SYNOPSIS

Analysis of Folate Data from the Second National Health and Nutrition Examination Survey (NHANES II)

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In recent years, surveys of selected population groups in the United States and reviews of data on folate intake have suggested that folate nutritional status may be suboptimal in groups such as pregnant women, elderly persons and adolescents of low socioeconomic status (1–10). The intake data available in 1974 led the Food and Nutrition Board to recommend folate fortification of cereal grain products (II). As part of its effort to determine the necessity for, and safety of, fortifying cereal grain products with nutrients, including folate, the Food and Drug Administration requested that the Life Sciences Research Office, Federation of American Societies for Experimental Biology, assemble an ad hoc Expert Scientific Working Group (ESWG)4 to assess the folate, zinc, and iron nutritional status of the U.S. population. The primary data examined were the biochemical and clinical data collected during the second National Health and Nutrition Examination Survey (NHANES II), conducted during the period 1976 through 1980. This report presents a summary of the ESWG’s conclusions regarding folate nutritional status and the NHANES II data analyses that undergird them.

The NHANES II was designed to supply health and nutritional information for the civilian, noninstitutionalized population of the United States aged 6 mo through 74 yr, by utilizing a stratified, multistage, probability sample. The protocol included questionnaires on demographic variables, medical history, diet, use of medications and dietary supplements, and behavior; medical examination by a physician; anthropometric measurements; hematological and biochemical assessments; and other tests. For detailed information on the design of NHANES II and the assessments made, see McDowell et al. (12).

Serum and red blood cell (RBC) folate data were not collected in NHANES II for the purpose of assessing the folate nutritional status of the U.S. population. Rather, determinations of serum and RBC folate levels were intended to serve as an interpretive tool in those subjects who had abnormal hematological indices (13). In addition to

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the assessments on subjects with abnormal hematological indices, reference data were obtained from a random sample, approximately 10% of the total NHANES II population whose identification number ended in 8 (13). Despite the relatively small sample size, the ESWG considered that the availability of serum and RBC folate data for more than 2400 persons presented an opportunity to examine pertinent questions concerning the prevalence of folate deficiency. Calculation of national probability estimates of low folate levels, with use of an appropriate weighting procedure and consideration of design effects in the statistical analyses, was consistent with FDA's goal.

In clinical settings, low circulating folate levels are not regarded as a basis for treatment in the absence of other signs, but low serum and RBC folate values have been used in nutritional surveys to estimate the number of subjects with depleted folate stores. The serum folate level reflects recent folate balance, and it decreases to the range usually associated with deficiency within 3 wk after cessation of folate consumption (14, 15). Hematological manifestations do not appear until 3–4 mo of folate deprivation. In apparently healthy groups, up to 10% of subjects may have low levels of serum folate (16). The RBC folate level appears to be less sensitive to short-term variations in folate balance than does the serum folate level, and its decrease reflects depletion of body stores of folate (17, 18). Many subjects with low RBC folate values have normal hematological status (19, 20), which may indicate that low RBC folate levels reflect depleted tissue stores that render subjects at higher risk for the development of megaloblastosis in the event of stress (21). However, virtually all patients with megaloblastic anemia have low serum and RBC folate levels, and population studies have shown that apparently healthy individuals living in communities with a high prevalence of megaloblastic anemia have a correspondingly high prevalence of low folate values (22–25).

The methodologies employed by the Clinical Chemistry Division of the Centers for Disease Control to measure serum and RBC folate levels have been described elsewhere (13). Because of quality control problems with the Lactobacillus casei bioassay initially employed, a decision was made to switch to a commercial competitive protein-binding radioassay (Quanta-Count® Folate, Bio-Rad Laboratories, Richmond, CA) after about 40% of the NHANES II samples had been analyzed. Despite a comparison study that suggested apparent comparability of the two assay methods (26), merging of the two sets of assay data to provide a single national probability sample proved acceptable only for a limited range of values (<6 ng/ml for serum folate and <150 ng/ml for RBC folate) because of substantial divergence in the two distributions at high serum and RBC folate levels. The prevalence of low folate values in various age-sex groups could be computed from the merged data, but groups could not be compared on the basis of mean folate values. The same quality control problems occasioned loss of RBC folate values from several locations, but the ESWG concluded that the potential sampling bias introduced by this loss was probably small.

The ESWG agreed to select cutoff values of <3.0 ng/ml for serum folate and <140 ng/ml for RBC folate as the basis for estimation of the prevalence of low folate values. These selections were based on consideration of folate values reported in the literature for subjects with folate-deficient megaloblastic anemia (27–37), but these criteria are not universally accepted and their utility for identifying a folate-deficient population is not well defined in relation to the NHANES II data. Because of the methodological and sampling problems encountered, caution must be exercised in interpreting the results of analyses of NHANES II folate data. The ESWG concluded that analyses of the NHANES II folate data for prevalence of low folate values (table 1) cannot be taken as definitive assessments of the population at risk of folate deficiency but can show relative differences among population groups.

