Dietary sources of vitamin B-12 and their association with plasma vitamin B-12 concentrations in the general population: the Hordaland Homocysteine Study[1–3]

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ABSTRACT

Background: Limited information is available on the association between vitamin B-12 status and intake from different dietary sources.

Objective: We investigated the relation of dietary intake of different food items with plasma vitamin B-12 concentrations in the general population.

Design: A cross-sectional, population-based study of 5937 subjects in 2 age groups (47–49 and 71–74 y) from the Hordaland Homocysteine Study in Norway was conducted by using a food-frequency questionnaire and measurements of plasma vitamin B-12 concentrations.

Results: A significant difference in plasma vitamin B-12 concentrations was observed with increasing total vitamin B-12 intake. A plateau was reached at an intake of $\approx$10 μg/d. Plasma vitamin B-12 was associated with intakes of increasing amounts of vitamin B-12 from dairy products or fish (*P* for trend $<$0.001 for both) but not with intakes of vitamin B-12 from meat or eggs. For the same content of vitamin B-12, intake from dairy products led to the greatest increase in plasma vitamin B-12. Total intake of vitamin B-12, particularly from milk and fish, decreased the risk of vitamin B-12 concentrations $<$200 pmol/L and impaired vitamin B-12 function (vitamin B-12 $<$200 pmol/L and methylmalonic acid $>$0.27 μmol/L) in the total group and in 71–74-y-old subjects.

Conclusions: Dietary intake of dairy products and fish are significant contributors to plasma vitamin B-12 and may improve plasma vitamin B-12 status. Vitamin B-12 appears to be more bioavailable from dairy products; guidelines for improving vitamin B-12 status should take this into consideration. *Am J Clin Nutr* 2009;89:1078–87.

INTRODUCTION

Low vitamin B-12 status may be associated with megaloblastic anemia and neurologic disorders, such as neuropathy, myelopathy, memory impairment, dementia, depression, brain atrophy, and cerebrovascular disease (1–6). Recent studies indicate that subnormal or borderline plasma vitamin B-12 concentrations can occur in infants (7) and are highly prevalent among the elderly (8–12). Prevention of low vitamin B-12 status is important because some of the neurologic signs and psychiatric symptoms can occur in patients with vitamin B-12 concentrations within the range formerly considered low-normal and without associated anemia or macrocytosis (1, 2, 6, 13, 14). Furthermore, increasing evidence suggests that low vitamin B-12 status may be of particular concern in subjects with a high intake of folate, as is often the case in the era of folic acid fortification (15).

Typical causes of cobalamin deficiency in the elderly include pernicious anemia and food-bound malabsorption, but these causes explain less than half of the low vitamin B-12 concentrations (16). Dietary insufficiency is considered rare (17) and is often ignored, because the dietary intake of vitamin B-12 is usually above dietary reference intakes in subjects consuming a mixed Western diet. However, these dietary reference intakes were defined as the amount needed to prevent the overt vitamin B-12 deficiency that causes megaloblastic anemia and to maintain blood concentrations $>$150 pmol/L (18). Because several morbidities may be associated with low-normal vitamin B-12 status $>$150 pmol/L, it is important to establish whether dietary interventions can increase vitamin B-12 status throughout the normal range.

The relation between dietary intake and vitamin B-12 status has been investigated in different populations, with conflicting results. One study concluded that low vitamin B-12 status in the

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[2] Supported by the Norwegian Foundation for Health and Rehabilitation through the Norwegian Health Association, the Johan Throne Holst Foundation for Nutrition Research, the Alzheimer's Research Trust (United Kingdom), the Charles Wolfson Charitable Trust (United Kingdom), the Advanced Research Programme of Norway, the Research Council of Norway, the Foundation to Promote Research into Functional Vitamin B-12 deficiency, and the Norwegian Cancer Society.

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Received June 26, 2008. Accepted for publication January 6, 2009.

First published online February 3, 2009; doi: 10.3945/ajcn.2008.26598.

elderly was not related to inadequate intake (17), whereas other reports showed significant associations between intake of vitamin B-12 and plasma concentrations (19–22). These discrepancies may arise in part from the different bioavailabilities of vitamin B-12 because the proportion absorbed differs according to food source, even in healthy adults (20, 23).

