by medical history and physical examinations, were removed from consideration; 98 healthy subjects were chosen from the remaining 175 subjects for study based on the locations of their dwellings to facilitate tablet delivery. Informed consent was obtained, and subjects were paid when they completed the study.

Dietary selenium intake
A nutrition survey of a sample of the study subjects was carried out in November 2006 by using a food-frequency questionnaire and local food tables. The survey estimated daily dietary selenium intakes of 16.5 ± 3.0 μg for men (n = 17) and 13.4 ± 2.8 μg for women (n = 23). An additional estimation of selenium intake was made by using a formula relating whole-blood selenium to intake (18). Selenium intakes of 13.3 ± 3.1 μg for men (n = 45) and 12.6 ± 2.8 μg for women (n = 53) were predicted. The selenium intakes obtained with these 2 methods differ only slightly, and their average is 14 μg/d. This value was used as the dietary selenium intake of the subjects.

Selenium supplements
The form of selenium administered was l-selenomethionine, henceforth referred to as selenomethionine. It was a gift from V Badmaev of Sabinsa Corp (Piscataway, NJ). Richard B Moon of Pharmacy Innovations (Jamestown, NY) compounded the tablets with a filler of magnesium stearate 1%, tablet premix 99%, and a trace amount of FD&C yellow number 5. The tablet premix consisted of colloidal silicon dioxide 2% and fine-grade microcrystalline cellulose 98%. The amounts of selenium intended to be in the supplements were 0, 20, 40, 60, 80, 100, and 120 μg per tablet. Ten tablets of each dose were assayed in our laboratory, and they contained a mean (±SD) of 0, 21 ± 2.7, 35 ± 2.7, 55 ± 6.5, 79 ± 3.9, 102 ± 7.2, and 125 ± 11 μg Se.

Each dose-amount group was assigned 14 subjects. Ten bottles containing 28 tablets each were prepared for each subject and labeled with a subject number chosen by using shuffled cards, on each of which was written a subject number. A document that linked subject numbers with selenium doses was prepared and sealed by 2 persons who were otherwise not involved in the study. The document was not opened until all assays had been performed.

Study protocol
The study was conducted from 18 March through 24 December 2007. The subjects were brought from their villages to the Center for Disease Control and Prevention in Mianing City on 18 March 2007 (the initiation of the study) and 4, 8, 12, 16, 20, 24, 32, and 40 wk later. All subjects were studied on the same day at each time point. On the first visit, subjects were assigned numbers from 1 to 98 that determined which selenium supplement they would receive for the entire 40 wk. Height, weight, and blood pressure were determined and recorded along with age and sex.

Blood (20 mL) was sampled by venipuncture at each visit before the daily study tablet was administered. The blood was treated with 1 mg disodium EDTA/mL, and plasma was separated by centrifugation for 15 min at 2000 × g. Plasma was frozen at liquid nitrogen temperature and transported to Chengdu, where it was stored at −70°C until it was shipped to Nashville on dry ice. In Nashville, the de-identified samples were maintained at −80°C until the assays were carried out.

Between visits, tablets were administered each day by 3 village residents under the supervision of a staff member of the Mianing Center for Disease Control and Prevention. This method was adopted to ensure compliance and safety. No important adverse effects were detected. The Ethical Review Committee (Institutional Review Board) of the Sichuan Center for Disease Control and Prevention and the Institutional Review Board at Vanderbilt University approved this protocol.

Assays
Plasma samples stored at −80°C were thawed and used the same day for measurement of SEPP1 and GPX activity. SEPP1 concentrations were measured by using an enzyme-linked immunosorbent assay developed in our laboratory (19). Plasma
Sample size and statistical analysis

The goal of this study was to determine the daily selenium requirement of healthy persons. The primary endpoint was prespecified as the mean plasma SEPP1 concentration after 40 wk of selenium supplementation. We planned to compare this endpoint among 7 groups randomly assigned to receive different amounts of selenium. Our previous research (14) suggested that there would be a plateau in the plasma SEPP1 concentration for amounts of selenium. Our previous research (14) suggested that, in the participants there would be a plateau in the plasma SEPP1 concentration for the next lowest dose, we were interested in detecting a 25% decrease in plasma SEPP1 concentrations, which was 4.2 mg/L. For the previous study (14, 23). We estimated that, in the participants the mean would be 5.6 mg/L with an SD of 1.0 mg/L. For the sample size required to detect a statistically significant difference at 40 wk was predetermined on the basis of our previous study (14, 23). We estimated that, in the participants with the lowest dose that provided optimization of plasma SEPP1, the mean would be 5.6 mg/L with an SD of 1.0 mg/L. For the next lowest dose, we were interested in detecting a 25% decrease in plasma SEPP1 concentrations, which was 4.2 mg/L. A sample size of 11 in each group was required to detect a statistically significant difference in means of 1.4, on the assumption that the common SD is 1.0 with a 2-group t test with a 2-sided significance level of 0.05 and 87% power. To account for potential dropouts in each group, we estimated that 14 persons in each of the 7 arms of the study, or 98 in all, would be required. Of the 98 randomly assigned subjects, one had initial selenium biomarkers >2 SD above the mean of the group and was excluded from the analysis before the code was broken. Another subject became pregnant, and a third moved from the study area. Thus, results from 95 subjects were analyzed.

