Methods of assessment of selenium status in humans: a systematic review 1–5

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ABSTRACT

Background: To understand the effect of selenium intake on health, it is important to identify sensitive and population-specific biomarkers of selenium status.

Objective: The objective of this systematic review was to assess the usefulness of biomarkers of selenium status in humans.

Design: The methods included a structured search strategy on Ovid MEDLINE, EMBASE (Ovid), and Cochrane databases; formal inclusion and exclusion criteria; data extraction into an Access database; validity assessment; and meta-analysis.

Results: The data from 18 selenium supplementation studies (of which 9 were randomized controlled trials and 1 was considered to be at low risk of bias) indicate that plasma, erythrocyte, and whole-blood selenium, plasma selenoprotein P, and plasma, platelet, and whole-blood glutathione peroxidase activity respond to changes in selenium intake. Although there is a substantial body of data for plasma selenium, more large, high-quality, randomized controlled trials are needed for this biomarker, as well as for the other biomarkers, to explore the reasons for heterogeneity in response to selenium supplementation. There was insufficient evidence to assess the usefulness of other potential biomarkers of selenium status, including urinary selenium, plasma triiodothyroxine/thyroxine ratio, plasma thyroxine, plasma total homocysteine, hair and toenail selenium, erythrocyte, and muscle glutathione peroxidase activity.

Conclusions: For all potentially useful biomarkers, more information is needed to evaluate their strengths and limitations in different population groups, including the effects of varying intakes, the duration of intervention, baseline selenium status, and possible confounding effects of genotype. Am J Clin Nutr 2009;89:1–15.

Clinical signs of selenium deficiency include Keshan disease, a cardiomyopathy mainly affecting young children and women of childbearing age, which is apparent in areas of China in populations with particularly low intakes (<15 μg/d) (6). Selenium status has also been inversely associated with other health problems, including cancer, infertility, impaired immune function (7), and mortality (8, 9). However, as there is a relatively narrow range of selenium intake between toxicity (>900 μg/d) and deficiency (<30 μg/d), functional biomarkers are critical for estimating intakes that are associated with risks and benefits to health.

Selenium is incorporated into 25 selenoproteins (10) with activities including protection against lipid peroxidation, thyroid hormone metabolism (7), T cell immunity (11), and modulation of inflammatory response (12). The most abundant selenoproteins in blood are selenoprotein P, which accounts for ~50% of plasma selenium (13, 14), and GPx, which accounts for 10–30% of plasma selenium (14).

For this systematic review, we considered the forms of selenium employed in supplementation studies that would represent dietary selenium. Selenomethionine is an organic form of selenium that is widely found in foods and in selenium-enriched yeast sold as selenium supplements, whereas inorganic selenium, such as selenite, is not naturally present in the diet and is metabolized differently (15). For this reason, studies involving supplementation with selenite were not accepted for this review. In relation to the minimum time period required to observe a change in selenium status, it has been shown that plasma selenoprotein P

INTRODUCTION

Dietary recommendations for selenium are currently based on the quantity of selenium required to optimize the activity of glutathione peroxidase (GPx), an enzyme involved in antioxidant defense. Selenium is found predominantly as selenomethionine and selenocysteine in foods such as bread, cereals, nuts, meat, fish, and other seafood, but the amount and the type of selenium in foods varies greatly and depends on the soil selenium content and composition (1, 2). Because the distribution of selenium in soil varies, there are regions in the world where the recommended intakes are exceeded [including regions of China (3) and the United States (4)] and regions where the recommended intakes are not met [including large parts of Europe (4, 5)].

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2 Presented at the EURRECA workshop “Biomarkers of Micronutrient Status,” held in Sveti Stefan, Montenegro, 9 June 2008.

3 This manuscript does not necessarily reflect the views of the Commission of the European Communities and in no way anticipates their future policy in this area.

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attained a maximal response after 4 wk in individuals supple-
mented with 200 μg Se/d as selenium-enriched yeast (16),
whereas platelet GPx reached a plateau at 45 d (~6 wk) and
urinary selenium at 30–60 d in individuals supplemented with
100 μg Se/d as selenomethionine (17). Plasma selenium can take
longer to reach a plateau and was still rising 60 d from the start
of an intervention in which individuals were given 100 μg Se/d
(17). We therefore selected 6 wk as the minimum period for
intervention because we considered it sufficient for changes to
occur in most recognized indexes of selenium status, even if
they have not yet reached a plateau.

The aim of this review was to assess the usefulness of com-
monly employed biomarkers of selenium status in humans. The
primary question to be answered by this review was: Which
measures (biomarkers) of selenium status appropriately reflect
change in selenium status over ≥6 wk?

METHODS

A general or main methodology was developed for this series
of reviews (18), and specific methodologies used for this review
that focus on differences from the main methodology are briefly
described below.

Types of study

To be included, a study needed to meet all of the following
criteria: 1) a controlled trial of selenium (including supple-
mentation with selenomethionine or selenium-enriched yeast or
selenium depletion); 2) reported selenium status at baseline and
after supplementation or depletion; 3) supplementation or de-
pletion lasting for ≥6 wk; 4) healthy human adults as partic-
ipants (excluded when participants were elderly, pregnant, or
postmenopausal women, unless stated otherwise); 5) written in
English; and 6) data presented in a usable format.

Search strategy

Electronic searches

We searched Ovid MEDLINE (www.ovid.com), EMBASE
(Ovid; www.ovid.com), and the Cochrane Library CENTRAL
(www.thecochranelibrary.com) databases from inception to
September 2007 for selenium intervention studies by using text
terms with appropriate truncation and relevant indexing terms.
The general structure of the search was “selenomethionine OR
yeast OR organoselenium compounds” and “intervention OR
supplementation OR depletion” and “humans.” The full Ovid
MEDLINE search strategy can be found in Supplemental Table
S1 under “Supplemental data” in the online issue. This strategy
was adapted for the other databases.

Reference search

An additional Ovid MEDLINE search was conducted for
reviews of the methods of selenium status assessment. Twelve
reviews were collected in full text, and their reference lists were
checked (19–30). Intervention studies that had not been already
assessed for inclusion were collected. Further relevant studies
were also identified via reference lists of included studies; and
2 experts in the field were asked whether there were any other
studies that should be included.