Foods, including breakfast cereals, were not fortified with vitamin B-12 in Norway for the duration of the study. Consequently, the vitamin B-12 intake in this population derives from natural food products or from vitamin supplements, the latter containing only low doses of vitamin B-12 (3–4 μg). We previously briefly reported correlations between components of the diet and plasma vitamin B-12 concentrations in subjects in the Hordaland Homocysteine Study (HHS) (24). In the present study, we investigated these associations in greater depth with a view to identifying the best dietary sources of bioavailable vitamin B-12 and to examining whether high vitamin B-12 intakes from certain foods can reduce the risk of low vitamin B-12 concentrations.

SUBJECTS AND METHODS

Study population

The HHS is a large population-based study of subjects aged 40–67 y living in the county of Hordaland in western Norway (25). Participant recruitment and examination were conducted in 2 periods ≈6 y apart. The first investigation (HHS-I) took place in 1992–1993. In 1997–1999, a follow-up study (HHS-II) was carried out in subjects living in Bergen and its surroundings and was part of the Hordaland Health Study (HUSK). The present study population includes participants from the HHS-II. All subjects underwent a brief health examination and provided a nonfasting blood sample. Information on diet, lifestyle, and medical history was collected via self-administered questionnaires. In total, 6140 of 7074 (87%) subject completed a food-frequency questionnaire (FFQ). Participants who provided questionnaires that were considered invalid were excluded from further analyses, which limited the total number of subjects to 5991. Of these, 5961 had plasma vitamin B-12 measured. We excluded 24 subjects who reported having injections of vitamin B-12, which left a total of 5937 subjects for analysis. The study protocol was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. All subjects gave their written consent to participate in the study.

Health examination and analytic procedures

The health examination included measurements of height, weight, and blood pressure. Blood was drawn from nonfasting subjects, and tubes with plasma containing EDTA were stored at −80°C for biochemical analyses. Plasma total homocysteine was measured by automated HPLC with fluorescence detection (26). The concentrations of plasma folate and vitamin B-12 were measured by *Lactobacillus casei* (27) and *Lactobacillus leichmannii* microbiological assays (28). Plasma methylmalonic acid (MMA) was measured by using a modified gas chromatography–mass spectrometry method based on ethylchloroformate derivatization (29). The concentration of serum creatinine was measured with a standard alkaline picrate colorimetric assay.

Assessment of dietary intake

Dietary data were collected with the use of a validated self-administered FFQ developed by the Department of Nutrition, University of Oslo (30). The FFQ was validated for the Norwegian adult population (30). Although not validated for vitamin B-12 intake, the protein intake obtained by the FFQ corresponded very well with the protein intake obtained by 14-d weighed records, which suggested that this FFQ was well suited for the assessment of vitamin B-12 intake. It included 169 food items, grouped according to Norwegian meal patterns, and was designed to obtain information on usual food intake during the past year. The FFQ includes frequency alternatives (from once a month to several times per day) and the number of units eaten or portion sizes (eg, slices, cups, pieces, spoons, and deciliters). The information from the FFQ is presented as individual food items, food groups (individual food items combined), and nutrients. The FFQ also includes questions about common brands of single-vitamin and multivitamin supplements. Subjects using at least one dose of a B vitamin–containing supplement per day regularly during the past year were classified as B vitamin supplement users ($n = 928$). Daily nutrient intakes were computed from a database and software system developed at the Department of Nutrition, University of Oslo (KOSTBEREGNINGSSYSTEM, version 3.2; University of Oslo, Oslo, Norway) (30). The nutrient database is mainly based on the official Norwegian food-composition table (31). For most of the foods, vitamin B-12 was determined at the National Institute of Nutrition and Seafood Research (Norway) using microbiological assays (meat, *Leuconostoc mesenteroides*; milk and fish, *Lactobacillus delbrueckii*). Vitamin B-12 in some food products was determined in other places, as listed in the food tables. Estimated total intake of vitamin B-12 includes cobalamin from natural dietary sources and supplements (fortification with vitamin B-12 was not permitted in Norway at that time). Intake was calculated without losses from preparation methods. Vitamin B-12 intake in supplements was calculated from information on the contents of vitamin supplements for sale during 1997–1999 (usual supplement dose of vitamin B-12 was 3–4 μg).

