Reliability and Validity of Self-Report of Vitamin and Mineral Supplement Use in the Vitamins and Lifestyle Study

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In the United States, dietary supplements contribute a large proportion of micronutrient intakes. Therefore, it is important to collect accurate information on supplement use for studies of micronutrients and disease risk. This report describes the test-retest reliability and validity of a detailed, self-administered mailed questionnaire on vitamin and mineral supplement use. Participants (n = 220) completed the questionnaire at baseline and 3 months later. During an in-person interview, participants provided spot urine and blood samples, and interviewers transcribed nutrient information from their supplement bottle labels. The questionnaire had very good test-retest reliability for mean supplement intake over the past 10 years, with intraclass correlations ranging from 0.69 for beta-carotene to 0.87 for vitamin E. Pearson’s correlation coefficients comparing current supplemental intakes from the questionnaire and interviews/label transcriptions were high, ranging from 0.58 for beta-carotene to 0.82 for chromium; however, for some nutrients, median intakes from the questionnaire were slightly lower than from the interviews. Beta-carotene, vitamin C, and vitamin E (alpha-tocopherol) showed clear linear trends of increasing blood concentrations with higher self-reported supplemental intakes (Pearson’s correlation coefficients adjusted for potential confounding factors and diet = 0.31, 0.29, and 0.69, respectively; all p < 0.0001). Creatinine-adjusted spot urinary calcium values were not associated with supplemental calcium intakes (Pearson’s r = −0.07). This self-administered questionnaire demonstrated high reproducibility and validity for collecting detailed information on supplement use.

dietary supplements; questionnaires; reliability; reproducibility of results; validity; vitamins

Abbreviation: VITAL, Vitamins and Lifestyle.

There is extensive evidence for a role of micronutrients in lowering chronic disease risk (1–3). In particular, epidemiologic, laboratory, and animal studies strongly suggest that some vitamins (e.g., vitamins A, C, and E and folic acid) and minerals (e.g., calcium and selenium) can play an important role in preventing several major chronic diseases, including cardiovascular disease and several cancers (1–5).

Vitamin and mineral supplements are an important source of micronutrient intakes in the United States (6–11). Furthermore, for many nutrients (e.g., vitamin E), the dose available from supplements (e.g., 180 mg from single supplements) is much larger than can be obtained from foods (about 8–10 mg) (9, 10). Thus, vitamin and mineral supplements represent a significant component of micronutrient exposure and should be added to intakes obtained from foods to determine total micronutrient intake in epidemiologic studies. There is also considerable interest in assessing the independent effects of vitamin and mineral supplements on cancer risk (12, 13), cardiovascular disease (14, 15), and other diseases (16–18). Therefore, it is important that researchers collect accurate and valid information about supplement use.

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Epidemiologic studies typically use personal interviews or self-administered questionnaires to obtain information on a few general classes of multiple vitamins (e.g., multivitamins, “stress”/B complex, antioxidant mixtures, and so on) and on the dose and, sometimes, frequency and/or duration of use of some single supplements (7, 8, 11). These brief and simple methods have been deemed adequate for assessment of nutrient intakes derived from supplements (8, 11). However, after the passage of the Dietary Supplement Health and Education Act in 1994 that deregulated the supplement industry, there was an explosion in the types of supplements and possible combinations of vitamin, mineral, and herbal products available to consumers (19). As a result, it is not clear that the brief and simple questionnaires used in previous studies can adequately capture nutrient intakes from supplements in today’s market.

Therefore, we designed a new approach/questionnaire to assess supplement use in the Vitamins and Lifestyle (VITAL) Study, a cohort investigation focused on the use of dietary supplements and cancer risk. Specifically, we developed an extensive self-administered questionnaire that elicits detailed information (frequency of use, duration of use, and usual dose) on total supplemental intakes of 10 vitamins and six minerals from multivitamins, single supplements, and mixtures. We then conducted a validation study to determine how accurately this comprehensive instrument collects information on supplement use.

The validation study of this questionnaire presented here had two objectives. First, we assessed the test-retest reliability (baseline and 3 months) of self-report of mean intake over the past 10 years. Second, we examined the validity of the self-administered questionnaire for current use of supplements in comparison with more objective measures: data derived from interviewing participants and transcribing the labels of their supplement bottles, as well as nutrient levels in blood and urine.

**MATERIALS AND METHODS**

**The Vitamins and Lifestyle Study**

The objectives of the VITAL Study are to investigate associations of supplemental vitamin C, vitamin E, calcium, multivitamins, and other supplements with cancer risk. To meet these aims, 75,000 men and women, aged 50–75 years, were recruited by mail within the 13 counties of western Washington State using a cover letter that targets supplement users. Respondents completed a 24-page baseline questionnaire that collects detailed information on vitamin, mineral, and herbal supplement use over the previous 10 years and information on other important cancer risk factors including dietary intake, physical activity, and demographic characteristics. Recruitment of the VITAL Study cohort began in October 2000 and continued through October 2002.

**Validation study participants and recruitment**

The validation-study sample consisted of randomly selected VITAL Study participants who completed the baseline questionnaire between October 2000 and February 2001. The sample was stratified to obtain an equal sex distribution. To better evaluate the relation between dose of supplements and biomarkers, we randomly oversampled high users of vitamin C, vitamin E, and calcium. Because all study procedures were administered at the participant’s home, we restricted our sample to respondents living in the Seattle metropolitan area (King County, Washington). We excluded potential participants who had Alzheimer’s disease, insulin-dependent diabetes, or any conditions that would prevent collection of a fasting blood sample.