Data collection

Titles and abstracts were screened for inclusion by a single
reviewer. The full text of all collected articles was screened for
inclusion by using an inclusion and exclusion form by a single
reviewer. For each step, a duplicate assessment of 10% by
a second reviewer was conducted, and when the 2 reviewers
disagreed, the study was discussed and a consensus decision
reached.

Data for each included study were extracted into a Microsoft
Access (Microsoft Corp, Redmond, WA) database file by a single
reviewer with independent duplicate assessment of a sample of
10% by a second reviewer. The data extraction form in Access
was tested on 2 articles by each of the reviewers and discussed
with the review team before beginning full data extraction. Data
extraction was as discussed in the main methodology article
(18).

Further information was requested, where possible, from the
study authors if the data format rendered extraction difficult (15,
31, 32). However, in many cases, certain assumptions had to be
made to use the available data. Many studies reported outcome
data in graphical format so data were taken from tables prefer-
entially, from the text where tables were not available, and from
graphs (enlarged and using a ruler) only where necessary. In
graphs, where bars representing the SD or SE overlapped so that
variance was unclear, the largest realistic SD or SE for each
point was used (as a conservative estimate, tending to reduce the
importance of the data in meta-analysis rather than to overstate
it). In many instances, the numbers of participants in each group
and at each time point were unclear, and here we assumed that
all participants remained in the study and were included in the
group analyses unless otherwise stated. In studies in which
variance data were incompletely reported, it was occasionally
necessary to use the largest of a stated range of SDs or, where
outcome SDs were not reported, assume that the baseline SD
also applied to the outcome data.

Data synthesis

Primary and secondary measures of interest were as stated in
the main methodology paper, and data were subsequently syn-
thesized as described (18). Briefly, the primary measures of
interest were the biomarkers reflecting selenium status after
6 wk intervention, and the secondary measures were how these
biomarkers are influenced by other factors, such as methods of
analysis, study design, length of intervention, supplemental
dose, population subgroups, sex, age, etc.

RESULTS

The flow diagram for this review appears in Figure 1. Of the
601 titles and abstracts screened after electronic and bibli-
ographic searches, 169 appeared to be potentially relevant and
168 were collected as full-text articles to be assessed for in-
clusion (one could not be located). After excluding 145 articles
for various reasons (see Figure 1), 18 studies (15, 17, 31–46)—
reported in 23 publications—fulfilled the inclusion criteria and
were included in this review. Nine of the 18 included studies
were randomized, but none described the method of randomi-
zation. Details of the included studies and their validity are
documented in Table 1 and Table 2. One study appeared to be at low risk of bias in that it was randomized, specified dropouts and reasons for dropouts, ensured that supplements were taken under staff supervision, and independently verified the dose of 10 tablets from each batch (32).

Biomarker efficacy

The results of the assessments of the efficacy of each biomarker are shown in Table 3.

Plasma selenium

Nine of the 14 studies that measured plasma selenium were randomized (15, 31, 32, 34, 42–46). These studies included 512 participants with between 6 (17) and 86 participants per arm (46). Overall, the effect of selenium supplementation was to significantly increase plasma selenium [weighted mean difference (WMD): 0.90 \( \mu \)mol/L; 95% CI: 0.67, 1.14; 14 studies, 512 participants; \( P_{\text{heterogeneity}} < 0.00001; I^2: 97\%\), although there was significant heterogeneity between the results of the different studies (Figure 2). This heterogeneity was not explained by subgrouping by study methodology, supplement type, dose, baseline status, assay type, duration of supplementation, or sex (Table 4). The results were statistically significant for all subgroups, although for some there were insufficient studies or participants to declare the marker useful (Table 4). The one study at low risk of bias suggested a result similar to the pooled studies (32; 0.89 \( \mu \)mol/L; 95% CI: 0.76, 1.02; 29 participants).

Erythrocyte selenium

Six supplementation studies assessed erythrocyte selenium, which included 137 participants, with between 6 (17) and 20 participants per arm (38). Only one of the 6 studies that measured erythrocyte selenium was randomized (45). None of the studies were at low risk of bias (Table 2). Four of the studies were carried out in Europe (one in a low-selenium area of Finland and one in the same area 2 y after supplementation of fertilizers with selenium), one in China (in a low-selenium area), and one in New Zealand. Of the 6 studies, 2 report erythrocyte selenium in micromoles per liter and 4 in nanomoles per gram hemoglobin, so unfortunately they could not be combined in a single meta-analysis. However, by using both units, the effect of selenium supplementation was statistically significant (WMD: 1.40 \( \mu \)mol/L; 95% CI: 1.16, 1.64; 52 participants; \( P_{\text{heterogeneity}} < 0.33; I^2: 0\%\) and 1.48 nmol/g hemoglobin, 95% CI: 0.45, 2.52; 85 participants; \( P_{\text{heterogeneity}} < 0.00001; I^2: 97\%\)) (Figure 3). With only 4 included studies available, subgrouping would not produce meaningful results, so we could not explore the reasons for this heterogeneity.

