Review of the magnitude of folate and vitamin B\textsubscript{12} deficiencies worldwide

Erin McLean, Bruno de Benoist, and Lindsay H. Allen

\textbf{Key words:} Folate deficiency, folic acid, homocysteine, methylmalonic acid, vitamin B\textsubscript{12} deficiency

\textbf{Abstract}

Human deficiencies of folate and vitamin B\textsubscript{12} result in adverse effects which may be of public health significance, but the magnitude of these deficiencies is unknown. Therefore, we examine the prevalence data currently available, assess global coverage of surveys, determine the frequency with which vitamin status assessment methods are used, and identify patterns of status related to geographical distribution and human development. Surveys were identified through PubMed and the Vitamin and Mineral Nutrition Information System at the World Health Organization (WHO). Since different thresholds were frequently used to define deficiency, measures of central tendency were used to compare blood vitamin concentrations among countries. The percentage of countries with at least one survey is highest in the WHO Regions of South-East Asia and Europe. Folate and vitamin B\textsubscript{12} status were most frequently assessed in women of reproductive age (34 countries), and in all adults (27 countries), respectively. Folate status assessment surveys assessed plasma or serum concentrations (55%), erythrocyte folate concentrations (21%), or both (23%). Homocysteine was assessed in one-third of the surveys of folate and vitamin B\textsubscript{12} status (31% and 34% respectively), while methylmalonic acid was assessed in fewer surveys of vitamin B\textsubscript{12} status (13%). No relationship between vitamin concentrations and geographical distribution, level of development, or population groups could be identified, but nationally representative data were few. More representative data and more consistent use of thresholds to define deficiency are needed in order to assess whether folate and vitamin B\textsubscript{12} deficiencies are a public health problem.

\textbf{Introduction}

Folate and vitamin B\textsubscript{12} deficiencies have long been known to have adverse effects on health, including anemia and neuropathy. Associations between low status of these vitamins and other health risks have been discovered more recently. Epidemiological research [1–3] and randomized, controlled trials [4] have demonstrated that increasing folic acid intake can reduce the incidence of neural tube defects. Homocysteine, high concentrations of which have been associated with cardiovascular disease (CVD) [5] and CVD mortality [6], can be lowered through folic acid or vitamin B\textsubscript{12} supplementation, even in individuals with normal plasma concentrations of the vitamins [7]. However, it has not been elucidated whether elevated homocysteine is a cause of increased CVD risk, or if it is a biomarker. Epidemiological evidence suggests higher folate intake or better folate status is associated with lower cancer risk [8]. Supplementation with vitamin B\textsubscript{12} or folate has resulted in decreased DNA damage in young adults with a low prevalence of deficiency, if such deficiency is defined by < 150 pmol/L for plasma vitamin B\textsubscript{12} concentrations, and by < 136 nmol/L for erythrocyte folate concentrations [9].

Thus, deficiencies of folate and vitamin B\textsubscript{12} have the potential to be a public health problem, but the magnitude of these deficiencies throughout the world is not known. Two recent reviews addressed vitamin B\textsubscript{12} deficiency in the Americas [10] and globally [11]. However, there are some national surveys to which the authors of the present article had access that were not included in previous reviews. The purpose of this paper is to expand on the earlier reviews regarding vitamin
B₁₂ deficiency, and to review data on folate deficiency to determine if there are sufficient data to ascertain the national and global prevalence of these deficiencies, and thus their potential public health importance.

Methodology

Identification and selection of surveys

PubMed was searched using the term “B₁₂ OR cobalamin OR folate” from January 1, 1995, through September 30, 2005. In some cases, articles found through this search strategy referred to others that were not identified by the search. Those articles were located and included if relevant. Other articles were identified through the WHO Vitamin and Mineral Nutrition Information System (VMNIS). Surveys were included if they were conducted in 1995 or later. If no survey date was indicated, articles were included only if they were published in or after January 1995. This approximate 10-year limit was set since both socioeconomic conditions and laboratory methodologies change over time.

Few surveys were designed to assess the vitamin status of the general population at the national or provincial level. Most data are derived from local surveys not representative of the general population. Given the paucity of data available, we also included local data using the following selection criteria:

- Document was available to WHO. For journals that were not accessible from WHO, an attempt to find contact information (e-mail addresses) for study authors was made and, if found, the article was requested.
- The subjects sampled were from the general population. Hospitalized and institutionalized subjects were not included. If a publication reported on healthy subjects from a survey in which those with anemia or poor vitamin status were excluded, the data were not included.
- Controls from case-control studies were eligible for inclusion if they were not specifically selected based on the absence of vitamin B₁₂ or folate deficiency.
- The article stated the thresholds used to determine deficiency (studies were excluded if they stated simply “no individuals were deficient” without providing a threshold), or expressed values as tertiles, quartiles, or quintiles, so an estimate of the proportion of the population below a specified vitamin concentration close to the usual thresholds could be derived. If no thresholds were provided, an attempt was made to follow-up with study authors and if data were obtained they were included.
- The sample size was at least 50.

Survey coverage

The number of countries covered by at least one survey was determined and the percentage of countries with data was classified by WHO Region and on a global level. These WHO regions are Africa, Americas, South-East Asia, Europe, Eastern Mediterranean, and Western Pacific.