Approximately 3 months after completion of the baseline questionnaire, we contacted potential participants to ask them to take part in the validation study. Participants received $75 for their time upon completion of the home interview. The study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center and was conducted from January to June of 2001.

Of the 290 eligible participants contacted, 220 (76 percent) completed the study protocol. Reasons for nonparticipation included the following: refusal (13 percent), failure to collect a blood sample (2 percent), and not reachable by telephone (9 percent). The final sample consisted of 112 men and 108 women and included 149 randomly selected VITAL Study respondents and 71 oversampled high users (5 or more years) of ≥1,000 mg of vitamin C (n = 26), ≥800 IU of vitamin E (n = 23), or ≥1,000 mg of calcium (n = 22).

**Data collection**

**Study procedures.** One week before their interview, each participant was sent a second VITAL Study questionnaire with instructions to complete it prior to the interview. We asked participants to refrain from all dietary supplements the day of their interview and from foods and beverages (except water) for at least 6 hours before their appointment.

**Assessment of supplement use.** We assessed supplement use using three methods: the self-administered mailed questionnaire, an in-person interview/label transcriptions, and biologic markers.

**Self-administered questionnaire (baseline and 3 months).** The VITAL Study supplement questionnaire was designed to assess the total intake of 10 vitamins and six minerals from all types of supplements over the previous 10 years. Therefore, respondents were asked about past and current use of all supplements during the 10 years preceding completion of the instrument. The questionnaire consists of two pages capturing information on multivitamin use and three pages on use of single supplements and mixtures; it takes 5–10 minutes to complete.

Respondents were first asked about their current multivitamins. To assess the type of multivitamin (defined as a mixture containing at least 10 vitamins and/or minerals) used, we provided a list of 16 brand names. If the respondent’s multivitamin was not listed, he or she was asked to provide information on the composition of the brand (i.e., specific doses of vitamins and minerals contained in the multivitamin). For multivitamins taken only in the past, respondents were given another list of brand names (reflecting past market availability) or allowed to answer, “Don’t know.” After completing the section on multivita-
mins, respondents were asked about their current and past intakes of 10 vitamins and six minerals from all other mixtures not classified as multivitamins (e.g., “stress”/B complex or antioxidant mixtures) and single supplements. Participants were asked to look at their supplement bottles when completing the form.

For multivitamins and each of the 16 vitamins and minerals, we used a closed-ended format to inquire about frequency of use (1–2, 3–4, 5–6, 7 days per week), duration of use over the previous 10 years (1–3, 4–6, 7–9, ≥10 years), and usual dose per day based on the most common formulations for each supplement, for example, vitamin C (60, 100, 250, 500, 1,000, 1,500 mg). Respondents were allowed to answer, “Don’t know,” to dose questions. Appendix figure 1 includes a sample page from the VITAL Study supplement questionnaire.

In-person interview and label transcriptions (criterion measure). During the home interview, for each supplement taken, interviewers used an open-ended format to query participants on frequency of use (per day, week, month, or year) and number of pills taken each time. The interviewer then transcribed the nutrient information (vitamin or mineral dose per pill) from each supplement bottle label.

Biologic markers. Phlebotomists used venipuncture to collect semidfasting (26 hours) blood samples that were analyzed for serum beta-carotene, serum alpha-tocopherol, and plasma vitamin C. Each participant also provided a spot (random) urine sample for analysis of urinary calcium. Although 24-hour urine collections are recommended for calcium analysis, we used spot urine samples because of their lower participant burden and evidence of very high correlation between calcium from 24-hour and creatinine-adjusted spot urine collections [r = 0.95 (20) and 0.79 (21); both p < 0.0001]. All specimens were put on ice immediately after collection.

Assessment of micronutrient intakes. Questionnaire and interview/label transcriptions. Average current daily intakes from single supplements were computed as “frequency (days per week) × dose per day / 7 (days)” from questionnaires and as “frequency (days per week) × number of pills taken each time × dose per pill / 7” from the interviews/label transcriptions. Current multivitamin use was “days per week.”

Average daily intakes from single supplements over the past 10 years were estimated as “duration (years) × frequency (days per week) × dose / [10 (years) × 7 (days)].” Average multivitamin use over the past 10 years (in days per week) was computed as “duration × frequency / 10.” We summed across intakes from multivitamins and single supplements to determine the total average daily intakes for each nutrient.

Nutrient information for multivitamin brands was obtained from bottle labels or the Physicians’ Desk Reference for Nonprescription Drugs and Dietary Supplements (22). Beta-carotene, vitamin D, and vitamin E were converted into activity units as follows: 1 IU of vitamin A = 0.3 μg of retinol and 0.6 μg of beta-carotene; 1 IU of vitamin D = 0.025 μg of cholecalciferol; and 1 IU of vitamin E = 0.45 mg of alpha-tocopherol.