The data suggest that erythrocyte selenium is likely to be a useful biomarker of selenium status, but more high-quality studies are needed to confirm this and to explore the reasons for the observed heterogeneity of response.
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention and control</th>
<th>Outcomes</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfthan et al, 1991 (33)</td>
<td>Mean (SD) age: 51 ± 7 y</td>
<td>Intervention: 200 µg/d as high-Se yeast</td>
<td>Plasma Se: electrothermal AAS</td>
<td>Study design: CCT Aim: to study the effect of 200 µg/d Se given in different supplement form and basal intake (100 µg/d) on status biomarker.</td>
</tr>
<tr>
<td>Country: Finland</td>
<td></td>
<td>Duration: 16 wk</td>
<td>Platelet GPx: coupled assay</td>
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<tr>
<td>Participants: middle-</td>
<td>No. interventions at latest</td>
<td>Erythrocyte Se: unclear</td>
<td>Urinary Se: acid-digestion fluorometry</td>
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<td>aged men from low-Se area, 2</td>
<td>time point: 10</td>
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<tr>
<td>y after Se fertilizers applied</td>
<td>No. controls at latest</td>
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<td></td>
<td>time point: 15</td>
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<tr>
<td></td>
<td>No. included: 25</td>
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<tr>
<td>Burk et al, 2006 (15)</td>
<td>Age: ≥18 y</td>
<td>Intervention: 158, 388, or 507 µg/d Se as selenomethionine or 226, 439, or 703 µg/d Se as high-Se yeast</td>
<td>Plasma GPx: coupled-enzyme method</td>
<td>Study design: RCT Aim: to study the effects of the chemical form of Se on plasma biomarkers and urinary excretion in replete individuals.</td>
</tr>
<tr>
<td>Country: United States</td>
<td></td>
<td>Duration: 16 wk</td>
<td>Plasma Se: fluorometric assay</td>
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<tr>
<td>Participants: healthy, non-</td>
<td>No. interventions at latest</td>
<td></td>
<td>Selenoprotein P: ELISA</td>
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<tr>
<td>pregnant women</td>
<td>time point: 6</td>
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<tr>
<td>No. included: unclear</td>
<td>No. controls at latest time</td>
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<td>point: 12</td>
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<tr>
<td>Duffield et al, 1999 (31)</td>
<td>Age: 19–59 y</td>
<td>Intervention: 10, 20, 30, or 40 µg/d L-selenomethionine</td>
<td>Plasma Se: AAS</td>
<td>Study design: RCT Aim: to study various amounts of supplemental Se on concentrations and GPx activity to calculate New Zealanders’ requirement.</td>
</tr>
<tr>
<td>Participants: Healthy men</td>
<td>No. interventions at latest</td>
<td></td>
<td>Selenoprotein P: radioimmunoassay</td>
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<tr>
<td>and women</td>
<td>time point: 10</td>
<td></td>
<td>Plasma thyroxine: radioimmunoassay</td>
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<tr>
<td>No. included: 41</td>
<td>No. controls at latest time</td>
<td></td>
<td>Whole-blood GPx: coupled-enzyme assay</td>
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<tr>
<td></td>
<td>point: 12</td>
<td></td>
<td>Whole-blood Se: flow injection AAS</td>
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<tr>
<td>Country: United States</td>
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<td>Duration: 9 mo</td>
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<tr>
<td>Participants: healthy</td>
<td>No. interventions at latest</td>
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<tr>
<td>African Americans and whites</td>
<td>time point: 17</td>
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<tr>
<td>No. included: 36</td>
<td>No. controls at latest time</td>
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<td></td>
<td>point: 19</td>
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<tr>
<td>Finley et al, 1999 (35)</td>
<td>Age: 18–45 y</td>
<td>Intervention: 20–40 µg Se/d as selenomethionine</td>
<td>Plasma Se: unclear</td>
<td>Study design: CCT Aim: to examine if changes in Se status after supplementation would be reflected in the retention of Se stable isotopes.</td>
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<tr>
<td>Country: New Zealand</td>
<td></td>
<td>Duration: 5 mo</td>
<td>Whole-blood GPx: unclear</td>
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<tr>
<td>Participants: healthy,</td>
<td>No. interventions at latest</td>
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<tr>
<td>nonsmoking men and women</td>
<td>time point: 18</td>
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<tr>
<td>No. included: 44</td>
<td>No. controls at latest time</td>
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<td></td>
<td>point: 9</td>
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<tr>
<td>Howard et al, 1994 (36)</td>
<td>Age: 25–36 y</td>
<td>Intervention: 200 µg/d selenomethionine (+Mg)</td>
<td>Erythrocyte GPx: modified coupled assay</td>
<td>Study design: CCT Aim: to study the effect of magnesium supplementation on red-blood-cell magnesium.</td>
</tr>
<tr>
<td>Country: United Kingdom</td>
<td></td>
<td>Duration: 2 mo</td>
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<tr>
<td>Participants: women with</td>
<td>No. interventions at latest</td>
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<tr>
<td>unexplained infertility</td>
<td>time point: 3</td>
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<tr>
<td>No. included: 6</td>
<td>No. controls at latest time</td>
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<td></td>
<td>point: 3</td>
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<tr>
<td>Levander et al, 1983 (37)</td>
<td>Age: 36–60 y</td>
<td>Intervention: 200 µg/d Se as yeast</td>
<td>Plasma Se: electrothermal AAS</td>
<td>Study design: CCT Aim: to compare various blood variables as ways of determining the availability of Se from different sources and to study the effect of Se on immune function.</td>
</tr>
<tr>
<td>Country: Finland</td>
<td></td>
<td>Duration: 11 wk</td>
<td>Plasma GPx: coupled-enzyme assay</td>
<td></td>
</tr>
<tr>
<td>Participants: healthy</td>
<td>No. interventions at latest</td>
<td></td>
<td>Platelet GPx: coupled assay</td>
<td></td>
</tr>
<tr>
<td>middle-aged men, low plasma</td>
<td>time point: 10</td>
<td></td>
<td>Erythrocyte Se: fluorometric method</td>
<td></td>
</tr>
<tr>
<td>Se</td>
<td>No. controls at latest time</td>
<td></td>
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<td></td>
<td>point: 30</td>
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(Continued)
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<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention and control</th>
<th>Outcomes</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luo et al, 1985 (38)</td>
<td>Mean (SD) age: 28 ± 1 y (intervention); 27 ± 2 y (control)</td>
<td>Intervention: 150 μg Se/d as selenomethionine Duration: 8 wk No. interventions at latest time point: 8 No. controls at latest time point: 20</td>
<td>Erythrocyte Se: modified fluorometry</td>
<td>Study design: CCT Aim: to study and compare the effects of Se and selenomethionine supplements on Se status of residents of a low-Se area.</td>
</tr>
<tr>
<td>Neve et al, 1988 (39)</td>
<td>Mean (SD) age: 28 ± 5 y (intervention); 33 ± 6 y (control) Country: Belgium Participants: healthy men and women No. included: 20</td>
<td>Intervention: 100 μg Se/d for 1 mo and then 200 μg/d for 1 mo of Se-enriched yeast Duration: 60 d No. interventions at latest time point: 10 No. controls at latest time point: 10</td>
<td>Plasma GPx: modified coupled assay Plasma Se: direct graphite-furnace AAS Platelet GPx: modified coupled assay Erythrocyte GPx: modified coupled assay Erythrocyte Se: graphite-furnace AAS Urinary Se: graphite-furnace AAS</td>
<td>Study design: CCT Aim: to study the biological effects of Se-enriched yeast supplements in healthy subjects on Se status and GPx activity.</td>
</tr>
<tr>
<td>Robinson et al, 1978 (40)</td>
<td>Age: 10–60 y Country: New Zealand Participants: persons suffering from muscular complaints No included: 24</td>
<td>Intervention: 100 μg/d Se as selenomethionine Duration: 12 wk No. interventions at latest time point: 12 No. controls at latest time point: 11</td>
<td>Whole-blood Se: modified fluorometry</td>
<td>Study design: CCT Aim: to study the effect of daily Se supplement on patients with muscular complaints.</td>
</tr>
<tr>
<td>Tessier et al, 1995 (43)</td>
<td>Mean (SD) age: 22.9 ± 2.1 y Country: France Participants: healthy, nonsmoking men No. included: 24</td>
<td>Intervention: 240 μg/d organic Se Duration: 10 wk No. interventions at latest time point: 11 No. controls at latest time point: 10</td>
<td>Muscle GPx from muscle biopsies Plasma Se: unclear</td>
<td>Study design: RCT Aim: to determine the changes in GPx activity in muscle after acute and chronic exercise and its dependence on Se.</td>
</tr>
</tbody>
</table>
Whole-blood selenium