Statistical analyses

All calculations were performed by using SPSS 15.0 (SPSS Inc, Chicago, IL) if not otherwise stated. Results are expressed as means or geometric means and 95% CIs or medians with 25th and 75th percentiles. Student's t test, Mann-Whitney U test, analysis of variance (ANOVA), Kruskal-Wallis test, and chi-square test were used to compare independent groups. Adjustment for multiple comparisons was performed by using the Bonferroni correction. Spearman's rank correlation coefficients were used to assess simple correlations between estimated dietary intake of food groups and plasma vitamin B-12. In the Spearman correlations, we compared the significance between the correlations using the Fisher r-to-z transformation.

For the association between plasma vitamin B-12 and diet, we used ANOVA according to groups of dietary factors divided into quartiles. Values for plasma vitamin B-12 were log-transformed for analysis and back transformed for presentation of geometric means and 95% CIs. We adjusted for sex (men or women), age (young or old), energy intake (continuous), intake of other vitamin B-12–containing foods, and intake of supplements with B vitamins (yes or no). We also examined the potential confounding effect by smoking status (current or noncurrent smoker) and alcohol intake (continuous). Using multivariate-adjusted logistic regression, we calculated the odds ratio for plasma vitamin B-12 <200 pmol/L or impaired vitamin B-12 function (vitamin B-12 <200 pmol/L combined with MMA >0.27 μmol/L) according to 3 categories of vitamin B-12 intake from the selected food items. The categories of intake (ranked according to sex) were chosen to examine whether a high intake (>87.5th percentile of intake) could reduce the risk of vitamin B-12 <200 pmol/L or impaired vitamin B-12 function, using <12.5th percentile of intake as reference. All regression models were adjusted for age, sex, energy intake, and intake of other vitamin B-12–containing food items. We also adjusted for creatinine (continuous) because it is a strong determinant of elevated MMA (11, 32). All *P* values are 2-sided, and values <0.05 were considered significant.

Gaussian generalized additive regression models implemented in S-PLUS for WINDOWS software (version 8.0; Insightful Corporation, Seattle, WA) were used to generate graphic representations of the dose-response relations between the vitamin B-12 intake from different food items and plasma vitamin B-12, after adjustment for age, sex, energy intake, intake of supplements with B vitamins and other vitamin B-12–containing food items. On the *y* axis, this nonparametric model generates a reference value of zero that approximately corresponds to the vitamin B-12 concentration associated with the mean intakes of food items for all subjects. Corresponding *P* values were obtained from multiple linear regression analyses.

RESULTS

Subject characteristics and dietary intake

Characteristics of the study population in the 4 age-sex groups are listed in **Table 1**. Plasma vitamin B-12 was significantly higher in younger than in older men and higher in women than in men within each age group. In all subjects, 4.9% had plasma vitamin B-12 concentrations <200 pmol/L and only 1.0% <150 pmol/L; in the elderly, the respective proportions were 6.5% and 1.7%, which indicated a good vitamin B-12 status in this population. Moreover, only 1.9% of all subjects and 3.1% of the elderly had plasma vitamin B-12 <200 pmol/L combined with plasma MMA values >0.27 μmol/L (impaired vitamin B-12 function). The distribution of plasma vitamin B-12 in the 4 age-sex groups is shown in **Figure 1**.

Food intake (kJ/d) and total vitamin B-12 intake (μg/d) from food were higher in men and in the younger groups ($P < 0.001$ for all). The mean total intake of vitamin B-12 ranged from 5.0 to 7.3 μg/d in the 4 age-sex groups. A lower intake of vitamin B-12 than recommended in the Nordic Nutritional Recommendations (2 μg/d) was observed among 2.3% ($n = 135$) of the subjects, but most of these subjects ($n = 125$) also had a very low energy intake (<6,500 kJ/d), which suggested either that they were dieting or did not complete their questionnaire correctly.