When the multivitamin brand or multivitamin contents were not provided on the questionnaire (i.e., closed-ended questions), we defaulted to the formulations for Centrum Silver (current use) and Centrum (past use) (both products from Wyeth, Madison, New Jersey) because they were the market leaders in 2001 and 1996, respectively, and the most frequent responses among VITAL Study participants. In most cases, we imputed missing information on duration, frequency, and dose as the most common responses given by VITAL Study participants. For example, when dose information was missing for single supplements, we imputed the most common dose given by VITAL Study respondents for that nutrient. However, when the most common response was the highest exposure category, we chose a more conservative value to ensure that classification of participants into the highest duration, frequency, or dose categories was always based on actual self-report. Overall, the mean amount of missing data was as follows: 2.8 percent for duration (years) of use, 5.6 percent for frequency (days per week) of use, and 4.9 percent for usual dose per day.

Biologic samples. Blood and urine samples were processed within 2 hours of collection. Blood samples were separated into aliquots of serum and plasma, and metaphosphoric acid/dithiothreitol was added to one aliquot of plasma to preserve and stabilize vitamin C. Urine samples were acidified to a pH of 1.5–2.0 with 6 M hydrochloric acid in order to dissolve calcium salts (23, 24). All samples were stored at −80°C until analysis.

Beta-carotene and alpha-tocopherol were analyzed by high performance liquid chromatography using previously published procedures (25). Total cholesterol was analyzed using standard enzymatic methods (26). Vitamin C was analyzed on a Roche Cobas Mira Plus chemistry analyzer (Physician Sales and Service, Inc., Oakdale, Pennsylvania) using a colorimetric procedure described by Lee et al. (27). Calcium concentrations in urine were determined with the o-cresolphthalein complexone method (24, 28) using commercially available reagent kits and a Hitachi 917 analyzer (ARUP Laboratories, Salt Lake City, Utah). Quality control samples were included in each batch.

Dietary intake. We assessed diet using a food frequency questionnaire developed at the Fred Hutchinson Cancer Research Center that asked about usual consumption of foods eaten during the past month. This food frequency questionnaire is a modification of the instrument used in the Women’s Health Initiative (10) and includes 16 adjustment questions on types of foods and preparation techniques and 110 food and beverage items with questions on the frequency of use and portion sizes. The nutrient database used to convert food frequency information into nutrients is from the University of Minnesota’s Nutrition Coordinating Center database (29), and the algorithms for analysis have been published (30).

Data analysis

Test-retest reliability. For each nutrient, the proportion of nonsupplement users (i.e., those who did not report using any supplement containing that nutrient) and distributions of nutrient intakes (from multivitamins, single supplements, and mixtures) among users over the previous 10 years were computed for both questionnaires (i.e., baseline and 3-month
readadministrations). The weighted kappa statistic and intraclass correlations were used to assess the test-retest reliability between the questionnaires (31). To calculate kappa, we used a 5 × 5 table with respondents categorized as follows: nonusers; 0–<25th percentile; 25th–<50th percentile; 50th–<75th percentile; and ≥75th percentile.

Validity. To examine agreement between current daily self-reported supplemental nutrient intakes and intakes from interviews/transcriptions of supplement bottle labels (criterion measure), we compared the proportion of non-supplement users and distributions of intakes among supplement users obtained by each method. We also computed Pearson’s correlation coefficients and their 95 percent confidence intervals between the two types of assessments.

To assess associations of self-report with nutrient values from biomarkers, we categorized supplement intakes from the second questionnaire into nonusers and quartiles among users. This was treated as a linear term in the model to assess linear trends of biomarker concentrations with supplement use. Pearson’s correlation coefficients measured associations of self-report of beta-carotene, vitamin C, vitamin E (alpha-tocopherol), and calcium with their respective blood and urinary values. Correlation coefficients and tests for trend were adjusted for demographic, behavioral, and other factors that have been reported to affect serum and urinary nutrient concentrations, including age, sex, race, current smoking, body mass index (weight (kg)/height (m)2), serum total cholesterol, dietary intake, and/or urinary creatinine (9, 32). Because inclusion of the oversampled high users might inflate associations, we present correlations on both the enhanced (i.e., randomly selected plus oversampled high users) and randomly selected samples. Since micronutrient and biomarker data were skewed (except plasma vitamin C), log or square root transformations were used as appropriate to improve normality. Because correlations in nutritional epidemiology are usually on the order of 0.5–0.7, we define any correlation coefficient greater than 0.7 as “high” or “very good” (32). We used data from the baseline questionnaire to assess the validity of our instrument against interviews/transcriptions (because there may be a “training effect” associated with the second questionnaire), but we used supplement and dietary values from the second questionnaire for biomarker comparisons because biologic markers can change markedly over a 3-month period (32). All analyses were performed using SAS version 6.12 software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Demographic and health-related characteristics of the validation study sample and the VITAL Study cohort (our sampling frame) are given in table 1. The mean age of the validation study participants was 62 (standard deviation, 7.7) years, about half were female, more than 90 percent were White, only 5 percent were current smokers, and less than one fifth were obese (defined as body mass index of >30 kg/m2) (33). Participants in the validation study were similar to the VITAL Study cohort with regard to most characteristics, except for education (52 percent of the validation study participants had college or advanced degrees compared with 41 percent of the VITAL Study cohort). This is attributable to the fact that the validation study participants were recruited from King County, and in the VITAL Study cohort, King County residents have higher levels of education than do participants from other western Washington counties (51 percent vs. 35 percent, p < 0.001).