Four supplementation studies that included 85 participants, with between 10 (31, 42, 45) and 12 participants per arm, assessed whole-blood selenium (40). None of the included studies were considered to be at low risk of bias (Table 2). One study was carried out in Europe and 3 in New Zealand. Two studies gave selenium-enriched yeast and the others selenomethionine. Duration was from 12 to 32 wk, and doses were 40, 100, or 200 \( \mu g/d \).

Meta-analysis of the 4 studies suggested a statistically significant effect of supplementation on whole-blood selenium (WMD: 1.07 \( \mu mol/L \); 95% CI: 0.39, 1.76; 85 participants; \( P_{\text{heterogeneity}} < 0.00001 \); \( I^2: 99% \) (Figure 4), but again there were insufficient studies for subgrouping to be usefully employed to explore the sources of the heterogeneity. However, it is notable that the study that chose participants for their low-selenium status showed the greatest change in whole-blood selenium (42).

The data suggest that whole-blood selenium is likely to be a useful biomarker of selenium status, but more high-quality studies are needed to explore the reasons for the observed heterogeneity of response.

Urinary selenium

Four supplementation studies assessed urinary selenium. These studies included 67 participants, with between 5 (33) and 12 participants per arm (45). The validity of the included studies is given in Table 2, although none of the studies were considered to be at low risk of bias.

Urinary selenium was measured as micromoles per day in 2 studies and as micromoles per gram creatinine in the other 2, so they could not be combined in one meta-analysis. However, meta-analysis with both sets of units showed statistically significant effects of selenium supplementation on urinary selenium (WMD: 1.20 \( \mu mol/d \); 95% CI: 0.88, 1.51; 31 participants;
<table>
<thead>
<tr>
<th>Study</th>
<th>Randomization</th>
<th>Dropouts/exclusions</th>
<th>Assessment of compliance and dose verification</th>
<th>Data problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfthan et al, 1991 (33)</td>
<td>CCT, not randomized</td>
<td>Intervention: not recorded</td>
<td>Compliance: none reported</td>
<td>Graphical format only</td>
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<td></td>
<td></td>
<td>Control: not recorded</td>
<td>DV: none reported</td>
<td>SE/SD bars overlapped on</td>
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<td></td>
<td></td>
<td>Reasons: unclear</td>
<td></td>
<td>graph</td>
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<tr>
<td>Burk et al, 2006 (15)</td>
<td>RCT, randomized, no</td>
<td>7 total (group not specified)</td>
<td>Compliance: pill count,</td>
<td>Participants unclear</td>
</tr>
<tr>
<td></td>
<td>method specified</td>
<td>Reasons: 2 unrelated, 4 odor</td>
<td>questionnaire; 1 noncompliance;</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>and minor GI complaints,</td>
<td>remaining compliance ~98.2%</td>
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<tr>
<td></td>
<td></td>
<td>1 noncompliance, 19 GPx analyses</td>
<td>DV: capsules assayed for Se in authors’</td>
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<td></td>
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<td>with processing error</td>
<td>laboratory (n = 3)</td>
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<tr>
<td>Duffield et al, 1999 (31)</td>
<td>RCT, randomized, no</td>
<td>Intervention: not recorded</td>
<td>Compliance: pill count</td>
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<tr>
<td></td>
<td>method specified</td>
<td>Control: not recorded</td>
<td>DV: None reported</td>
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<td></td>
<td></td>
<td>Reasons: unclear</td>
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</tr>
<tr>
<td>El-Bayoumy et al, 2002 (34)</td>
<td>RCT, no method specified</td>
<td>Intervention: 7</td>
<td>Compliance: capsule counts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control: 9</td>
<td>DV: analyzed for Se content</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reasons: none given</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finley et al, 1999 (35)</td>
<td>CCT, not randomized</td>
<td>Intervention: not recorded</td>
<td>Compliance: none reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control: not recorded</td>
<td>DV: none reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reasons: unclear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Howard et al, 1994 (36)</td>
<td>CCT, not randomized</td>
<td>Intervention: not recorded</td>
<td>Compliance: none reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control: not recorded</td>
<td>DV: none reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reasons: unclear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levander et al, 1983 (37)</td>
<td>CCT, not randomized</td>
<td>Intervention: not recorded</td>
<td>Compliance: pill count</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control: not recorded</td>
<td>DV: none reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reasons: unclear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luo et al, 1985 (38)</td>
<td>CCT, not randomized</td>
<td>Intervention: not recorded</td>
<td>Compliance: none reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control: not recorded</td>
<td>DV: none reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reasons: unclear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neve et al, 1988 (17)</td>
<td>CCT, not randomized</td>
<td>Intervention: not recorded</td>
<td>Compliance: none reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control: not recorded</td>
<td>DV: none reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reasons: unclear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neve et al, 1988 (39)</td>
<td>CCT, not randomized</td>
<td>Intervention: not recorded</td>
<td>Compliance: none reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control: not recorded</td>
<td>DV: none reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reasons: unclear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robinson et al, 1978 (40)</td>
<td>CCT, not randomized</td>
<td>Intervention: 0</td>
<td>Compliance: none reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control: 1</td>
<td>DV: Solution prepared at location of study</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reasons: none given</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schrauzer et al, 1978 (41)</td>
<td>CCT, not randomized</td>
<td>Intervention: not recorded</td>
<td>Compliance: none reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control: not recorded</td>
<td>DV: routinely analyzed, contain ±7% stated Se</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reasons: unclear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seppanen et al, 2000 (42)</td>
<td>RCT, randomized, no</td>
<td>7 total (group not specified)</td>
<td>Compliance: none reported but 3 exclusions due</td>
<td></td>
</tr>
<tr>
<td></td>
<td>method specified</td>
<td>Reasons: did not attend last</td>
<td>to low serum Se</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>examination, 3 noncompliant</td>
<td>DV: none reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tessier et al, 1995 (43)</td>
<td>RCT, randomized, no</td>
<td>Intervention: not recorded</td>
<td>Compliance: none reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td>method specified</td>
<td>Control: not recorded</td>
<td>DV: none reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reasons: unclear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thomson et al, 2005 (44)</td>
<td>RCT, randomized in</td>
<td>12 total (group not specified)</td>
<td>Compliance: None reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td>double-blind manner</td>
<td>Reasons: none given</td>
<td>DV: None reported</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
The data from all 4 studies suggested that urinary selenium may be a useful marker of selenium status, but more studies are needed to confirm this and to explore the reasons for the observed heterogeneity.