The coverage was also assessed by population groups. Surveys were grouped by infants (0 to 11.9 months) and preschool-aged children (12.0 to 59.9 months) combined, school-aged children (5 to 14 years), pregnant and lactating women combined, women of reproductive age (15 to 49 years), and adults which included several population groups: men, both men and women when results were reported together, or women whose age range exceeded reproductive age (15 to 59 years), and the elderly (> 60 years).

Indicators used to assess folate and vitamin B₁₂ status

In the surveys reviewed, the primary indicators used to assess folate and vitamin B₁₂ status included plasma or serum folate, red blood cell folate, plasma or serum vitamin B₁₂, plasma or serum homocysteine, and plasma or serum methylmalonic acid (MMA). Plasma or serum concentrations of the vitamins were used preferentially in this review, but red blood cell folate was used when serum folate was unavailable.

The measures of central tendency provided by the surveys included arithmetic means, geometric means, and medians. While these do not provide identical information, they were used to provide information on the general status of the populations surveyed. The thresholds used to delineate normal from deficient values for the blood concentration of folate and vitamin B₁₂ vary widely. Since no standard threshold exists, surveys were included regardless of the threshold used in the survey. However, this made comparing the prevalence of deficiencies among countries difficult, and necessitated the use of other methods for comparing data, including looking at measures of central tendency rather than the prevalence of deficiency.

Comparing folate and vitamin B₁₂ status among countries

As indicated above, it was not possible to compare the prevalence values among surveys. Thus, a crude analysis was performed to compare a measure of central tendency with the prevalence provided by each survey. The resulting analysis indicated an inverse relationship: as mean concentration increased, prevalence of deficiency decreased. Thus, the decision was made to compare measures of central tendency with 95% confidence intervals among countries. Therefore, all surveys were identified that presented a mean or
a geometric mean and a 95% confidence interval, or a standard deviation and sample size, or a standard error, or the interquartile range, from which the 95% confidence interval could be calculated. From these surveys, one was selected to represent each country and each population group for this comparison of available data. With the exception of large national survey data, it was not assumed that these data from smaller local or regional studies represent the actual situation in that country. In selecting a survey, the objective was to choose one that was the most representative of all of the surveys for that country, although it is recognized that none of these surveys were necessarily representative. Thus, when more than one survey was available, the selection process was as follows, in order of priority: the survey carried out at the highest administrative level, the most recent survey, and then the survey with the largest number of participants.

To compare folate and vitamin B\textsubscript{12} status by stage of development, countries were divided into two categories using the 2005 Human Development Index (HDI), which is a composite score of life expectancy, education, and gross domestic product. Countries with High Human Development (0.80 < HDI < 1.00) were placed in one category and all other countries were placed in a second category (HDI < 0.80). In 2005, 57 of the 177 countries analyzed fell into the category of High Human Development.

The objective of this report was to examine the relationships between geography, stage of development, and folate and vitamin B\textsubscript{12} status. Thus, for countries with mandatory fortification programs, prefortification values were used, but this could not be done for countries with voluntary fortification programs because such programs usually lack a precise start date and are phased in over time.

When comparing national data, the prevalence for the provided threshold was used unless data for multiple thresholds were available. In the latter case, the closest threshold to the thresholds used most frequently in the data collected, 6.8 nmol/L for folate and 148 pmol/L for vitamin B\textsubscript{12}, were utilized for this report. In the 1990s, technical problems were identified with a widely used kit for the measurement of folate [12]. As a result, the thresholds applied to the last national survey in the United States were reduced from 6.8 nmol/L to 4.5 nmol/L. However, since it was unclear whether the same kit was used for other country surveys included in this report, the 6.8 nmol/L cutoff was applied to the US data as it was to other countries.

**Results**

**Estimate of the dataset coverage**

Table 1 shows that that the number of countries with a survey on at least one population group at the national level is limited to nine for folate and to seven for vitamin B\textsubscript{12}, with most of the national surveys being conducted in the Americas (four for folate and three for vitamin B\textsubscript{12}) and in Europe (five for folate and three for vitamin B\textsubscript{12}). The remaining 42 countries covered by surveys for folate, and 43 countries covered by surveys for vitamin B\textsubscript{12}, had subnational data, with mostly local (35 in the case of folate and 38 for vitamin B\textsubscript{12}) rather than provincial or state level data (seven for folate, five for vitamin B\textsubscript{12}).

Table 2 provides information on the surveys available by population groups. Data are available for women of childbearing age, men or adults, and the elderly for the greatest number of countries. However, the population groups represented vary by region. For example, school-aged children have been assessed more frequently than any other population group in the WHO African Region.