Table 2 describes the test-retest reliability for supplemental nutrient intakes (from multivitamins plus single supplements and mixtures) over the past 10 years between self-administered questionnaires completed at baseline and 3 months later. Participants reported high levels of supplement use: 58 percent reported using a multivitamin, and among the individual nutrients, the most commonly used were vitamin C (74 percent), vitamin E (77 percent), and calcium (69 percent). The questionnaire had very good reproducibility, with intraclass correlations ranging from 0.69 for beta-carotene to 0.87 for vitamin E (mean, 0.79). Because correlation coefficients are sensitive to outliers and supplemental nutrient intakes are often analyzed in categories, agreement (weighted kappas) between questionnaires was examined after recoding intakes from both questionnaires into quartiles. Weighted kappa statistics ranged from 0.58 for calcium to 0.78 for multivitamins (mean, 0.69). In addition, for each nutrient, fewer than 15 percent of participants switched user/nonuser categories, and about half reported the same 10-year dose (data not shown).

Current supplemental nutrient intakes assessed from the self-administered questionnaire and from in-person interviews/transcriptions of supplement bottle labels (criterion measure), as well as correlations between the two types of assessments, are given in table 3. There were high levels of current vitamin and mineral supplement use, similar to the 10-year values. Estimates of median current supplemental intakes from the questionnaire were identical to those obtained by interviews/label transcriptions for eight nutrients, but questionnaire estimates were 12–50 percent lower for the other eight nutrients. Pearson’s correlation coefficients comparing intakes from the questionnaire and the interviews were high, ranging from 0.58 for beta-carotene to 0.82 for chromium, with a mean of 0.72. Correlation coefficients for some nutrients of scientific interest were 0.81 for vitamin E, 0.77 for vitamin C and selenium, 0.76 for folate, and 0.69 for calcium.

Associations of biomarker values for beta-carotene, vitamin C, alpha-tocopherol, and calcium with corresponding current self-reported supplemental nutrient intakes adjusted for potential confounding factors and diet are given in table 4. Concentrations of serum beta-carotene, plasma vitamin C, and serum alpha-tocopherol increased linearly with increasing supplemental intakes (all p for trend < 0.0001), but no trend was observed for creatinine-adjusted spot urinary calcium with supplemental calcium intakes (p = 0.97). There were modest correlations between serum betacarotene and plasma vitamin C and their corresponding self-reported supplemental values (r = 0.31 and 0.29, respectively) and a high correlation between serum and supplemental alpha-tocopherol (r = 0.69), all p < 0.0001. Urinary calcium was not correlated with self-reported supplemental calcium intakes. Excluding the oversampled high users did not change these associations appreciably (table 4), and
unadjusted correlation coefficients were only slightly lower than the adjusted values (data not shown). Finally, except for calcium, correlations of biomarker values with intakes from our criterion measure (i.e., interviews/transcriptions) were higher than those from the self-administered questionnaires ($r = 0.32$ for beta-carotene, $0.38$ for vitamin C, $0.75$ for vitamin E, and $0.06$ for calcium; data not shown).

**DISCUSSION**

The self-administered questionnaire on dietary supplement use examined in this validation study of older adults had high test-retest reliability for supplement use over the previous 10 years. It also had very good validity for both current supplemental nutrient intakes and multivitamin use in comparison with interviews/transcriptions of supplement bottle labels and most nutrient biomarkers.

The nutrient intraclass correlations between the first and second administrations of the VITAL Study supplement questionnaire ranged from $0.69$ to $0.87$. We know of no research on the reproducibility of nutrient estimates from vitamin and mineral supplements with which to compare our findings. Although there have been several reproducibility studies of food frequency questionnaires and other dietary assessment instruments (32, 34), direct comparisons of correlations of nutrient intakes from supplements with those from diet may not be reasonable, primarily because of differ-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Randomly selected validation study sample ($n = 149$)</th>
<th>Enhanced validation study sample ($n = 220$)†</th>
<th>VITAL Study cohort through November 2001 ($n = 40,703$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$50–59$</td>
<td>52.3</td>
<td>49.1</td>
<td>46.5</td>
</tr>
<tr>
<td>$60–69$</td>
<td>25.5</td>
<td>30.5</td>
<td>34.6</td>
</tr>
<tr>
<td>$&gt;69$</td>
<td>22.1</td>
<td>20.5</td>
<td>18.9</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Males</td>
<td>51.0</td>
<td>50.9</td>
<td>49.1</td>
</tr>
<tr>
<td>Females</td>
<td>49.0</td>
<td>49.1</td>
<td>50.9</td>
</tr>
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<td>Education§</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>11.4</td>
<td>12.3</td>
<td>20.2</td>
</tr>
<tr>
<td>Some college</td>
<td>36.9</td>
<td>34.1</td>
<td>37.7</td>
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<tr>
<td>College graduate/advanced degree</td>
<td>51.7</td>
<td>53.2</td>
<td>40.6</td>
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<td>Race</td>
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<td>White</td>
<td>93.3</td>
<td>94.1</td>
<td>91.8</td>
</tr>
<tr>
<td>Non-White</td>
<td>6.7</td>
<td>5.5</td>
<td>6.7</td>
</tr>
<tr>
<td>Smoking history</td>
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<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>51.0</td>
<td>51.4</td>
<td>46.3</td>
</tr>
<tr>
<td>Former smoker</td>
<td>43.6</td>
<td>43.2</td>
<td>44.4</td>
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<tr>
<td>Current smoker</td>
<td>5.4</td>
<td>5.0</td>
<td>8.7</td>
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<tr>
<td>Body mass index</td>
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<tr>
<td>Normal ($18–24.9$ kg/m$^2$)</td>
<td>38.9</td>
<td>35.5</td>
<td>31.8</td>
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<tr>
<td>Overweight ($25–29.9$ kg/m$^2$)</td>
<td>43.6</td>
<td>44.5</td>
<td>39.3</td>
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<tr>
<td>Obese ($\geq 30$ kg/m$^2$)</td>
<td>14.8</td>
<td>16.4</td>
<td>23.3</td>
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* Percentages may not add up to 100% because of rounding and missing data.
† Includes randomly selected participants ($n = 149$) and oversampled high users (5 years or more) of $\geq 1,000$ mg of vitamin C ($n = 26$), $\geq 800$ IU of vitamin E ($n = 23$), or $\geq 1,000$ mg of calcium ($n = 22$).
‡ VITAL, Vitamins and Lifestyle.
§ More college-educated participants in the validation study samples compared with the VITAL Study cohort ($p < 0.001$).
TABLE 2. Test-retest reliability (baseline and 3 months) of self-reported supplemental nutrient intakes and multivitamin use over the past 10 years (n = 149), Vitamins and Lifestyle Study, 2001*