### TABLE 3
Summary of results for selenium biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Study design</th>
<th>Weighted mean difference, random effects (95% CI)</th>
<th>$I^2$</th>
<th>Biomarker useful?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma selenium ($\mu$mol/L)</td>
<td>RCTs (9 (397)) CCTs (5 (115))</td>
<td>0.90 (0.67, 1.14)</td>
<td>97</td>
<td>Yes (but significant heterogeneity between studies)</td>
</tr>
<tr>
<td>Erythrocyte selenium (nmol/g Hb)</td>
<td>RCTs (1 (21)) CCTs (3 (64))</td>
<td>1.48 (0.45, 2.52)</td>
<td>97.4</td>
<td>Yes (but significant heterogeneity between studies)</td>
</tr>
<tr>
<td>Whole-blood selenium ($\mu$mol/L)</td>
<td>RCTs (3 (62)) CCTs (1 (23))</td>
<td>1.07 (0.39, 1.76)</td>
<td>98.8</td>
<td>Yes (but significant heterogeneity between studies)</td>
</tr>
<tr>
<td>Urinary selenium (µmol/d)</td>
<td>RCTs (1 (21)) CCTs (1 (27))</td>
<td>1.20 (0.88, 1.51)</td>
<td>0</td>
<td>Unclear (insufficient studies)</td>
</tr>
<tr>
<td>Plasma GPx activity ($\mu$mol NADPH oxidized $\cdot$ min$^{-1}$ $\cdot$ g protein$^{-1}$)</td>
<td>RCTs (3 (209)) CCTs (1 (27))</td>
<td>0.37 (0.15, 0.60)</td>
<td>51.8</td>
<td>Yes (but marginally significant heterogeneity between studies)</td>
</tr>
<tr>
<td>Erythrocyte GPx activity ($\mu$mol NADPH oxidized $\cdot$ min$^{-1}$ $\cdot$ g Hb$^{-1}$)</td>
<td>RCTs (0 (0)) CCTs (3 (42))</td>
<td>3.37 (0.99, 7.74)</td>
<td>86.6</td>
<td>Unclear (sample size not large enough)</td>
</tr>
<tr>
<td>Platelet GPx activity (U/g protein)</td>
<td>RCTs (1 (21)) CCTs (3 (72))</td>
<td>69.42 (12.64, 126.19)</td>
<td>84.9</td>
<td>Yes (but significant heterogeneity between studies)</td>
</tr>
<tr>
<td>Whole-blood GPx activity (U/g Hb)</td>
<td>RCTs (2 (42)) CCTs (2 (31))</td>
<td>3.18 (0.07, 6.29)</td>
<td>85.6</td>
<td>Yes (but significant heterogeneity between studies)</td>
</tr>
<tr>
<td>Muscle GPx activity (IU/g protein)</td>
<td>RCTs (1 (21)) CCTs (0 (0))</td>
<td>8.50 (−0.09, 15.77)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Plasma selenoprotein P (µg/mL)</td>
<td>RCTs (3 (68)) CCTs (0 (0))</td>
<td>2.19 (0.25, 4.12)</td>
<td>94.9</td>
<td>Unclear (insufficient studies)</td>
</tr>
<tr>
<td>Plasma T3/T4</td>
<td>RCTs (2 (227)) CCTs (0 (0))</td>
<td>0.00095 (−0.00178, 0.00369)</td>
<td>52.7</td>
<td>Unclear (insufficient studies)</td>
</tr>
<tr>
<td>Plasma thyroxine (nmol/L)</td>
<td>RCTs (1 (21)) CCTs (0 (0))</td>
<td>−10 (−31.72, 11.72)</td>
<td>NA</td>
<td>Unclear (insufficient studies)</td>
</tr>
<tr>
<td>Plasma total homocysteine ($\mu$mol/L)</td>
<td>RCTs (1 (167)) CCTs (0 (0))</td>
<td>0.30 (−0.37, 0.97)</td>
<td>NA</td>
<td>Unclear (insufficient studies)</td>
</tr>
</tbody>
</table>

1 RCTs, randomized controlled trials; CCTs, nonrandomized controlled trials; GPx, glutathione peroxidase; Hb, hemoglobin; NA, not applicable; T3, triiodothyroxine; T4, thyroxine.
Eight supplementation studies assessed plasma GPx activity with a total of 319 participants, with between 6 (15, 17) and 86 participants per arm (46). Only one study (32) was assessed as being at low risk of bias (Table 2). Three studies were carried out in Europe, 3 in New Zealand, one in the United States, and one in China. Five studies gave selenium-enriched yeast and the others selenomethionine (one study had arms giving both); only the data from the selenomethionine supplementation were used in these analyses. Duration was from 8 to 32 wk, and doses were from 40 to 507 µg/d.