**Indicators used**

Of the 145 studies that met the inclusion criteria for folate, the majority assessed folate status by plasma or serum concentrations (78.6%, \( n = 114 \)), while fewer assessed status by measuring erythrocyte folate (44.8%, \( n = 65 \)). In addition, 31.0% (\( n = 45 \)) of the studies measured plasma or serum homocysteine. For vitamin B\textsubscript{12}, 127 studies met the inclusion criteria and measured

<table>
<thead>
<tr>
<th>WHO Region</th>
<th>No. of countries</th>
<th>Vitamin B\textsubscript{12}</th>
<th></th>
<th></th>
<th>Folate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>National data (%)</td>
<td>Subnational data (%)</td>
<td>Total (%)</td>
<td>National data (%)</td>
</tr>
<tr>
<td>Africa</td>
<td>46</td>
<td>0 (17.4)</td>
<td></td>
<td>8 (17.4)</td>
<td>0 (17.4)</td>
</tr>
<tr>
<td>Americas</td>
<td>35</td>
<td>3 (8.6)</td>
<td>7 (20.0)</td>
<td>10 (28.6)</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>11</td>
<td>0 (54.5)</td>
<td>6 (54.5)</td>
<td>6 (54.5)</td>
<td>0 (54.5)</td>
</tr>
<tr>
<td>Europe</td>
<td>52</td>
<td>3 (5.8)</td>
<td>15 (28.8)</td>
<td>18 (34.6)</td>
<td>5 (9.6)</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>21</td>
<td>0 (19.0)</td>
<td>4 (19.0)</td>
<td>4 (19.0)</td>
<td>0 (19.0)</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>27</td>
<td>1 (3.7)</td>
<td>3 (11.1)</td>
<td>4 (14.8)</td>
<td>0 (18.5)</td>
</tr>
<tr>
<td>Total</td>
<td>192</td>
<td>7 (3.6)</td>
<td>43 (22.4)</td>
<td>50 (26.0)</td>
<td>9 (4.7)</td>
</tr>
</tbody>
</table>

\( a \). Maximum coverage, countries with data, even if there is only one survey or one population group.
plasma or serum vitamin B₁₂. Plasma or serum homocysteine was also measured in 33.9% \( (n = 43) \) of these studies on vitamin B₁₂, while 12.6% \( (n = 16) \) measured plasma or serum methylmalonic acid (MMA). These figures are displayed by region in Table 3.

### Thresholds used

A range of thresholds were reported with relatively similar “low” (~100 to 150 pmol/L for vitamin B₁₂ and ~5 to 8 nmol/L for folate) or “high” (~200 to 250 pmol/L for vitamin B₁₂ and ~10⁻¹² nmol/L for folate) thresholds used. For folate, 63.4% of the studies provided a low threshold only, 26.9% provided both a low and a high threshold, and 9.7% provided only a high threshold. For vitamin B₁₂, 64.0% of the studies provided only a low threshold, while 26.3% provided both a low and a high threshold, and 9.6% provided only a high threshold.

#### Folate and vitamin B₁₂ status of the population at a global level

The measures of central tendency for folate concentra-

<table>
<thead>
<tr>
<th>WHO Region (no. of countries)</th>
<th>Vitamin</th>
<th>Infants</th>
<th>Preschool children</th>
<th>School children</th>
<th>Women of reproductive age</th>
<th>Pregnant women</th>
<th>Men or adults</th>
<th>Elderly</th>
<th>Total no. of countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa (46)</td>
<td>B₁₂</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Folate</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Americas (35)</td>
<td>B₁₂</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Folate</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>South-East Asia (11)</td>
<td>B₁₂</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Folate</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Europe (52)</td>
<td>B₁₂</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>10</td>
<td>2</td>
<td>8</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Folate</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>14</td>
<td>4</td>
<td>5</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Eastern Mediterranean (21)</td>
<td>B₁₂</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Folate</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Western Pacific (27)</td>
<td>B₁₂</td>
<td>3</td>
<td>4</td>
<td>12</td>
<td>26</td>
<td>10</td>
<td>27</td>
<td>19</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Folate</td>
<td>3</td>
<td>5</td>
<td>11</td>
<td>34</td>
<td>14</td>
<td>21</td>
<td>14</td>
<td>51</td>
</tr>
</tbody>
</table>

**Folate and vitamin B₁₂ status according to WHO Region**

<table>
<thead>
<tr>
<th>WHO Region</th>
<th>Vitamin B₁₂ status</th>
<th>Folate status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Studies that met inclusion criteria</td>
<td>Studies that assessed homocysteine</td>
</tr>
<tr>
<td>Africa</td>
<td>8</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Americas</td>
<td>45</td>
<td>13 (28.9)</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>11</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>Europe</td>
<td>47</td>
<td>19 (40.4)</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>5</td>
<td>2 (40.0)</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>11</td>
<td>4 (36.4)</td>
</tr>
<tr>
<td>Total</td>
<td>127</td>
<td>43 (33.9)</td>
</tr>
</tbody>
</table>

*a. Number of studies (% of total).

b. Included in this total is the Mexico National Survey, which in fact used whole-blood folate and not red blood cell folate.*
tions in plasma or serum varied from 3.6 nmol/L in a local survey of Iranian men [13] to 32.0 nmol/L in a local survey of Kenyan schoolchildren [14] (or 50.1 nmol/L in elderly women from the United States, if postfortification concentrations are included [15]). For vitamin B₁₂, these concentrations ranged from 100 pmol/L in men in a local Cuban survey [16] to 779 pmol/L in nonpregnant women in a local survey in the Republic of Korea [17]. Red blood cell folate values were not included in the comparison of central tendencies because they cannot be compared with serum or plasma folate concentrations, and the few data available did not warrant a separate comparison.