<table>
<thead>
<tr>
<th>Supplement use (average daily intake over the previous 10 years)†,‡</th>
<th>Distributions by baseline questionnaire</th>
<th>Distributions among users by the following percentiles</th>
<th>Weighted kappa</th>
<th>95% confidence interval</th>
<th>Intraclass correlation coefficient§</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonusers (%)</td>
<td>25th</td>
<td>50th (median)</td>
<td>75th</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinol (µg)¶</td>
<td>38.4</td>
<td>255.0</td>
<td>778.9</td>
<td>1,170.0</td>
<td>0.65</td>
<td>0.55, 0.74</td>
</tr>
<tr>
<td>Beta-carotene (µg)¶</td>
<td>41.1</td>
<td>630.0</td>
<td>1,575.0</td>
<td>2,828.6</td>
<td>0.67</td>
<td>0.57, 0.77</td>
</tr>
<tr>
<td>Vitamin C (mg)</td>
<td>26.2</td>
<td>50.0</td>
<td>143.0</td>
<td>500.0</td>
<td>0.71</td>
<td>0.61, 0.80</td>
</tr>
<tr>
<td>Vitamin D (cholecalciferol) (µg)#</td>
<td>37.2</td>
<td>2.0</td>
<td>5.5</td>
<td>10.0</td>
<td>0.62</td>
<td>0.52, 0.73</td>
</tr>
<tr>
<td>Vitamin E (alpha-tocopherol) (mg)**</td>
<td>23.5</td>
<td>16.2</td>
<td>40.2</td>
<td>144.6</td>
<td>0.65</td>
<td>0.54, 0.76</td>
</tr>
<tr>
<td>Vitamin B1 (thiamin) (mg)</td>
<td>37.6</td>
<td>0.4</td>
<td>1.2</td>
<td>2.3</td>
<td>0.69</td>
<td>0.59, 0.80</td>
</tr>
<tr>
<td>Vitamin B2 (riboflavin) (mg)</td>
<td>34.9</td>
<td>4.3</td>
<td>15.7</td>
<td>20.0</td>
<td>0.72</td>
<td>0.63, 0.82</td>
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<tr>
<td>Vitamin B3 (niacin) (mg)</td>
<td>35.6</td>
<td>0.6</td>
<td>2.0</td>
<td>5.1</td>
<td>0.75</td>
<td>0.65, 0.85</td>
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<tr>
<td>Folate (µg)</td>
<td>34.9</td>
<td>100.0</td>
<td>314.3</td>
<td>400.0</td>
<td>0.75</td>
<td>0.66, 0.84</td>
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<tr>
<td>Vitamin B6 (mg)</td>
<td>34.9</td>
<td>3.0</td>
<td>6.0</td>
<td>13.8</td>
<td>0.73</td>
<td>0.63, 0.82</td>
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<tr>
<td>Calcium (mg)</td>
<td>31.1</td>
<td>81.0</td>
<td>194.3</td>
<td>500.0</td>
<td>0.58</td>
<td>0.47, 0.70</td>
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<tr>
<td>Iron (mg)</td>
<td>46.3</td>
<td>3.6</td>
<td>9.0</td>
<td>15.9</td>
<td>0.66</td>
<td>0.55, 0.77</td>
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<tr>
<td>Magnesium (mg)</td>
<td>41.6</td>
<td>20.0</td>
<td>70.0</td>
<td>100.0</td>
<td>0.66</td>
<td>0.56, 0.76</td>
</tr>
<tr>
<td>Zinc (mg)</td>
<td>39.2</td>
<td>3.2</td>
<td>10.1</td>
<td>15.0</td>
<td>0.71</td>
<td>0.61, 0.80</td>
</tr>
<tr>
<td>Selenium (µg)</td>
<td>38.9</td>
<td>5.0</td>
<td>19.6</td>
<td>25.0</td>
<td>0.70</td>
<td>0.61, 0.80</td>
</tr>
<tr>
<td>Chromium (µg)</td>
<td>43.0</td>
<td>20.4</td>
<td>52.0</td>
<td>92.0</td>
<td>0.66</td>
<td>0.55, 0.76</td>
</tr>
<tr>
<td>Multivitamins (days/week)††</td>
<td>41.6</td>
<td>1.5</td>
<td>3.5</td>
<td>7</td>
<td>0.78</td>
<td>0.69, 0.87</td>
</tr>
</tbody>
</table>