Plasma GPx activity was measured as µmol NADPH oxidized \( / \text{C1 min} / \text{g protein} \) in 4 studies and as nmol NADPH oxidized \( / \text{C1 min} / \text{ml plasma} \) in another 4 studies and so could not be combined in one meta-analysis. However, meta-analysis with both sets of units showed an increase with selenium supplementation, a statistically significant effect when measured in µmol NADPH oxidized \( / \text{C1 min} / \text{g protein} \) (WMD: 0.37; 95% CI: 0.15, 0.60; 4 studies; 236 participants; \( P \text{heterogeneity}, 0.10; I^2: 52\% \)) but not in nmol NADPH oxidized \( / \text{C1 min} / \text{ml plasma} \) (WMD: 38.2; 95% CI: −8.0, 84.4; 4 studies; 83 participants; \( P \text{heterogeneity}, 0.0002; F^2: 85\% \)) (Figure 5A), but there were too few studies to use subgrouping to attempt to explain the heterogeneity.

Three supplementation studies assessed erythrocyte GPx activity, which included 42 participants, with between 3 (36) and 10 participants per arm (17, 39). Pooling the 3 studies did not provide sufficient participants to be clear on whether there was a significant effect of selenium supplementation on erythrocyte GPx activity (WMD: 3.37 µmol, NADPH oxidized \( / \text{C1 min} / \text{g hemoglobin} \); 95% CI: −0.99, 7.74; 3 studies; 42 participants; \( P \text{heterogeneity}, 0.0006; F^2: 87\% \)) (Figure 5C), and there were too few studies to use subgrouping.

GPx activity: plasma

Eight supplementation studies assessed plasma GPx activity with a total of 319 participants, with between 6 (15, 17) and 86 participants per arm (46). Only one study (32) was assessed as being at low risk of bias (Table 2). Three studies were carried out in Europe, 3 in New Zealand, one in the United States, and one in China. Five studies gave selenium-enriched yeast and the others selenomethionine (one study had arms giving both); only the data from the selenomethionine supplementation were used in these analyses. Duration was from 8 to 32 wk, and doses were from 40 to 507 µg/d.

Plasma GPx activity was measured as µmol NADPH oxidized \( / \text{C1 min} / \text{g protein} \) in 4 studies and as nmol NADPH oxidized \( / \text{C1 min} / \text{ml plasma} \) in another 4 studies and so could not be combined in one meta-analysis. However, meta-analysis with both sets of units showed an increase with selenium supplementation, a statistically significant effect when measured in µmol NADPH oxidized \( / \text{C1 min} / \text{g protein} \) (WMD: 0.37; 95% CI: 0.15, 0.60; 4 studies; 236 participants; \( P \text{heterogeneity}, 0.10; I^2: 52\% \)) but not in nmol NADPH oxidized \( / \text{C1 min} / \text{ml plasma} \) (WMD: 38.2; 95% CI: −8.0, 84.4; 4 studies; 83 participants; \( P \text{heterogeneity}, 0.0002; F^2: 85\% \)) (Figure 5A), but there were too few studies to use subgrouping to attempt to explain the heterogeneity.

Three supplementation studies assessed erythrocyte GPx activity, which included 42 participants, with between 3 (36) and 10 participants per arm (17, 39). Pooling the 3 studies did not provide sufficient participants to be clear on whether there was a significant effect of selenium supplementation on erythrocyte GPx activity (WMD: 3.37 µmol, NADPH oxidized \( / \text{C1 min} / \text{g hemoglobin} \); 95% CI: −0.99, 7.74; 3 studies; 42 participants; \( P \text{heterogeneity}, 0.0006; F^2: 87\% \)) (Figure 5C), and there were too few studies to use subgrouping.
One supplementation study assessed muscle GPx activity (43) and included 21 participants. There was insufficient evidence in this study to assess whether muscle GPx activity is a useful marker of selenium status (Table 4).

Four studies, including 73 participants with between 2 (41) and 18 participants per arm, assessed whole-blood GPx activity (35). Participants of 3 studies were healthy volunteers, and the other study included participants chosen for being from a low-selenium-status population in New Zealand. Meta-analysis suggested a statistically significant effect of supplementation on whole-blood GPx activity (WMD: 3.18 U/g hemoglobin; 95% CI: 0.07, 6.29; 4 studies; 73 participants; $P_{\text{heterogeneity}} = 0.0001; I^2: 86\%$) (Figure 5D), but again there were insufficient numbers of studies for subgrouping to be usefully employed to explore the sources of the heterogeneity.

### TABLE 4: Plasma selenium subgrouping

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of studies</th>
<th>Weighted mean difference (95% CI)</th>
<th>$I^2$</th>
<th>Biomarker useful?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall analysis</td>
<td>14 (512)</td>
<td>0.90 (0.67, 1.14)</td>
<td>97</td>
<td>Yes</td>
</tr>
<tr>
<td>RCTs only</td>
<td>9 (397)</td>
<td>1.09 (0.75, 1.43)</td>
<td>98</td>
<td>Yes</td>
</tr>
<tr>
<td>CCTs only</td>
<td>5 (115)</td>
<td>0.61 (0.30, 0.92)</td>
<td>95</td>
<td>Yes</td>
</tr>
<tr>
<td>Selenomethionine only</td>
<td>7 (196)</td>
<td>0.71 (0.43, 0.99)</td>
<td>96</td>
<td>Yes</td>
</tr>
<tr>
<td>Se-enriched yeast only</td>
<td>7 (316)</td>
<td>1.08 (0.75, 1.41)</td>
<td>97</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt; 100 \mu g/d$</td>
<td>3 (77)</td>
<td>0.45 (0.00, 0.91)</td>
<td>96</td>
<td>Yes</td>
</tr>
<tr>
<td>100–199 $\mu g/d$</td>
<td>4 (116)</td>
<td>0.46 (0.33, 0.59)</td>
<td>77</td>
<td>Yes</td>
</tr>
<tr>
<td>200–299 $\mu g/d$</td>
<td>6 (297)</td>
<td>1.19 (0.89, 1.49)</td>
<td>94</td>
<td>Yes</td>
</tr>
<tr>
<td>$\geq 300 \mu g/d$</td>
<td>1 (22)</td>
<td>2.77 (2.24, 3.30)</td>
<td>—</td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Baseline status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low, $&lt; 60 \mu g/L$ plasma Se</td>
<td>2 (50)</td>
<td>1.28 (0.51, 2.05)</td>
<td>97</td>
<td>Unclear</td>
</tr>
<tr>
<td>Intermediate, 60–100 $\mu g/L$ plasma Se</td>
<td>9 (379)</td>
<td>0.60 (0.37, 0.83)</td>
<td>96</td>
<td>Yes</td>
</tr>
<tr>
<td>High, $&gt; 100 \mu g/L$ plasma Se</td>
<td>3 (83)</td>
<td>1.80 (0.47, 3.12)</td>
<td>97</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (43)</td>
<td>0.86 (0.13, 1.60)</td>
<td>98</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>9 (392)</td>
<td>0.78 (0.51, 1.05)</td>
<td>97</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2 (57)</td>
<td>1.72 (1.33, 1.92)</td>
<td>0</td>
<td>Unclear</td>
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</tr>
<tr>
<td><strong>Analysis by AAS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (43)</td>
<td>1.20 (0.51, 2.05)</td>
<td>98</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>9 (392)</td>
<td>0.78 (0.51, 1.05)</td>
<td>97</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2 (57)</td>
<td>1.72 (1.33, 1.92)</td>
<td>0</td>
<td>Unclear</td>
<td></td>
</tr>
</tbody>
</table>