After the code was broken, we compared baseline selenium biomarkers and other characteristics of the participants to assess the effectiveness of the randomization (Table 1). No significant differences were found for these baseline factors between the 7 groups.

Table 1
Baseline comparison of intervention and control groups by selenium dose

<table>
<thead>
<tr>
<th>Selenium dose</th>
<th>Placebo (n = 14)</th>
<th>21 µg/d (n = 14)</th>
<th>35 µg/d (n = 14)</th>
<th>55 µg/d (n = 13)</th>
<th>79 µg/d (n = 12)</th>
<th>102 µg/d (n = 14)</th>
<th>125 µg/d (n = 14)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>37.7 ± 6.6&lt;sup&gt;2&lt;/sup&gt;</td>
<td>39.8 ± 6.1</td>
<td>35.2 ± 7.1</td>
<td>35.9 ± 7.6</td>
<td>37.9 ± 7.9</td>
<td>36.1 ± 6.2</td>
<td>36.0 ± 4.2</td>
<td>0.62&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Female (%)</td>
<td>64</td>
<td>43</td>
<td>50</td>
<td>54</td>
<td>60</td>
<td>60</td>
<td>71</td>
<td>0.78&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161.4 ± 8.2</td>
<td>162.2 ± 7.2</td>
<td>163.2 ± 8.5</td>
<td>160.8 ± 8.4</td>
<td>160.4 ± 6.8</td>
<td>163.1 ± 6.8</td>
<td>159.4 ± 7.3</td>
<td>0.90&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>57.4 ± 9.1</td>
<td>57.0 ± 9.1</td>
<td>58.4 ± 9.0</td>
<td>59.3 ± 5.6</td>
<td>57.5 ± 7.6</td>
<td>58.2 ± 6.7</td>
<td>56.7 ± 6.8</td>
<td>0.98&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>40.3 ± 3.2</td>
<td>41.4 ± 3.0</td>
<td>41.0 ± 3.2</td>
<td>42.7 ± 3.0</td>
<td>40.8 ± 4.7</td>
<td>40.9 ± 3.9</td>
<td>39.9 ± 3.4</td>
<td>0.66&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>112 ± 12</td>
<td>118 ± 10</td>
<td>111 ± 12</td>
<td>116 ± 10</td>
<td>118 ± 15</td>
<td>117 ± 19</td>
<td>111 ± 9.3</td>
<td>0.60&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>73 ± 8.9</td>
<td>73 ± 7.7</td>
<td>73 ± 8.8</td>
<td>75 ± 7.8</td>
<td>74 ± 10</td>
<td>75 ± 9.7</td>
<td>72 ± 8.1</td>
<td>0.99&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plasma selenium (µg/L)</td>
<td>37.3 ± 9.8</td>
<td>37.8 ± 8.5</td>
<td>35.4 ± 7.7</td>
<td>34.9 ± 7.2</td>
<td>40.9 ± 7.2</td>
<td>35.3 ± 6.3</td>
<td>38.5 ± 6.5</td>
<td>0.37&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>SEPP1 (mg/L)</td>
<td>1.96 ± 0.73</td>
<td>1.92 ± 0.59</td>
<td>1.81 ± 0.47</td>
<td>1.86 ± 0.76</td>
<td>2.08 ± 0.71</td>
<td>1.80 ± 0.48</td>
<td>1.96 ± 0.64</td>
<td>0.92&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plasma GPX activity (U/L)</td>
<td>67 ± 16</td>
<td>76 ± 19</td>
<td>67 ± 16</td>
<td>57 ± 16</td>
<td>65 ± 20</td>
<td>61 ± 14</td>
<td>70 ± 12</td>
<td>0.14&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup> BP, blood pressure; SEPP1, selenoprotein P; GPX, glutathione peroxidase.
<sup>2</sup> Mean ± SD (all such values).
<sup>3</sup> Kruskal-Wallis test.
<sup>4</sup> Pearson’s chi-square test.
pattern. Thus, it is not clear whether the seasonal variation was caused by differences in selenium intake or by other factors.