* Randomly selected sample.
† Includes intakes from multivitamins and single supplements.
‡ Total daily intakes over the previous 10 years computed as follows: years taken × days per week × dose per day / [7 (days) × 10 (years)].
§ Log-transformed variables.
¶ 1 IU of vitamin A = 0.3 µg of retinol and 0.6 µg of beta-carotene.
# 1 IU of vitamin D = 0.025 µg of cholecalciferol.
** 1 IU of vitamin E = 0.45 mg of alpha-tocopherol.
†† Multivitamin use calculated as follows: years taken × days per week / 10 (years).

ences in variability of intake. Specifically, supplements may provide a much broader range of intake for some nutrients (e.g., vitamin E) than diet alone because of extremes in supplemental intakes, that is, nonusers and those taking very high doses.

Using both detailed in-person interviews/label transcription and biomarkers for beta-carotene, vitamin C, and vitamin E, we found that our supplement assessment instrument proved to be a valid measure of current supplemental nutrient intakes. There were high correlations for most nutrients when comparing self-report with interviews/label transcriptions (i.e., the criterion measure), although nutrient intakes from the interviews were somewhat higher than those from the questionnaire. This finding may be due to the closed-ended format of the questionnaire, which did not allow respondents to give their actual dose if this amount exceeded the largest dose option on the questionnaire. In addition, during the in-person interviews, several participants reported taking more than one pill each time they used a particular supplement; however, it is not clear that this supplement-use behavior was reported on the questionnaire.

Finally, some participants may have changed their supplement-use patterns during the 3 months between completion of the baseline questionnaire and the home interview.

There is ample evidence from experimental studies that supplement use increases nutrient concentrations in biologic markers (32, 35–40). In this study, beta-carotene, vitamin C, and alpha-tocopherol showed clear and significant linear trends of increasing blood concentrations with higher supplemental intakes. In addition, we demonstrated that, after excluding single-supplement users, biomarker values of these nutrients increased with more frequent multivitamin use (i.e., nonusers to use 7 days a week). To our knowledge, no other investigators have validated measures of multivitamin use.

The partial Pearson’s correlation of 0.68–0.69 between questionnaire and biomarker (serum) estimates for vitamin E is generally higher than has been reported in other studies (9, 32, 39, 40). White et al. (9) reported that supplemental vitamin E assessed by interview/transcription was the strongest predictor of serum alpha-tocopherol concentrations among 1,047 postmenopausal women (Pearson’s r = 0.60).
TABLE 3. Validation of current self-reported supplemental nutrient intakes by comparison with intakes from interviews/label transcriptions (criterion measure) (n = 149), Vitamins and Lifestyle Study, 2001

<table>
<thead>
<tr>
<th>Supplement use (current daily supplemental intake)†¶</th>
<th>Distributions by baseline questionnaire</th>
<th>Distributions by interview/transcription§</th>
<th>Questionnaire vs. interview/ transcri prion</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonusers (%)</td>
<td>Distributions among users by the following percentiles</td>
<td>Nonusers (%)</td>
<td>Distributions among users by the following percentiles</td>
</tr>
<tr>
<td></td>
<td>25th</td>
<td>50th</td>
<td>75th</td>
<td>25th</td>
</tr>
<tr>
<td>Retinol (µg)#</td>
<td>46.6</td>
<td>765.0</td>
<td>1,200.0</td>
<td>1,500.0</td>
</tr>
<tr>
<td>Beta-carotene (µg)#</td>
<td>52.1</td>
<td>1,767.9</td>
<td>1,800.0</td>
<td>3,471.4</td>
</tr>
<tr>
<td>Vitamin C (mg)</td>
<td>32.9</td>
<td>60.0</td>
<td>440.0</td>
<td>620.0</td>
</tr>
<tr>
<td>Vitamin D (cholecalciferol) (µg)**</td>
<td>45.3</td>
<td>7.9</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Vitamin E (alpha-tocopherol) (mg) ††</td>
<td>29.5</td>
<td>35.4</td>
<td>180.0</td>
<td>200.3</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;1&lt;/sub&gt; (thiamin) (mg)</td>
<td>46.3</td>
<td>1.2</td>
<td>15.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;3&lt;/sub&gt; (niacin) (mg)</td>
<td>43.6</td>
<td>15.7</td>
<td>20.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;6&lt;/sub&gt; (mg)</td>
<td>42.3</td>
<td>2.0</td>
<td>2.4</td>
<td>20.0</td>
</tr>
<tr>
<td>Folate (µg)</td>
<td>41.6</td>
<td>314.3</td>
<td>400.0</td>
<td>400.0</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt; (µg)</td>
<td>40.3</td>
<td>6.0</td>
<td>12.5</td>
<td>31.0</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>35.8</td>
<td>127.3</td>
<td>400.0</td>
<td>1,000.0</td>
</tr>
<tr>
<td>Iron (mg)</td>
<td>59.9</td>
<td>4.0</td>
<td>9.0</td>
<td>18.0</td>
</tr>
<tr>
<td>Magnesium (mg)</td>
<td>51.0</td>
<td>78.6</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Zinc (mg)</td>
<td>46.6</td>
<td>11.8</td>
<td>15.0</td>
<td>22.5</td>
</tr>
<tr>
<td>Selenium (µg)</td>
<td>48.3</td>
<td>20.0</td>
<td>25.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Chromium (µg)</td>
<td>53.0</td>
<td>65.0</td>
<td>120.0</td>
<td>130.0</td>
</tr>
</tbody>
</table>