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**Selenoprotein P**

Three supplementation studies, all randomized controlled trials (RCTs), assessed plasma selenoprotein P (15, 31, 32) and included 68 participants with between 6 (15) and 19 participants per arm (32). Two studies included healthy volunteers, and one included farmers from a Keshan endemic area in China. Pooling the 3 RCTs suggested a statistically significant effect of

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**FIGURE 3.** Erythrocyte selenium response to selenium supplementation ($\mu m/L$). RCT, randomized controlled trials; CCT, nonrandomized controlled trials; WMD, weighted mean difference.
selenium supplementation on selenoprotein P (WMD: 2.19 μmol/L; 95% CI: 0.25, 4.12; 68 participants; \( P < 0.0001 \); \( I^2 = 99.1\% \)) (Figure 6); however, there were insufficient studies to explore the reasons for heterogeneity.

Other biomarkers

The review identified 3 additional biomarkers, namely plasma triiodothyronine:thyroxine ratio (T3:T4), plasma thyroxine, and plasma total homocysteine, but in each case the data were limited. Meta-analysis of 2 randomized supplementation studies assessing plasma T3:T4 (44, 46) did not suggest a statistically significant effect of selenium supplementation on this biomarker (WMD: 0.00095; 95% CI: \(-0.00178, 0.00369\); 227 participants; \( P_{\text{heterogeneity}} < 0.00001 \); \( I^2 = 95\% \)) (Figure 6). Only one RCT assessed plasma thyroxine (31), but the results did not suggest a statistically significant effect of selenium on plasma thyroxine (\(-10.0\) mmol/L; 95% CI: \(-31.7, 11.7\); 21 participants). Plasma total homocysteine was also evaluated in only one study (46), but again there was no suggestion from this large trial of a significant effect of selenium supplementation on this potential indicator of status (0.30 μmol/L; 95% CI: \(-0.37, 0.97\); 167 participants). Consequently, it was not possible to draw any firm conclusions about the effectiveness of these biomarkers because of insufficient numbers of subjects and available studies.

**FIGURE 4.** Whole-blood selenium response to selenium supplementation (μmol/L). RCT, randomized controlled trials; CCT, nonrandomized controlled trials; WMD, weighted mean difference.

**TABLE 4.** Whole-blood selenium response to selenium supplementation (μmol/L). RCT, randomized controlled trials; CCT, nonrandomized controlled trials; WMD, weighted mean difference.

**DISCUSSION**

The data from the 18 studies of selenium supplementation included in this systematic review suggest that plasma, erythrocyte, and whole-blood selenium, plasma selenoprotein P, and plasma, platelet, and whole-blood GPx activity are all likely to be useful markers of selenium status. There was insufficient evidence for other potential biomarkers of selenium status, including urinary selenium, plasma T3:T4 ratio, plasma thyroxine, or plasma total homocysteine, erythrocyte, and muscle GPx activity (Table 3). It was not possible to draw any meaningful conclusion from subgroup analysis by type of study, age, sex, BMI, etc, for all the biomarkers except plasma selenium (Table 4) because of the paucity of the data available.

One observation derived from the forest plots of the selenium biomarkers is that results from some studies show significant responses to change in selenium intake, whereas others do not. Although we tried to use subgrouping to help determine when the biomarkers were responsive, this was rarely useful due to limited data. For this reason it is important that further research is undertaken to define the circumstances under which particular biomarkers can be used. It is likely that the response to a change in selenium intake in some biomarkers is dependent on the baseline level, ie, on whether or not the marker is on the dose-response plateau at the start of the intervention. Plasma selenium is an exception in that a response is observed regardless of the baseline concentration (see further discussion below).

Despite our best efforts in using a rigorous and systematic methodology to undertake this review, the outcomes are somewhat limited because of problems with gaining accurate data from the included studies (see Methods) and a lack of data from studies with a low risk of bias. Ideally, all included studies would have been RCTs and would have provided clearly tabulated data. We did consider conducting a sensitivity analysis, removing data where we had to make assumptions or measure from graphs, but this would have left us with few remaining studies. Similarly, there was only one RCT considered to be at low risk of bias. The lack of consistency between the units used for the same measurements (eg, urinary selenium measured either in micromoles per day or in micromoles per gram creatinine) also meant that many results could not be combined in the analysis, weakening the overall results. We therefore recommend that universal units should be agreed upon among experts, on the basis of the accuracy of each measurement, and adopted for future research studies. Finally, because we confined our search to studies published before September 2007, relevant, and potentially important, studies published afterward were not included in our analysis (47–50).