There is no clear relationship between the mean concentration of plasma or serum folate or vitamin B₁₂ and the geographical distribution, the level of development of countries, or the age and biological groups. Measures of central tendencies and their 95% confidence intervals are displayed for adults for folate (fig. 1), and vitamin B₁₂ (fig. 2). This population group had the most data; however, trends were similar for preschool-aged children, school-aged children, pregnant or lactating women and the elderly.

In the four countries for which pre- and postfortification data were available and where food fortification with folic acid is mandatory (Canada, Chile, Costa Rica, and the United States), the mean values of the postfortification period are higher than the mean values of the prefortification period for all age and biological groups. These postfortification values are the highest mean values among all of the surveys, irrespective of age and biological grouping. For instance, the mean blood concentration of folate postfortification varies from 26.6 nmol/L in Costa Rican adolescents to 46.4 nmol/L in American preschool-aged children and 37.2 nmol/L in Chilean adults.

From the national surveys reviewed, the prevalence of low blood folate concentrations does not seem to be related to the geographical regions, the level of development, or the biological groups (fig. 3). Comparing national survey data on preschool children from Costa Rica (prefortification), the United States (prefortification), and Venezuela, the percentages of plasma/serum folate concentrations below 6.8 to 7.0 nmol/L are 2.3%, 0.5%, and 33.8%, respectively. In adults, the prevalence of low plasma/serum concentrations in the United States and Costa Rica (prefortification) was 24.5% and 4.0%, respectively.

National level survey data for vitamin B₁₂ indicates that the prevalence of low serum or plasma values is unrelated to geographical distribution, and as shown in (fig. 4), there are large variations within a given age group, even within the same geographical area. In adults, the prevalence of low serum or plasma vitamin B₁₂ concentrations (< 130 to 148 pmol/L) varies from 2.7% in the United States, to 8.3% in the United Kingdom, and 14.7% in Germany. In the elderly, the prevalence values range from 2.7% in the United States, to 12.0% in New Zealand, and 31.8% in the United Kingdom.

FIG. 1. Folate concentrations for surveys from countries according to Human Development Index (HDI) group and vitamin concentration.
FIG. 2. Vitamin B₁₂ concentrations for countries according to Human Development Index (HDI) group and vitamin concentration.

FIG. 3. Prevalence of folate deficiency in countries with nationally representative data.

FIG. 4. Prevalence of vitamin B₁₂ deficiency in countries with nationally representative data.
A relationship between the prevalence of low serum or plasma vitamin B$_{12}$ concentrations and level of development may exist; however, the number of surveys available to us was limited. For national data, there is only one report from a country with an HDI score less than 0.8, Venezuela, making it impossible to evaluate this relationship. When local data are examined, the greatest number of individuals with low serum or plasma vitamin B$_{12}$ concentrations (<130 to 170 pmol/L) are in countries with an HDI score of less than 0.8 for all age or biological groups, reaching figures of 40% to 50% in Jordanian men [37], Indian adults [59], and Kenyan school-aged children [14]. Only one country with a higher HDI score, Chile, has a prevalence of vitamin B$_{12}$ deficiency in this range, but in the elderly [60]. In pregnant women, who are known to have lower concentrations of the vitamin, a prevalence of 60% was reported in Venezuela [49].

**Folate and vitamin B$_{12}$ status of the population in countries where national or state level surveys were carried out**

Few studies have assessed vitamin B$_{12}$ and folate status at the national or state level. Results from those countries that assessed status on these administrative levels in the last 10 years are described below.

**National**

**Costa Rica**

A national survey was conducted in 1996 prior to folic acid fortification of flour. Folate status was assessed in preschool-aged children [51], women of reproductive age [55], and lactating women [52]. At that time, serum folate concentrations <6.8 nmol/L were present in 2%, 4%, and 49% of preschool-aged children, women of reproductive age, and lactating women, respectively. In a local postfortification study, no serum folate concentrations <7 nmol/L were observed among the 399 male and female adults (20 to 40 years) surveyed [61]. Vitamin B$_{12}$ status was assessed on a national level only in lactating women, in 1996 [52]. Five percent of lactating women had a serum vitamin B$_{12}$ concentration <148 pmol/L. After fortification with folic acid, a local study of adults (20 to 40 years) revealed that 18% of the women ($n = 213$) and 17% of the men ($n = 186$) had serum vitamin B$_{12}$ concentrations <165 pmol/L [18].

**France**

Between 1994 and 2001, a national survey was conducted in France through SUVIMAX, a multiple micronutrient supplementation project [62]. Subjects were randomly assigned to receive a low-dose vitamin and mineral supplement containing both folic acid and vitamin B$_{12}$, or a placebo. B vitamin status was assessed after 2 years (1996–97) of supplementation in a subsample of participants. Therefore, approximately half of the participants had been taking the vitamin and mineral supplement for 2 years. Erythrocyte folate concentrations were assessed in a randomly selected national subsample [54]. Plasma folate concentrations were measured only in participants in Paris [24]. Six percent of men ($n = 946$) and 8% of women ($n = 1,143$) had erythrocyte folate <340 nmol/L. Ten percent of men and women in the Paris cohort ($n = 291$) had plasma folate concentrations <5.9 nmol/L. Plasma vitamin B$_{12}$ concentrations were measured in the Paris cohort only, and none of the subjects ($n = 313$) had plasma vitamin B$_{12}$ <148 pmol/L.