* Randomly selected sample.
† Includes intakes from multivitamins and single supplements.
‡‡ Average current daily supplemental intake from questionnaire computed as follows: days per week × dose per day / 7 (days).
§ Average current daily supplemental intake from interview/transcription calculated as follows: frequency of use × number of pills taken each time × dose per pill / 7 (days).
¶ Log-transformed variables.
# 1 IU of vitamin A = 0.3 µg of retinol and 0.6 µg of beta-carotene.
** 1 IU of vitamin D = 0.025 µg of cholecalciferol.
†† 1 IU of vitamin E = 0.45 mg of alpha-tocopherol.

adjusted for age, ethnicity, cholesterol, triglycerides, and body mass index. The correlations for beta-carotene reported here (r = 0.25–0.31) are similar to those seen from other dietary instruments, for example, Pearson’s r = 0.24 between plasma and food frequency questionnaire estimates of beta-carotene in the Carotene and Retinol Efficacy Trial (25) and Spearman’s r = 0.22–0.32 between intakes from food frequency questionnaires and 7-day food records and plasma beta-carotene in the Whitehall study (41). Although blood levels of beta-carotene have been shown to be more responsive to supplemental beta-carotene than from food sources (32), the modest associations we observed may be partly due to the fact that our participants did not appear to be using very large doses of supplemental beta-carotene (75th percentile = 3,471 µg; table 3). The correlations between plasma and supplemental vitamin C in our study (r = 0.26–0.29) were similar to those reported by other investigators (32, 41, 42). Although our sample included a high number of vitamin C supplement users, one reason the observed associations may be small is because plasma vitamin C levels reflect intake from the previous few hours (32), and we asked participants not to use dietary supplements on the day of their appointment.

The use of biomarkers as a validation method can be limited by the lack of good biologic measures for some nutrients of interest, such as calcium. Because calcium is under tight homeostatic control and calcium excretion is higher among those with high calcium intakes compared with those with low intakes (43), the most commonly used biomarker for calcium is multiple 24-hour urine collections. Although there have been reports of excellent correlations between 24-hour and spot urine collections (20, 21), we found no associations between creatinine-adjusted spot urinary calcium values and supplemental calcium intakes, even when calcium intakes were assessed using our criterion measure (i.e., interviews/label transcriptions). We note that most studies that have reported increases in urinary calcium excretion with increased calcium intake were within-person
experimental studies, used at least two 24-hour urine collections, and supplemented at very high doses (1 g or greater) of calcium (44–47). Given that the other biomarker data suggested that the questionnaire accurately assessed multivitamin, beta-carotene, vitamin C, and vitamin E intakes, we conclude that a spot urine collection is not a useful indicator of calcium intake in cross-sectional studies.

It is informative to compare the performance of our questionnaire with that of a similar but less extensive supplement use assessment instrument. In a validation study of adult supplement users (n = 104) in Washington State, Patterson et al. (11) compared supplement intake data derived from a self-administered questionnaire with data collected from an in-person interview and transcription of the labels of supplement bottles (i.e., a criterion measure). The questionnaire was similar to that used in the National Cancer Institute/Block Health Habits Questionnaire (8), and it utilized a closed-ended response format to assess the frequency and duration of use of multivitamins, antioxidant mixtures, and single supplements, as well as usual doses of vitamin C, vitamin E, and calcium only. Correlation coefficients comparing current daily supplemental vitamin and mineral intakes from the questionnaire with the criterion measure ranged from 0.08 to 0.76 (r = 0.08 for iron, 0.26 for folate, 0.35 for selenium, 0.61 for calcium, 0.73 for vitamin E, and 0.76 for vitamin C; mean r = 0.50). The VITAL Study supplement questionnaire therefore had slightly better results for commonly used supplements (vitamin C, vitamin E, and calcium) and greater accuracy for those taken less often as single supplements and for which information on usual dose was not collected (iron, folate, and selenium). Thus, this approach to assessing supplement use in which duration of use, frequency of use, and usual doses of different types of vitamin and mineral supplements are

<table>
<thead>
<tr>
<th>TABLE 4. Validation of current self-reported supplemental nutrient intakes by comparison with biomarker concentrations, Vitamins and Lifestyle Study, 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>Mean supplemental nutrient intakes and biomarker concentrations</em>, † within groups based on self-reported supplemental intakes (n = 220):</em>*</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Nonusers</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Beta-carotene</td>
</tr>
<tr>
<td>Intake from supplements (mg)</td>
</tr>
<tr>
<td>Serum beta-carotene (µmol/liter)</td>
</tr>
<tr>
<td>Vitamin C</td>
</tr>
<tr>
<td>Intake from supplements (mg)</td>
</tr>
<tr>
<td>Plasma vitamin C (µmol/liter)</td>
</tr>
<tr>
<td>Alpha-tocopherol</td>
</tr>
<tr>
<td>Intake from supplements (mg)</td>
</tr>
<tr>
<td>Serum alpha-tocopherol (µmol/liter)</td>
</tr>
<tr>
<td>Calcium</td>
</tr>
<tr>
<td>Intake from supplements (mg)</td>
</tr>
<tr>
<td>Spot urinary calcium (mmol/liter)</td>
</tr>
</tbody>
</table>