Plasma selenium, although generally not considered to be an ideal biomarker of selenium status, is the most widely used in the literature (51). Our results demonstrate that, overall, plasma selenium significantly increased after supplementation, and subgroup analysis specifically confirmed its usefulness as a biomarker in mixed-sex adults and in adult males and in relation to all quantities and forms of selenium that met our criteria (Table 4). These analyses also confirmed the effectiveness of plasma selenium in reflecting changes in intake (supplementation) in subjects with either intermediate- or high-selenium status at baseline. Consequently, it is probable that plasma selenium
FIGURE 5. (A) Plasma (μmol NADPH oxidized \cdot min^{-1} \cdot g hemoglobin^{-1} or NADPH oxidized \cdot min^{-1} \cdot mL plasma^{-1}), (B) platelet (U/g protein), (C) erythrocyte (μmol NADPH oxidized \cdot min^{-1} \cdot g hemoglobin^{-1}), and (D) whole-blood (U/g hemoglobin) glutathione peroxidase activity response to selenium supplementation. RCT, randomized controlled trials; CCT, nonrandomized controlled trials; WMD, weighted mean difference.
techniques are being used in an attempt to develop novel indi-
biomarker that is both specific and sensitive, molecular biology
that were selenium replete before supplementation was begun (15).
selenium intakes (31, 58) but not in populations with high intakes
dertaken for this review. Other reports confirm that it is a relatively
was found to be a useful biomarker in the meta-analysis un-
demonstrated that an increase in selenium intake (100–300
2 independent studies published since our search was run have
dicated that plasma T3:T4, plasma thyroxine, or plasma total homo-
marker of selenium status due to the lack of data. It is unlikely
selenoprotein P accounts for 50% of selenium in the blood and
As investigators continue to search for the ideal selenium
would also be useful in assessing status in depleted individuals,
but unfortunately we were unable to confirm this due to the lack
of suitable studies. Additionally, this review highlights the
usefulness of erythrocyte and whole-blood selenium as markers
of selenium status, both of which are reported to be markers of
long-term status (52).
According to our analysis, plasma, platelet, and whole-blood
GPx activity reflected the intake of selenium, but there were
insufficient data to be clear about erythrocyte or muscle GPx
activity. Although our analysis assessed the effect of selenium
supplementation on total GPx activity, there are reports in the
literature referring to the use of specific members of the GPx
family in platelets as biomarkers of selenium status. Platelet
GPx1 and GPx4 activities are believed to be an accurate reflection
of selenium status (17, 48, 53, 54), although the response of
GPx1 activity in platelets reaches a plateau when plasma sele-
nium is relatively low, namely 100 ng/mL (27, 54), and so use of
platelet GPx activity as a biomarker of status is potentially
limited to populations with low-selenium status at baseline.
We were unable to draw any firm conclusions from our
analysis about the usefulness of urinary selenium plasma T3:T4,
plasma thyroxine, or plasma total homocysteine as a valid bio-
marker of selenium status due to the lack of data. It is unlikely
that plasma T3:T4, plasma thyroxine, or plasma total homocys-
teine would be reliable specific biomarkers of selenium status
because concentrations of these 3 biomarkers can be altered by
other dietary constituents and factors. For example, plasma
homocysteine can be altered by folate and vitamin B-12 status
(55) and plasma T3:T4 and thyroxine can be altered by iodine
intake, certain drugs, and various diseases (56, 57). In addition,
2 independent studies published since our search was run have
demonstrated that an increase in selenium intake (100–300 μg/d
as selenium-enriched yeast) did not alter the plasma T3:T4 ratio
significantly (49) or serum thyroxine or T3 concentrations (50).
Urinary selenium has also been shown to be a reliable marker
for recent intake of selenium (48) rather than a robust biomarker
for selenium status.
Selenoprotein P accounts for 50% of selenium in the blood and
was found to be a useful biomarker in the meta-analysis un-
dertaken for this review. Other reports confirm that it is a relatively
reliable biomarker in populations with relatively low-to-moderate
selenium intakes (31, 58) but not in populations with high intakes
that were selenium replete before supplementation was begun (15).
As investigators continue to search for the ideal selenium
biomarker that is both specific and sensitive, molecular biology
techniques are being used in an attempt to develop novel indi-
cators of selenium status. For example, selenoprotein W and
GPx1 mRNA concentrations seem to be sensitive markers of
selenium status in animal models (59, 60). However, in humans,
within a relatively small range of selenium intake, mRNA
concentrations of the selenoproteins W, H, and P and GPx 1, 3,
and 4 do not correlate significantly with plasma selenium
concentration (61). Nevertheless, other candidate molecular markers
may be useful indicators of selenium status in relation to intake of
different forms of selenium. Supplementation of healthy
volunteers with sodium selenite (100 μg/d) significantly
increased the expression of several genes encoding ribosomal
proteins L30, L37A, and eukaryotic translation elongation factor
1 epsilon 1 (62). However, the use of these selenium-responsive
genes awaits further validation especially due to the relatively
small change in gene expression (<1.5-fold increase) quantified
after selenium supplementation. A good candidate molecular
marker ideally would require more pronounced effects of sele-
nium supplementation on selenium-responsive gene expression
before a significant difference could be detected at a population
level or among groups with differing selenium status because of
interindividual variation and the effect of single nucleotide
polymorphisms, which can alter the responsiveness of several
selenoprotein biomarkers (63, 64). Unfortunately, because of the
novelty of this research and the lack of data, none of these novel
biomarkers could be examined in this systematic review, but the
development of functional markers of selenium status is clearly
a high priority.
Most of the data relate to plasma selenium, but more large,
high-quality RCTs are needed for all of the potentially sensitive
and useful biomarkers, particularly the most promising newer
biomarkers such as selenoprotein P, to explore the reasons for the
heterogeneity in response to selenium supplementation. Also, for
all potential biomarkers, more information is needed to un-
derstand the limitations of applicability for different population
groups, the possible effects of genotype, supplementation doses,
duration, baseline status, etc. Ideally, this information would be
obtained from large and well-conducted RCTs with a variety of
selenium doses and undertaken over periods of several months
and where initial selenium status is well defined. Use of a wide
range of potential biomarkers in each study would allow us to
understand the effectiveness of each biomarker for individuals
and populations and to compare the relative sensitivity of bio-
markers. Data in published studies need to be clearly presented
in tabular form and with unambiguous information on the numbers
of participants at each point and relevant variance data, together
with detailed methods of analysis and universally accepted units

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FIGURE 6. Plasma selenoprotein P response to selenium supplementation (μg/mL). RCT, randomized controlled trials; WMD, weighted mean difference.
of enzyme activity or protein concentration. Eventually, the results of such studies will lead to the development of evidence-based dietary recommendations specific to all subgroups of the population, which to date has not been feasible. (Other articles in this supplement to the Journal include references 18, 55, and 65–70.)

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