**Germany**

A national survey was conducted in women of childbearing age in Germany in 1998 [46]. Of 1,266 women, 1% had serum folate concentrations <7.5 nmol/L and the same proportion had erythrocyte folate concentrations <300 nmol/L. The 25th percentile of serum vitamin B$_{12}$ concentrations in these German women was 173 pmol/L and 14.7% had a serum vitamin B$_{12}$ concentration <148 pmol/L.

**Mexico**

A national survey conducted in Mexico in 1999 assessed folate status in children less than 12 years of age and women of childbearing age (12 to 49 years) [50]. Status was assessed using a dried blood spot method so the results are not comparable to other surveys. In a subsample of women, hemoglobin folate and erythrocyte folate were compared, and the resulting regression equation suggested that a cutoff of 57 ng/mL (129 nmol/L) for hemoglobin folate was equivalent to 140 ng/mL (317 nmol/L) for erythrocyte folate. Five percent of the women ($n = 603$) and 11.3% of children under 12 ($n = 1,305$) had a folate concentration below this cutoff. The prevalence was highest in 3- and 4-year-old children (11.2%), and lowest in 11-year-old children (2.3%).

**New Zealand**

New Zealand conducted a National Nutrition Survey in 1997 as an extension of the 1996–97 Health Survey, which included a population-based sample. Thirty percent of the elderly (>65 years) from the population-based sample participated in the National Nutrition Survey [63]. Twelve percent of these subjects had serum vitamin B$_{12}$ concentrations <148 pmol/L and another 28% had concentrations between 148 and 221 pmol/L.

**Norway**

A randomly selected subset of serum samples collected from newborns, as part of routine testing in Norway in 1999, was analyzed for serum vitamin B$_{12}$ ($n = 4,874$), methylmalonic acid ($n = 993$), and total homocysteine
(n = 4,712) [57]. The purpose was to evaluate homocysteine screening of newborns for the detection of homocystinuria and vitamin B₁₂ deficiency. While there are no established cutoffs for newborns, 3.3% of this sample had a serum vitamin B₁₂ concentration < 100 pmol/L. Homocysteine was > 15 μmol/L in 2.7% and the 5th percentile for methylmalonic acid concentrations was 0.60 μmol/L.

**Switzerland**

A representative national survey was conducted in 1999 of 300 pregnant women in their second and third trimester. Four percent of these women had serum folate < 5.7 nmol/L [53]. The prevalence was greater in women in their third trimester (5%, n = 159) than those in their second trimester (2%, n = 138).

**United Kingdom**

A National Diet and Nutrition Survey was conducted in adults (19 to 64 years) in 2000–2001 [21] and in institutionalized and noninstitutionalized elderly (≥ 65 years) in 1994–95 [56]. One percent of men (n = 636) and 0% of women (n = 678) had low serum folate concentrations, defined as 6.3 or 7.0 nmol/L. Erythrocyte folate concentrations were < 230 nmol/L in 1% and 0% of men and women, and < 350 nmol/L in 5% of both groups. In a subgroup of women of reproductive age (19 to 49 years), none had low serum folate concentrations or erythrocyte folate concentrations < 230 nmol/L, but 5% had erythrocyte folate < 350 nmol/L.

In free-living (noninstitutionalized) elderly, 6% had serum folate concentrations < 5 nmol/L and 15% were < 7 nmol/L (n = 939). Erythrocyte folate concentrations were < 230 nmol/L and 345 nmol/L in 8% and 29% respectively. In adults, 6% of men (n = 632) and 10% of women (n = 667) had a serum vitamin B₁₂ concentration < 150 pmol/L. In women of reproductive age (19 to 49 years), 11% had serum vitamin B₁₂ < 150 pmol/L (n = 476). Serum vitamin B₁₂ concentrations fell below 130 pmol/L in 31% of the elderly. Thus, vitamin B₁₂ deficiency in the United Kingdom elderly may be a problem of public health significance.

**United States**

In the United States, the National Health and Nutrition Examination Survey (NHANES) provides nationally representative data. The first cycle (1999–2000) of postfortification results has been analyzed [15]. Only 0.5% of the population had a serum folate concentration < 6.8 nmol/L. In preschool-age children (3 to 5 years), school-age children (6 to 11 years), and the elderly (> 60 years), the prevalence of low concentrations was 0%, while the prevalence was 0.8% in women of childbearing age (12 to 49 years), and 0.5% in men. Vitamin B₁₂ concentrations < 148 pmol/L were present in 0% of preschool and school-age children. In women of childbearing age, and in men, concentrations were below this cutoff in 1.9% and 1.7% of individuals, respectively. In the elderly, 2.7% had a vitamin B₁₂ concentration below the cutoff.