### Responses of plasma selenoproteins to supplementation

Plasma GPX activity, which reflects the activity of GPX3, was more variable than the other biomarkers, especially at the initial time point (Figure 1A; see supplemental Table S1 under “Supplemental data” in the online issue). All supplement groups were indistinguishable statistically at 20 wk and beyond, however. Thus, this biomarker was optimized by 21 μg Se/d—the smallest supplement that was used. Combining that supplement with a dietary intake of 14 μg Se/d allows the conclusion that 35 μg Se/d optimized this selenium-dependent activity. Earlier studies using this activity as an end-point had similar outcomes (14, 15).

SEPP1 optimization required higher selenium doses and longer supplementation times than did optimization of GPX activity (Figure 1B; see supplemental Table S2 under “Supplemental data” in the online issue). SEPP1 concentrations in subjects who received the highest 3 doses, 79–125 μg, increased rapidly into the range of values of selenium-replete US residents and were not different from one another at 8 wk (Figure 1B). SEPP1 concentrations in the groups receiving lower doses increased with time so that by the end of the trial only the placebo and 21-μg groups remained significantly different from the higher dose groups.

At 40 wk, the average SEPP1 concentration for the group who received the 35-μg selenium supplement was not significantly different from the concentrations of groups who received higher doses of selenium. Thus, a total daily intake of 49 μg Se for 40 wk optimized plasma SEPP1 concentration in the study subjects. If the trial had been terminated at 32 wk, the lowest total intake optimizing SEPP1 would have been 69 μg Se and at 16 wk it would have been 93 μg. These results indicate that the length of the supplementation period as well as the dose of selenium affects the optimization of SEPP1.

### Response of plasma selenium concentration to supplementation

The plasma selenium concentration responded differently to supplementation than did selenoprotein values. The plasma selenium values reflected the supplementation dose at all time points, with no indication of optimization (Figure 2 and Figure 3; see supplemental Table S3 under “Supplemental data” in the online issue).

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**TABLE 2**

Characteristics of participants at the beginning of the study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>37 ± 7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162 ± 8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58 ± 8</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>41 ± 4</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>115 ± 13</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>73 ± 9</td>
</tr>
</tbody>
</table>

1 All values are means ± SDs.

**TABLE 3**

Plasma biomarkers of selenium status at the beginning of the study

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
<th>P2</th>
<th>All subjects</th>
<th>Nashville subjects</th>
<th>Percentaged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selenoprotein P (mg/L)</td>
<td>1.9 ± 0.7</td>
<td>2.0 ± 0.6</td>
<td>0.21</td>
<td>1.9 ± 0.6</td>
<td>5.3 ± 0.9</td>
<td>36</td>
</tr>
<tr>
<td>Glutathione peroxidase activity (U/L)</td>
<td>68 ± 17</td>
<td>64 ± 17</td>
<td>0.23</td>
<td>66 ± 17</td>
<td>159 ± 32</td>
<td>42</td>
</tr>
<tr>
<td>Selenium (μg/L)</td>
<td>37 ± 8</td>
<td>37 ± 7</td>
<td>0.72</td>
<td>37 ± 8</td>
<td>122 ± 13</td>
<td>30</td>
</tr>
</tbody>
</table>

1 n values as shown in Table 1.
2 Comparisons between men and women were made by using Wilcoxon’s rank-sum test.
3 Values taken from reference 19; n = 81 for selenoprotein P and selenium and 62 for glutathione peroxidase activity.
4 Values in the present study as a percentage of the values in the Nashville study.
5 Mean ± SD (all such values).
online issue). Thus, the plasma selenium concentration did not become saturated, as did the 2 selenoproteins. This indicated that the plasma selenium concentration reflects a nonsaturable pool of selenium in addition to the selenium in SEPP1 and GPX3 (Figure 4). Because of this, the plasma selenium concentration cannot be used to estimate the selenium intake required to optimize selenoproteins in the body.

DISCUSSION

Optimization of SEPP1 required the intake of more selenium than did optimization of GPX activity (Figure 1). This difference reflects selenium metabolism in the tissues that synthesize these selenoproteins. Kidney proximal tubule cells synthesize most of the GPX3 in plasma (13). Those cells have a privileged receptor-mediated supply of selenium (26, 27) and thus are not representative of most tissues in the body. On the other hand, the liver, which synthesizes most of the SEPP1 in plasma, regulates whole-body selenium transport and homeostasis (28). These physiologic considerations are compatible with plasma SEPP1 reflecting the selenium status of the whole organism better than plasma GPX activity.

The plasma selenium concentration is often used as a selenium biomarker, but its response to selenium supplementation is different from the response of selenoproteins, as shown in Figures 1 and 2. The plasma selenium concentration includes the selenium of the 2 plasma selenoproteins and the selenium in selenomethionine that substitutes nonspecifically for methionine in proteins (Figure 4). Selenomethionine is not a participant in regulated selenium metabolism; its contribution to plasma selenium depends largely on the amount of selenomethionine ingested (29).