Dietary sources of vitamin B-12

Main dietary sources of vitamin B-12 are listed in **Table 2**. Intakes of meat and eggs were significantly higher among the younger groups and men. However, old men consumed more fish than did young men, $P < 0.001$. Milk intake was higher in men, whereas consumption of dairy products was significantly

TABLE 1
Characteristics of the study population: the Hordaland Homocysteine Study

	Men		Women		
	47–49 y ($n = 1329$)	71–74 y ($n = 1310$)	47–49 y ($n = 1742$)	71–74 y ($n = 1556$)	*P* value[1]
Characteristics					
BMI (kg/m^2)[2]	26.1 (25.9, 26.3)[3,4]	26.0 (25.8, 26.1)[3]	24.9 (24.7, 25.0)[4]	26.2 (25.9, 26.4)	<0.001
Smokers (%)	32.0[3]	16.0	33.8[3]	13.6	<0.001
Vitamin supplement users (%)[5]	15.0[3,4]	10.5[3]	20.7[4]	14.9	0.008
Plasma variables					
Vitamin B-12 (pmol/L)[6]	354 (348, 360)[3,4]	340 (332, 348)[3]	358 (352, 364)	358 (350, 366)	<0.001
Folate (nmol/L)[6]	6.5 (6.4, 6.7)[3]	6.4 (6.3, 6.6)[3]	7.3 (7.1, 7.5)	7.7 (7.5, 7.9)	<0.001
Total homocysteine (μmol/L)[6]	10.4 (10.3, 10.6)[3,4]	12.4 (12.2, 12.6)[3]	8.8 (8.7, 8.9)[4]	11.0 (10.9, 11.2)	<0.001
Methylmalonic acid (μmol/L)[6]	0.16 (0.16, 0.17)[4]	0.20 (0.19, 0.20)	0.16 (0.16, 0.17)[4]	0.20 (0.20, 0.21)	<0.001
Nutrient intake					
Energy (kJ/d)[6]	10,183 (10,032, 10,337)[3,4]	8,216 (8086, 8349)[3]	7,642 (7542, 7744)[4]	6,413 (6318, 6509)	<0.001
Protein (g/d)[6]	94 (92, 95)[3,4]	77 (75, 78)[3]	73 (72, 74)[4]	61 (60, 62)	<0.001
Fat (g/d)[6]	88 (86, 89)[3,4]	68 (66, 69)[3]	65 (64, 66)[4]	51 (50, 52)	<0.001
Carbohydrates (g/d)[6]	294 (290, 299)[3,4]	244 (240, 248)[3]	224 (221, 227)[4]	198 (195, 201)	<0.001
Vitamin B-12 (μg/d)[6]	7.3 (7.1,7.5)[3,4]	6.9 (6.6, 7.0)[3]	5.4 (5.3, 5.6)[4]	5.0 (4.9, 5.1)	<0.001
Folate (μg/d)[6]	255 (250, 259)[3,4]	220 (215, 224)[3]	227 (223, 231)[4]	197 (193, 201)	<0.001

[1] ANOVA or chi-square test followed by pairwise comparison with Bonferroni corrections.
[2] Values are means; 95% CIs in parentheses.
[3] Significant difference between sexes within the age group, $P < 0.05$.
[4] Significant difference between age groups within sex, $P < 0.05$.
[5] Use of multivitamins or other supplements that contained B vitamins.
[6] Values are geometric means; 95% CIs in parentheses.