**Venezuela**

A national survey in 2001–02, which examined children in Caracas and 16 other cities throughout the country, revealed that 33.0% of 0- to 7-year-old children had serum folate concentrations < 6.8 nmol/L (n = 1,792) and 11.4% had serum vitamin B₁₂ concentrations < 148 pmol/L (n = 1,795) [49]. In Gran Caracas, 36.3% and 61.3% of pregnant women (n = 1,283) had serum folate and vitamin B₁₂ concentrations < 6.8 nmol/L and 148 pmol/L, respectively [49].

**State**

**Canada**

Provincial surveys have been conducted in the elderly in British Columbia and Ontario [64] and in pregnant [65] and nonpregnant women in Newfoundland [28]. In the elderly, 6.3% had serum folate concentrations < 6 nmol/L before fortification (n = 4,572) and 0.9% fell into this category after fortification (n = 11,092), while figures for vitamin B₁₂ concentrations < 133 pmol/L were 12.4% and 9.7%, respectively. In pregnant women, 2.4% had serum folate concentrations < 7 nmol/L before fortification with folic acid and 25.3% had serum vitamin B₁₂ concentrations < 130 pmol/L. In nonpregnant women in Newfoundland, the geometric mean serum folate concentration increased from 13.5 nmol/L (n = 233) to 18.1 nmol/L (n = 204) pre- to postfortification, while serum vitamin B₁₂ concentrations below 133 pmol/L were 0% post-folic acid fortification [28].

**China**

In Taiwan, China, a nutrition and health survey with a multistage, stratified sampling design indicated that none of the elderly had a serum folate concentration < 7 nmol/L, and that 7.2% of women and 12.0% of men had a serum vitamin B₁₂ concentration < 258 pmol/L [66]. No information using a lower threshold for vitamin B₁₂ concentrations was provided.

**Philippines**

A survey took place in two states, Negros Occidental and Davao, but was designed to look at mothers of children born with orofacial clefts and controls [36]. In the control mothers, erythrocyte folate < 317 nmol/L was not detected in any women in Negros Occidental (n = 195), but was present in 1.3% in Davao (n = 395). No vitamin B₁₂ deficiency was detected in either state, although the threshold used was not provided.

**Spain**

In Spain, state level surveys have been conducted in
the Canary Islands [67] and in Andalusia [32]. In the Canary Islands, 0.13% of 6- to 75-year-olds had serum folate concentrations < 6.8 nmol/L, while in Andalusia, 12.8% of those aged 25 to 60 years were below the same threshold. Vitamin B$_{12}$ concentrations < 148 pmol/L occurred in 3.4% in the Canary Islands and 11% in Andalusia.

**Sweden**

A case-control study, which compared folate status of women who had a spontaneous abortion with that of pregnant control women who did not, ascertained that 43.1% of the pregnant controls ($n = 921$) in Uppsala county had a plasma folate concentration < 6.8 nmol/L [68]. In two case-control studies in Vasterbotten and Norbatten counties, serum folate concentrations were < 6.8 nmol/L in 34.7% and 30.1% of men ($n = 150$) and adults ($n = 156$) respectively [31, 69]. In the same subjects, serum vitamin B$_{12}$ concentrations were < 148 pmol/L in 3.3% of men and 2.6% of adults.

**Tajikistan**

The Ministry of Health conducted a micronutrient status survey in four states in 2003 [43]. For folate status, one state (Regions of Republican Subordination) was selected, and 5-methyl-tetrahydrofolate (5-methyl-THF) assessment by high-performance liquid chromatography (HPLC) indicated that 73.7% of women ($n = 300$) had a serum 5-methyl-THF concentration < 6.8 nmol/L. Women in rural areas were more affected than women in urban areas (78.3% vs. 58.6%). However, since this assessment technique differs from that used in the other surveys presented here, the results may not be directly comparable.

**Countries with local- or district-level data and a high prevalence of low blood concentrations of folate and vitamin B$_{12}$**

Several surveys stood out because they revealed an extremely high prevalence of folate and/or vitamin B$_{12}$ deficiency in at least one population group in a country for which no national or state surveys were available. These surveys are discussed below under their respective countries, grouped by poor folate or vitamin B$_{12}$ status, and the prevalence data for both vitamins included where available.

**Countries with local- or district-level data and a high prevalence of low blood folate concentrations**

**Bangladesh**

In Bangladesh, 34% of men had plasma folate concentrations < 6.8 nmol/L, but only 19% of the women had concentrations that low [39]. Vitamin B$_{12}$ deficiency was not as prevalent: 12% of women and 8% of men had plasma concentrations < 150 pmol/L.