* Serum beta-carotene, urinary calcium, and micronutrient (supplemental and dietary) values were log transformed, serum alpha-tocopherol was transformed as 1/square root, and plasma vitamin C was not transformed.
† All nutrient biomarker values, p for trend, and correlation coefficients were adjusted for age, sex, race, and current smoking. In addition, serum beta-carotene was adjusted for serum total cholesterol and dietary beta-carotene; plasma vitamin C was adjusted for dietary vitamin C; serum alpha-tocopherol was adjusted for serum total cholesterol, body mass index, and dietary alpha-tocopherol; and urinary calcium was adjusted for urinary creatinine and dietary calcium.
‡ Includes randomly selected participants (n = 149) and oversampled high users (5 years or more) of ≥1,000 mg of vitamin C (n = 26), ≥800 IU of vitamin E (n = 23), or ≥1,000 mg of calcium (n = 22).
inquired about appears valid in comparison with criterion measures, such as transcriptions of supplement bottle labels and more rigorously objective biomarkers.

This study has some limitations. The generalizability of our findings may be limited by the fact that our participants were primarily White, generally highly educated, had a high prevalence of supplement use, and were motivated to participate in this research study. Nevertheless, the study sample is comparable with the VITAL Study cohort to whom the questionnaire is being administered. These results should also be generally applicable to other populations, although the instrument might be more valid in study samples with a wide variability in supplement use (31). The length and detailed nature of our instrument may limit its use for certain investigations, such as studies in which supplement use is a secondary exposure or in populations with low levels of supplement use. In such cases, we believe that the instrument can be modified slightly without seriously compromising the validity of our findings. For example, the section on multivitamins could be simplified by providing a longer list of brand names to choose from rather than asking respondents to report the dose of each vitamin and/or mineral in their multivitamin if their brand is not included on the list. Also, respondents could be queried on a smaller group of commonly used single supplements.

Another potential limitation is measurement error. The high reproducibility observed might be the result of correlated (systematic within-person) error, which can result in spuriously high correlations. Blood and urinary measures reflect concentrations at a single point in time only and are subject to laboratory error, and our analyses could not control for differences in the absorption and metabolism of some nutrients and physiologic variations. Nonetheless, we did attempt to control for potential demographic and behavioral factors that have been shown to affect biomarker nutrient levels.

In conclusion, the detailed self-administered questionnaire described in this report appears to provide reproducible and valid measures of vitamin and mineral supplement intake. These results demonstrate the feasibility of collecting detailed data on supplement use with a self-administered instrument, even in a complex market. Furthermore, our findings suggest that the VITAL Study is well poised to support etiologic inferences regarding supplement use and cancer risk.

ACKNOWLEDGMENTS

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REFERENCES


35. Record IR, Dreosti IE, McNerney JK. Changes in plasma antioxidant status following consumption of diets high or low in fruit and vegetables or following dietary supplementation with an antioxidant mixture. Br J Nutr 2001;85:459–64.


APPENDIX

25. In the past 10 years, did you take a different brand of MULTIVITAMIN than you take now?
   ○ No  →  Go to Question 27
   ○ Yes

26. In the past 10 years, what brand of MULTIVITAMIN did you take most often? Mark only one.
   ○ Centrum®
   ○ Centrum Silver®
   ○ NatureMade® Multivitamin with minerals
   ○ NatureMade® 50+ Multivitamin with minerals
   ○ One-A-Day® Multivitamin with minerals
   ○ One-A-Day® Multivitamin (no minerals)
   ○ Theragran-M® with minerals
   ○ Theragran® (no minerals)
   ○ Unicap® M tablets with minerals
   ○ Unicap® Plus Iron Multivitamin
   ○ Unicap® Senior tablets
   ○ Generic or store brand
   ○ Other brands
   ○ Don't know

VITAMINS, MINERALS AND OTHER SUPPLEMENTS (not including multivitamins)

27. In the past 10 years, have you taken any dietary supplements other than a multivitamin for at least a year? Include vitamins, minerals, herbals, and mixtures. Also include calcium, Tums® and other antacid tablets that contain calcium.
   ○ No
   ○ Less than once a week  →  Go to Question 29, Page 10
   ○ Yes, at least once a week for a year

28. In the past 10 years, which vitamins, minerals, and herbals are (or were) in your supplements? Do NOT include multivitamins. If you have the bottles, please look at the labels.

   Vitamin A
   ○ Yes, take now
   ○ Only took in the past
   ○ 1-3
   ○ 4-6
   ○ 7-9
   ○ 10+
   ○ 1-2
   ○ 3-4
   ○ 5-6
   ○ 7
   ○ Closest amount per day:
     ○ 5000 IU
     ○ 7500 IU
     ○ 10,000 IU
     ○ 15,000 IU
     ○ 20,000 IU
     ○ Don't know

   Beta-carotene
   ○ Yes, take now
   ○ Only took in the past
   ○ 1-3
   ○ 4-6
   ○ 7-9
   ○ 10+
   ○ 1-2
   ○ 3-4
   ○ 5-6
   ○ 7
   ○ Closest amt. per day:
     ○ 5000 IU
     ○ 7500 IU
     ○ 10,000 IU
     ○ 15,000 IU
     ○ 20,000 IU
     ○ Don't know