Percentages of individuals with low serum folate, low RBC folate, and both low serum and RBC folate values were lowest in children aged 6 mo–9 yr (2, 2 and 2%, respectively), males aged 10–19 yr (3, 5 and 2%, respectively), and females aged 45–74 yr (9, 4 and 2%, respectively). Females aged 20–44 yr appear to be the group at greatest risk for developing folate deficiency even though the
TABLE 1

Percent of persons aged 6 mo through 74 yr with low serum and/or red blood cell (RBC) folate levels, by sex and age: NHANES II, 1976-1980

<table>
<thead>
<tr>
<th>Sex and age</th>
<th>Estimated population in thousands</th>
<th>Serum folate</th>
<th>RBC folate</th>
<th>Serum folate and RBC folate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated population</td>
<td>% with low values&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No. of examined persons</td>
<td>% with low values&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo–9 yr</td>
<td>15,780</td>
<td>294</td>
<td>2 ± 1.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>243</td>
</tr>
<tr>
<td>10–19 yr</td>
<td>20,297</td>
<td>204</td>
<td>3 ± 1.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>178</td>
</tr>
<tr>
<td>20–44 yr</td>
<td>35,987</td>
<td>362</td>
<td>18 ± 2.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>299</td>
</tr>
<tr>
<td>45–74 yr</td>
<td>37,018</td>
<td>606</td>
<td>10 ± 2.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>503</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo–9 yr</td>
<td>15,345</td>
<td>240</td>
<td>3 ± 2.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>301</td>
</tr>
<tr>
<td>10–19 yr</td>
<td>17,885</td>
<td>210</td>
<td>12 ± 3.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>173</td>
</tr>
<tr>
<td>20–44 yr</td>
<td>40,403</td>
<td>462</td>
<td>15 ± 3.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>389</td>
</tr>
<tr>
<td>45–74 yr</td>
<td>30,859</td>
<td>532</td>
<td>9 ± 2.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>439</td>
</tr>
</tbody>
</table>

<sup>a</sup>All statistics are weighted to represent the U.S. population at the midpoint of the survey (March 1, 1978) by a method that accounts for the complex survey design. Low folate criteria were serum folate values <3.0 ng/ml and RBC folate value <140 ng/ml. Value after ± is the SE of the percent. <sup>b</sup>Values for percent within a sex group with a common superscript are not significantly different at P < 0.05, based on one-tailed t-test, Bonferroni multiple comparison method (36).

percentages of subjects with deficient values of serum folate, RBC folate and both (15, 13 and 6 %, respectively) were not statistically different (P < 0.05) from those for males aged 20–44 yr (18, 8 and 5 %, respectively) or females aged 10–19 yr (12, 8 and 2 %, respectively). Effects of pregnancy and parity would be expected to increase the risk of folate deficiency in females in the age group 20–44 yr. The percentages of low folate values for adolescents, females of childbearing age, and older adults found in NHANES II are substantially lower than those reported in several smaller studies of these population groups. At least part of the difference between these reports and the NHANES II data may be attributed to the nature of the smaller samples in the reported studies, which were not selected to be representative of the U.S. population, and differences in analytical methodology and cutoff values used.

Excluding persons aged 20–64 yr with serum folate values <3.0 ng/ml or RBC folate values <140 ng/ml had no effect on median hemoglobin concentration, mean corpuscular volume, or percentage of individuals with macrocytosis, indicating that relatively few subjects with low folate values had low hemoglobin levels, or increased MCV, or large numbers of macrocytic red blood cells.

In unweighted folate data obtained by either the microbiological or radioassay methods, median serum and RBC folate values were higher in children aged 6 mo–2 yr, 3–4 yr, and 5–9 yr than in older age groups. Whether the relatively high levels were attributable to diet or to age-related changes in folate metabolism could not be determined.

The effects of several characteristics of persons aged 20–74 yr on prevalences of low folate values were examined in univariate analyses. Percentages of females with low serum and/or RBC folate values were significantly lower (P < 0.05) in users of vitamin/mineral supplements than in nonusers. More smokers tended to have low folate values than nonsmokers, but the difference was significant only for serum folate in females. The percentage of black males with low RBC folate values was higher (P < 0.01) than that of white males. The percentages of low
folate values did not differ significantly in aspirin users vs. nonusers, regular medication users vs. nonregular users, fasting vs. nonfasting subjects, or persons with incomes above the poverty level vs. those with incomes below the poverty level. Although pregnancy, oral contraceptive agent use, and parity were associated with increased percentages of females aged 20–44 yr with low folate values, the increases were not significant at \( P < 0.05 \). These results might be altered if a multivariate model with controls for confounding variables were used in the analyses. The full report of the ESWG contains recommendations for additional analyses of the NHANES II folate data and for the assessment of folate status in future nutritional surveys.

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LITERATURE CITED