When optimized, SEPP1 and GPX3 together contain \( \approx 80–90 \ \mu g \ Se/L \) plasma (30). Thus, a plasma selenium concentration \( < 80 \ \mu g/L \) indicates that selenoproteins are not optimized, as was the case at the beginning of the present study (Table 3). When the plasma selenium concentration is >90 \( \mu g/L \), selenoproteins are usually optimized and the selenium in plasma >90 \( \mu g/L \) reflects selenomethionine (Figures 2 and 4). Therefore, the plasma selenium concentration is a useful biomarker for the intake of selenomethionine, as illustrated in Figure 2 and as discussed in detail previously (19). It is not, however, a precise biomarker for selenoproteins.

The values in Figure 1B indicate that both the duration and dose of supplementation were important in optimizing the SEPP1 concentration. For example, the 3 largest doses optimized SEPP1 by 8 wk. Smaller doses required longer times of supplementation to achieve optimization and the smallest supplement, 21 \( \mu g/d \), did not optimize the SEPP1 concentration. This pattern of increasing SEPP1 concentrations over the course of the study in subjects receiving the lower-dose supplements is compatible with the sequential filling of selenium pools—possibly representing sequential optimization of pools of selenoproteins. There is ample evidence for differential responses of selenoproteins to the supply of selenium. Some tissues, including brain, testis, and kidney, have receptor-mediated uptake of selenium (31) and optimize their selenoproteins under low-selenium conditions. Even within tissues, there is a “hierarchy” of selenoproteins with respect to selenium supply (32). Thus, the increase in SEPP1 concentration over the entire supplementation period is compatible with its representation of selenoproteins throughout the body, supporting its value as a biomarker for all selenoproteins.

Supplementation with 35 \( \mu g \ Se/d \) for 40 wk optimized the SEPP1 concentration in this healthy selenium-deficient population (Figure 1B). By combining the 35 \( \mu g \) supplement with the 14 \( \mu g \) dietary intake, we concluded that an intake of 49 \( \mu g \ Se/d \) optimized the plasma SEPP1 concentration in this population. GPX activity was optimized by a total intake of 35 \( \mu g/d \). If SEPP1 is accepted as a biomarker for all selenoproteins and optimization of selenoproteins is considered to signify that the supply of selenium is adequate, these results will be useful in estimating the selenium requirement. Adjustment for the difference in weight between the Chinese subjects (58 kg) and US residents (76 kg) and

![Figure 2](image2.png)

**FIGURE 2.** Mean plasma selenium concentrations in 12–14 selenium-deficient subjects supplemented for 40 wk with selenium as selenomethionine or with placebo. Variation is shown in Figure 3. At every time point, each group is significantly different from the mean value of subjects receiving larger supplements. The values used to construct this figure and their SDs are shown in Table S3 under “Supplemental data” in the online issue.
for variation among individuals would yield a selenium requirement for US adults of ~75 µg/d. Thus, if SEPP1 were used as the nutritional biomarker for selenium, the RDA would likely be increased from its present value of 55 µg/d for adults.

Studies in Europe and New Zealand, where daily selenium intakes are commonly 60 µg or less, have shown that plasma selenoprotein values are lower than in the United States. In addition, administration of selenium caused an increase in selenoproteins to US values (33–36), which indicated that selenium intake in those countries is not adequate to optimize selenoproteins and, therefore, that the people in those countries are mildly selenium deficient. As shown in this study, people in some areas of China are even more selenium deficient than are those in Europe and New Zealand. Thus, mild-to-moderate selenium deficiency occurs in several parts of the world, and intervention studies with health-related endpoints need to be carried out in those areas to assess the need for selenium supplementation.

Selenoproteins are optimized in residents of the United States because their dietary selenium intakes are >80 µg/d (16), and supplementation with selenium does not affect plasma selenoproteins (19). Unless a salutary biological effect of selenium in addition to supporting selenoprotein synthesis can be identified, no scientific rationale can be presented for supplementing people in the United States whose selenoproteins are optimized.

The authors’ responsibilities were as follows—RFB: full access to all of the data and responsibility for the integrity of the data and the accuracy of data analysis; RFB and YY: study concept and design; PL, JX, DZ, AKM, and KEH: data acquisition; DWB, LW, YY, RFB, and KEH: data analysis and interpretation; RFB, YY, KEH, and DWB: drafting of the manuscript; PL, JX, DZ, AKM, and LW: critical revision of the manuscript for important intellectual content; DWB and LW: statistical analysis; and YY, JX, PL, and KEH: study supervision. None of the authors had a conflict of interest or financial interest regarding the material reported in this article.

REFERENCES