**China**

Through a birth defects surveillance system in China in 1993, a much higher prevalence of neural tube defects was observed in the North than in the South, and it was speculated that folate status was different in these areas [4]. In 2001, a large survey was conducted in both regions to determine folate status in the spring and fall in both men and women (35 to 64 years) [70]. In the South, plasma concentrations were < 6.8 nmol/L in 9.2% of the men in the spring and 12.8% in the fall. For women, the prevalence was 1.0% in the spring and 2.7% in the fall. Erythrocyte folate concentrations in the South were < 363 nmol/L in 7.2% and 6.2% of men in the spring and fall, respectively, and in 2.0% and 1.4% of women. In the North, deficiency was much more prevalent. Plasma concentrations were < 6.8 nmol/L in 60.0% and 42.9% of men in the spring and fall, respectively, and in 35.1% and 13.0% of women in both seasons. Erythrocyte folate concentrations were deficient in 35.0% and 25.2% of men in the spring and fall and in 31.8% and 12.4% of women by season. This large study did not evaluate vitamin B$_{12}$ status. However, two local studies in Anquing and Beijing suggest that while concentrations < 148 pmol/L may not be prevalent in women of childbearing age (2.1% to 4.5%), moderately low concentrations (148 to 221 pmol/L) may be more prevalent (9.8% to 32.8%) [40, 71].

**Countries with local- or district-level data and a high prevalence of low blood vitamin B$_{12}$ concentrations**

**India**

In India, where vegetarianism is high, 49% of 63 healthy controls in a case-control study in Pune, Maharashtra, had serum vitamin B$_{12}$ concentrations < 148 pmol/L [59]. Twenty seven percent of the subjects were vegetarian. To what extent this small study represents the general population cannot be determined. In the same study, 16% of subjects had serum folate concentrations < 6.8 nmol/L. An assessment of 283 pregnant women in 6 villages in Haryana state revealed that 26% had serum folate < 6.8 nmol/L [72].

**Kenya**

In Kenya, a large local survey in the district of Embu ($n = 512$) revealed that 40% of school-aged children had plasma vitamin B$_{12}$ concentrations below 148 pmol/L and another 28% had concentrations between 148 and 221 pmol/L [14]. However, no child had a plasma folate concentration < 6.8 nmol/L and only 1% had concentrations between 6.8 and 13.6 nmol/L.

**Nepal**

In the Sarlahi district in Nepal, 28% of 1,158 pregnant women had serum vitamin B$_{12}$ concentrations < 150 pmol/L.
Folate and vitamin B\textsubscript{12} deficiencies worldwide

pmol/L while 12\% had serum folate concentrations $< 6.7 \text{ nmol/L}$ [73].

**New Zealand**

In addition to the national data on the elderly, data on vitamin B\textsubscript{12} status in a population-based sample of women of childbearing age and adolescent boys in Dunedin were produced during a 1999 prefortification (folate) survey [74]. Twenty percent of women in this survey had serum vitamin B\textsubscript{12} concentrations $< 150 \text{ pmol/L}$ and 7\% of adolescent boys fell into the same category.

**Countries with a higher prevalence of elevated blood concentrations of homocysteine and methylmalonic acid (MMA)**

From the surveys selected because they contained prevalence data for folate and vitamin B\textsubscript{12} deficiency, countries with a high prevalence of elevated homocysteine concentrations or high population mean concentrations were identified. “High” was relative to other countries with data for the same population subgroups.

**Bangladesh**

In Bangladesh, 63\% of adult men ($n = 676$) and 26\% of women ($n = 972$) had elevated homocysteine concentrations ($> 11.4 \mu\text{mol/L}$ in men and $> 10.4 \mu\text{mol/L}$ in women) [39].

**China**

In adults (35 to 49 years) in Beijing, 44\% of men ($n = 55$) had a plasma homocysteine concentration $> 12 \text{ nmol/L}$ and 22\% of women ($n = 64$) had concentrations $> 11 \text{ nmol/L}$ [71].

**Islamic Republic of Iran**

Homocysteine concentrations were determined to be high in a population-based study of adults in Tehran [13]. The geometric mean concentration for the entire population ($n = 1,191$) was $15.7 \pm 1.5 \mu\text{mol/L}$. The geometric mean concentrations of serum folate and vitamin B\textsubscript{12} were $3.9 \pm 1.7 \text{ nmol/L}$ and $262.9 \pm 1.8 \text{ pmol/L}$, respectively.

**Nigeria**

In Nigeria, 95\% of adolescent girls ($n = 162$) had homocysteine concentrations $> 10.3 \mu\text{mol/L}$ despite a relatively low prevalence of vitamin B\textsubscript{12} and folate deficiencies; 14.2\% had serum vitamin B\textsubscript{12} concentrations $< 148 \text{ pmol/L}$ and 2.4\% had serum folate $< 6.8 \text{ nmol/L}$ [35].

**Sweden**

In Sweden, 57\% of elderly in Goteburg ($n = 209$) had homocysteine concentrations $> 16 \mu\text{mol/L}$ and 16\% had MMA concentrations $> 0.34 \mu\text{mol/L}$. Plasma vitamin B\textsubscript{12} concentrations were $< 148$ and $221 \text{ pmol/L}$ in 6\% and 25\%, respectively, and plasma folate was $< 6 \text{ nmol/L}$ and 10 nmol/L in 1\% and 13\%, respectively.

**Syrian Arab Republic**

Of Syrian adults who served as healthy controls in a case-control study ($n = 159$), 44\% had homocysteine concentrations $> 12 \mu\text{mol/L}$ [75].

**Togo**

In a survey designed to establish homocysteine determinants in West Africa, 276 subjects from coastal Togo and Benin, and the savanna in Togo, demonstrated a high prevalence (56\%) of elevated homocysteine concentrations ($> 15 \mu\text{mol/L}$) [76]. The prevalence on the coast was 62\% compared with 29\% of those in the savanna. A subgroup was identified in the coastal region with a different distribution of homocysteine and significantly poorer vitamin B\textsubscript{12} and folate status.

