RESEARCH LETTER

Contributions of Total Daily Intake of Folic Acid to Serum Folate Concentrations

To the Editor: Recent literature has associated potential adverse effects with daily use of folic acid supplements (1000 µg),1 high concentrations of serum folate (26.5 ng/mL or greater [to convert to nmol/L, multiply by 2.266]),2 or high folic acid intake,3 but researchers have not adequately considered the source of folic acid. We examined the relative contribution of different sources of folic acid to serum folate concentrations among US adults.

Methods. Data were obtained from a single 24-hour dietary recall from the National Health and Nutrition Examination Survey (NHANES) 2001 through 2004 for 8655 non-pregnant participants aged 19 years and older who also had serum folate concentrations measured. The 24-hour dietary recall in NHANES underestimates energy intake by 11% by 11%4; daily folic acid intake from individual fortified foods was calculated.5 Average daily intake of folic acid from supplements over the prior 30 days was calculated.6 The 3 main sources of dietary folic acid are enriched cereal-grain products (ECGPs) fortified at 140 µg of folic acid per 100 grams of flour, ready-to-eat cereals (RTEs) such as breakfast cereals with up to 400 µg of folic acid per serving, and supplements containing folic acid.

Serum folate concentration was log-transformed because the distribution was not Gaussian. Serum folate concentration quintiles were calculated for each source of folic acid.8 Differences across serum folate quintiles for each intake source and for proportion of supplement users were tested using Satterthwaite adjusted F statistic. All analyses were weighted, taking into account the complex sampling design of NHANES, using SUDAAN version 9.0 (RTI, Research Triangle Park, North Carolina), and adjusted for age, sex, and race/ethnicity. In NHANES, race/ethnicity is designated by the participant through a series of multiple-choice questions and an “other” write-in response. Statistical hypotheses were tested at a 2-tailed α = .05 level of significance.

Results. Participants in the highest serum folate quintile were more likely to be older, female, and non-Hispanic white (P < .001 for each comparison) (Table). Across the serum folate quintiles, the daily intake of folic acid from ECGPs was about 140 µg per day and showed a statistically significant but small variation (P = .01) (Figure). However, from the first to the fifth quintile, daily intake from RTEs varied from 14 to 107 µg per day (P < .001) and daily intake from supplements varied from 42 to 392 µg per day (P < .001). The adjusted proportion of ECGP-only users varied from 82.1% to 13.9% (P < .001) and supplement users varied from 10.9% to 74.6% (P < .001), respectively (Table).

Table. Characteristics of Participants Aged 19 Years or Older, National Health and Nutrition Examination Survey, 2001 – 2004

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Serum Folate Quintiles</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum folate concentration, geometric mean (95% CI), ng/mL</td>
<td>5.9 (5.8-6.1)</td>
<td>.001a</td>
</tr>
<tr>
<td>Age, mean (95% CI), y</td>
<td>40.2 (39.4-40.9)</td>
<td>.001b</td>
</tr>
<tr>
<td>Female sex, % (95% CI)</td>
<td>45.4 (42.5-48.3)</td>
<td>.001b</td>
</tr>
<tr>
<td>Race/ethnicity, % (95% CI)</td>
<td>81.2 (78.9-83.2)</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>Adjusted prevalence of ECGP-only users, % (95% CI)</td>
<td>10.9 (8.2-13.7)</td>
<td>&lt;.001d</td>
</tr>
<tr>
<td>Adjusted prevalence of supplement users, % (95% CI)</td>
<td>21.8 (18.4-25.2)</td>
<td>&lt;.001d</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval; ECGP, enriched cereal-grain product.
SI conversion factor: To convert serum folic acid to nmol/L, multiply by 2.266.
*Using t test.
Using χ² test.
Using Satterthwaite adjusted F test.
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In the highest quintile, the total adjusted mean folic acid intake was 643 µg per day and the mean serum folate was 24.3 ng/mL. Of these participants, 75% used supplements containing folic acid, which on average contributed 61% of the total daily folic acid intake. Enriched cereal-grain products contributed 22% of total daily intake. Refer to Table for quintile ranges.

Comment. High serum folate concentrations were primarily associated with the use of supplements containing folic acid. Folic acid fortification of ECGPs appears unlikely to produce the high serum folate concentrations reported in recent studies to be associated with potential adverse effects. Researchers should differentiate folic acid intake contributed by voluntary consumption of supplements and RTEs from folic acid intake due to mandatory fortification of ECGPs before attributing research findings to a particular source of folic acid. Current and planned public health prevention strategies to fortify food with folic acid should be based on information about appropriate dietary sources.

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Analysis and interpretation of data: Yeung, Yang, Berry.
Drafting of the manuscript: Yeung, Berry.
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REFERENCES