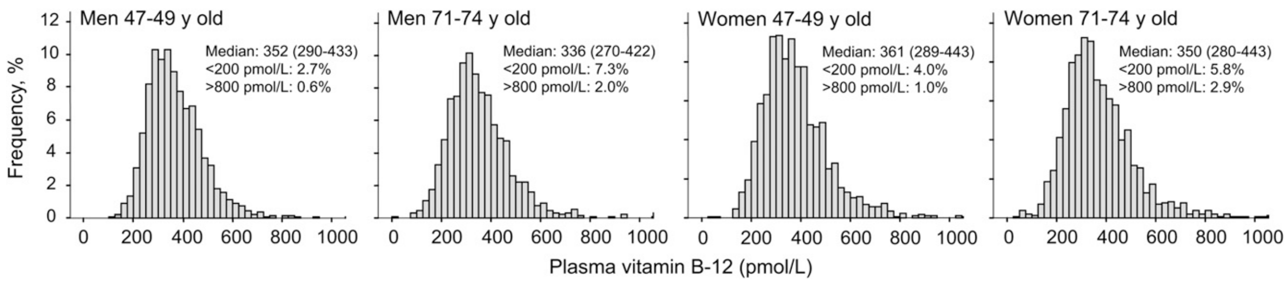

FIGURE 1. Histograms of the frequency distribution of plasma vitamin B-12 concentrations in the 4 age-sex groups. Medians with 25th and 75th percentiles are presented for each age-sex group. Significance between the 4 age-sex groups was first tested by the Kruskal-Wallis test ($P < 0.001$) followed by pairwise comparison between the relevant groups with Bonferroni correction. The median plasma vitamin B-12 concentration differed significantly between young men and old women ($P < 0.001$ for both).

higher in old than in young women. In all 4 age-sex groups, fish, meat, and milk represented the most important sources of vitamin B-12, followed by cheese and eggs. The use of supplements that contained B vitamins was reported by 15.6% of the population and was significantly higher in women and in the younger groups. Vitamin B-12 intake from supplements represented ≈1% of the mean total intake for the whole sample (data not shown).

Simple correlations

Spearman's rank correlation coefficients between plasma vitamin B-12 and vitamin B-12–containing food items are shown for the 4 sex-age groups as supplemental data (*see* Table 1S under "Supplemental Data" in the online issue). For all subjects, the strongest positive correlations were observed between plasma vitamin B-12 and total vitamin B-12 intake ($r_s = 0.11$), intake of dairy products ($r_s = 0.13$), and in particular milk ($r_s = 0.13$), followed by fish ($r_s = 0.07$). Intakes of milk and fish were also associated with plasma vitamin B-12 in each age-sex group, whereas intakes of meat or cheese were not significantly associated with plasma vitamin B-12 in any subgroup. There was a significant difference between the correlations for total vitamin B-12 intake and some food items between old and young men, consistent with weaker associations in older men, but not between men and women in either age group. A separate analysis in older subjects, in whom associations of plasma vitamin B-12 with food intake tended to be weaker, confirmed the significance of the associations after the exclusion of subjects with a high

TABLE 2
Relative contribution of vitamin B-12 intake from different food groups to total vitamin B-12 intake: the Hordaland Homocysteine Study

	Men		Women		
	47–49 y old (n = 1329)	71–74 y old (n = 1310)	47–49 y old (n = 1742)	71–74 y old (n = 1556)	P value[1]
Meat and meat products					
Food intake (g/d)	138 (96, 182)[2,3,4]	85 (58, 118)[3]	98 (70, 132)[4]	59 (36, 87)	<0.001
Vitamin B-12 intake (μg/d)	1.6 (1, 2.5)[3,4]	1.0 (0.5, 1.7)[3]	1.1 (0.7, 1.7)[4]	0.6 (0.3, 1.3)	<0.001
Fish and shellfish					
Food intake (g/d)	84 (54, 118)[3,4]	99 (66, 137)[3]	65 (43, 93)	66 (41, 98)	<0.001
Vitamin B-12 intake (μg/d)	2.8 (1.6, 4.6)[3,4]	3.4 (2, 5.3)[3]	2.2 (1.3, 3.4)[4]	2.1 (1.2, 3.5)	<0.001
Eggs					
Food intake (g/d)	16 (9, 27)[3,4]	16 (8, 27)[3]	16 (8, 19)[4]	15 (8, 18)	<0.001
Vitamin B-12 intake (μg/d)	0.2 (0.1, 0.4)[4]	0.2 (0.1, 0.4)	0.2 (0.1, 0.3)[4]	0.2 (0.1, 0.3)	<0.001
Dairy products[5]					
Food intake (g/d)	389 (218, 571)[3,4]	325 (192, 487)	248 (138, 401)[4]	323 (189, 440)	<0.001
Vitamin B-12 intake (μg/d)	1.8 (1.1, 2.6)[3,4]	1.5 (0.9, 2.1)	1.3 (0.8, 1.9)[4]	1.4 (0.9, 2)	<0.001
Milk					
Food intake (g/d)	320 (144, 488)[3,4]	257 (150, 412)[3]	173 (48, 324)[4]	228 (152, 350)	<0.001
Vitamin B-12 intake (μg/d)	1.3 (0.6, 1.9)[3,4]	1 (0.6, 1.6)[3]	0.7 (0.2, 1.3)[4]	0.9 (0.6, 1.4)	<0.001
Yogurt					
Food intake (g/d)	7 (0, 27)[3,4]	0 (0, 19)[3]	13 (0, 46)[4]	2 (0, 32)	<0.001
Vitamin B-12 intake (μg/d)	0.0 (0.0, 1.0)[3,4]	0.0 (0.0, 0.0)[3]	0.0 (0.0, 1.0)[4]	0.0 (0.0, 1.0)	<0.001
Cheese					
Food intake (g/d)	26 (13, 48)[4]	21 (10, 36)[3]	28 (14, 44)[4]	23 (12, 36)	<0.001
Vitamin B-12 intake (μg/d)	0.3 (0.2, 0.6)[4]	0.3 (0.1, 0.5)[3]	0.4 (0.2, 0.6)[4]	0.3 (0.2, 0.5)	<0.001