**United Kingdom**

In the national survey in the United Kingdom, 22\% of women and 33\% of men had homocysteine concentrations $> 12 \mu\text{mol/L}$ [21].

**Discussion**

This review provides some indication of the magnitude of folate and vitamin B\textsubscript{12} deficiencies around the world. In the majority of countries for which national surveys are available, folate and vitamin B\textsubscript{12} deficiencies appear to be a public health problem. If we consider 5\% to be the threshold above which a prevalence of low serum or plasma folate and vitamin B\textsubscript{12} is indicative of a country-wide public health problem, six out of eight countries are deficient in folate, and five out of seven are deficient in vitamin B\textsubscript{12}. These deficiencies occur in different age and biological groups. For folate, the main groups affected by deficiency are preschool children in Venezuela (33.8\%), pregnant women in Costa Rica (48.8\%) and Venezuela (25.5\%), and the elderly in the United Kingdom (15.0\%). In the United States, prior to folic acid fortification, folate deficiency was present in school-age children (2.3\%), adults (24.5\%), and the elderly (10.8\%), whereas it is now under control. In contrast, vitamin B\textsubscript{12} deficiency is prevalent in school-age children in Venezuela (11.8\%), in pregnant women in both Venezuela (10.9\%) and Costa Rica (5.3\%), and in the elderly in the United Kingdom (31.8\%) and New Zealand (12.0\%).

However, these data and the others collected for this review do not allow us to assess the folate or vitamin B\textsubscript{12} status of the entire population; either at the regional or the global level. It is therefore difficult to draw any definitive conclusions on the extent of folate and vita-
min B₁₂ deficiencies throughout the world. As shown above, some countries have conducted surveys at the national or subnational level, covering large segments of the population (province or state), but they are very few, and the surveys addressed different age or physiological groups in the population so that extrapolation to the regional level is inappropriate. Moreover, very few surveys have been conducted to specifically assess the vitamin B₁₂ and/or folate status in the general population. Additionally, status has often been assessed in small, nonrepresentative groups of individuals, or populations suspected of having a deficiency. Much of the available data comes from case-control studies where controls have been selected for not having a condition that may be associated with folate or vitamin B₁₂ deficiency. These types of studies are likely to portray a higher prevalence of deficiency than exists where disadvantaged populations are studied, and to portray a lower prevalence of deficiency than exists where “healthy” controls are studied.

Many studies utilized the data as a linear variable and prevalence data are therefore missing in the literature. In many cases, the reason for this is the poorly defined cutoffs for deficiencies of vitamin B₁₂ and folate. Moreover, the indicators for deficiency currently in use may not be the best for determining the prevalence of deficiency in populations. Concerns have been raised over assay variability and validity for both serum folate [77–79] and erythrocyte folate [12, 80]. A round-robin comparison among laboratories demonstrated that the correlation among different laboratories is inadequate for the assessment of serum, plasma, or blood folate concentrations, and the problem is greatest at the low end (deficient range) of folate concentrations [81]. Despite these concerns, blood folate concentration is the most widely used indicator at the population level, and an appropriate alternative remains to be developed.

In addition, for both folate and vitamin B₁₂, there is no clear consensus about the threshold of the blood concentrations of these vitamins that should be used to distinguish the normal from the deficient status. Only one-fourth of the studies reported included the two thresholds currently proposed for folate and vitamin B₁₂ to estimate the prevalence. Prevalence was therefore estimated using the low threshold since it is used most frequently.

Conclusions

There is some indication that folate and vitamin B₁₂ deficiencies may be a public health problem in some countries, but there is no evidence that prevalence is associated with the level of development or the geographical location. There is also no evidence that some specific groups are more affected by deficiency than others. However, surveys on preschool children and pregnant women, who are the most at risk for deficiencies, are underrepresented compared with the surveys on adults or the elderly. It is necessary to be cautious with these conclusions, because the data are few and there are concerns about the indicators used and the cutoffs applied to define deficiency.

The main issues that need to be addressed to obtain a better understanding of the magnitude of folate and vitamin B₁₂ deficiencies are as follows:

- Population-based studies that are designed specifically to assess folate and vitamin B₁₂ status in the whole population should be encouraged.
- Information is needed on the status of population groups, and in particular those usually considered at risk, such as infants and pregnant women.
- Consensus is needed on the best indicators for assessing folate and vitamin B₁₂ deficiencies in different age and physiological groups, and for monitoring responses to interventions for their prevention and control. There is no evidence that the current cutoffs apply to pregnant women or to infants.
- Agreement on a cutoff to define the severity of deficiency must be reached.

References


63. Green TJ, Venn BJ, Skeaff CM, Williams SM. Serum vitamin B_{12} concentrations and atrophic gastritis in older
75. Herrmann W, Obeid R, Jouma M. Hyperhomocysteinemia and vitamin B₁₂ deficiency are more striking in Syrians than in Germans—causes and implications. Atherosclerosis 2003;166:143–150.