[1] Kruskal-Wallis test followed by pairwise comparison with Bonferroni corrections.
[2] Median; 25th and 75th percentile in parentheses (all such values).
[3] Significant difference between sexes within the age group, $P < 0.05$.
[4] Significant difference between age groups within sex, $P < 0.05$.
[5] Includes milk, yogurt, cheese, cream, and ice cream.

MMA (>0.27 μmol/L) concentration ($n = 437$). Likewise, after the exclusion of subjects with possible malabsorption, defined as a vitamin B-12 intake greater than the median combined with plasma vitamin B-12 <200 pmol/L ($n = 72$) or a high MMA concentration ($n = 181$), the associations changed only modestly but with weaker significance (data not shown).

Plasma vitamin B-12 and dietary intake of vitamin B-12

The adjusted associations between plasma vitamin B-12 and vitamin B-12 intake from different foods are presented in **Table 3** for the total group and the 2 age groups. The dose-response curves for total vitamin B-12 intake and vitamin B-12 intake from fish, dairy products, and meat for all subjects are shown in

TABLE 3
Adjusted mean and 95% CI plasma vitamin B-12 concentrations by quartile of vitamin B-12 intake of selected food items in subjects who participated in the Hordaland Homocysteine Study[1]

Dietary vitamin B-12 intake from food items	All subjects ($n = 5937$)	Subjects aged 47–49 y ($n = 3067$)	Subjects aged 71–74 y ($n = 2861$)
	pmol/L	*pmol/L*	*pmol/L*
Vitamin B-12			
≤4.2 μg/d	329 (322, 336)	323 (314, 332)	334 (323, 345)
4.3–5.9 μg/d	346 (340, 353)	348 (340, 356)	345 (334, 356)
6.0–8.3 μg/d	362 (355, 369)	365 (357, 373)	358 (346, 370)
≥8.4 μg/d	375 (367, 383)	385 (376, 395)	364 (351, 378)
P for trend	<0.001	<0.001	0.008
Vitamin B-12 intake from dairy products[2,3]			
≤0.9 μg/d	324 (318, 330)	331 (324, 338)	318 (309, 328)
1.0–1.4 μg/d	340 (334, 346)	343 (335, 351)	335 (327, 344)
1.5–2.1 μg/d	356 (350, 362)	372 (363, 381)	341 (332, 349)
≥2.2 μg/d	373 (366, 380)	388 (378, 397)	358 (348, 368)
P for trend	<0.001	<0.001	<0.001
Vitamin B-12 intake from milk (μg/d)[4]			
≤0.3	323 (317, 329)	331 (324, 338)	317 (307, 327)
0.4–0.8	340 (334, 346)	345 (337, 353)	335 (326, 344)
0.9–1.4	354 (347, 360)	367 (358, 376)	340 (331, 349)
≥1.5	373 (366, 380)	388 (379, 397)	357 (347, 367)
P for trend	<0.001	<0.001	<0.001
Vitamin B-12 intake from cheese[5]			
≤0.1 μg/d	342 (336, 349)	346 (338, 355)	337 (328, 347)
0.2–0.3 μg/d	346 (340, 351)	355 (347, 362)	336 (328, 344)
0.4–0.5 μg/d	345 (339, 352)	349 (341, 358)	341 (331, 350)
≥0.6 μg/d	358 (351, 364)	370 (362, 378)	343 (332, 355)
P for trend	0.008	0.001	0.707
Vitamin B-12 intake from meat and meat products[6]			
≤0.5 μg/d	349 (342, 356)	355 (344, 366)	340 (332, 349)
0.6–1.0 μg/d	344 (338, 350)	349 (342, 357)	338 (329, 247)
1.1–1.8 μg/d	345 (338, 351)	356 (348, 363)	332 (322, 343)
≥1.9 μg/d	353 (347, 359)	362 (354, 369)	342 (332, 354)
P for trend	0.140	0.189	0.522
Vitamin B-12 intake from fish and shellfish[7]			
≤1.4 μg/d	330 (324, 336)	339 (331, 346)	321 (311, 330)
1.5–2.5 μg/d	344 (338, 350)	354 (346, 361)	333 (324, 343)
2.6–4.1 μg/d	349 (343, 355)	361 (353, 369)	336 (327, 345)
≥4.2 μg/d	367 (361, 374)	375 (366, 385)	359 (350, 369)
P for trend	<0.001	<0.001	<0.001
Vitamin B-12 intake from eggs[8]			
≤0.1 μg/d	348 (343, 354)	356 (350, 363)	339 (331, 347)
0.2–0.3 μg/d	349 (343, 355)	356 (348, 364)	342 (333, 352)
0.3–0.4 μg/d	345 (337, 352)	352 (342, 362)	338 (326, 350)
>0.4 μg/d	346 (340, 353)	358 (349, 366)	334 (324, 344)
P for trend	0.818	0.837	0.677

[1] ANOVA adjusted for sex, age groups (except within the age groups), energy, and the use of supplements containing B vitamins.
[2] Includes milk, yogurt, cheese, cream, and ice cream.
[3] Also adjusted for total intakes of fish, meat, and eggs.
[4] Also adjusted for total intakes of fish, meat, cheese, and eggs.
[5] Also adjusted for total intakes of fish, meat, milk, and eggs.
[6] Also adjusted for total intakes of fish, dairy products, and eggs.
[7] Also adjusted for total intakes of dairy products, meat, and eggs.
[8] Also adjusted for total intakes of fish, meat, and dairy products.

Figure 2. The associations with plasma vitamin B-12 were first evaluated for the intake of the selected food items (*see* Table 2S under "Supplemental data" in the online issue) and without adjustment for the vitamin B-12 intake from the other vitamin B-12–containing food groups. The associations, in both cases, were similar to those presented. There were positive associations between vitamin B-12 intakes from fish and dairy products (specifically from milk) and plasma vitamin B-12. However, the differences in the mean of plasma vitamin B-12 across quartiles of vitamin B-12 intakes were higher for the younger group. The association between vitamin B-12 intake from cheese and plasma vitamin B-12 was statistically significant but only after adjustment for the vitamin B-12 intake from other food items. Vitamin B-12 intakes from meat and eggs were not significantly associated with plasma vitamin B-12 in any of the groups. For all subjects, the difference in plasma vitamin B-12 between the top and bottom quartiles of vitamin B-12 intakes was 14.0% (47 pmol/L) for total vitamin B-12 intake, 15.2% (50 pmol/L) for vitamin B-12 from dairy products, and 11.2% (37 pmol/L) for vitamin B-12 intake from fish. The magnitude of the mean differences in plasma vitamin B-12 between the highest and lowest quartiles of vitamin B-12 intake from foods listed in Table 3 ranged from 4.5% to 15.3%. Further adjustment for smoking and alcohol intake did not change the associations (data not shown).

For total vitamin B-12 intake, we observed a dose-response curve that reached a plateau after an intake of ≈10 μg/d (Figure 2). In the graphs in Figure 2 we used similar scales on both axes to allow comparison of bioavailability. There is a steep dose-response curve for vitamin B-12 from dairy products, which indicates that its bioavailability from this source, specifically milk (*see* Supplemental Figure 1 under "Supplemental Data" in the online issue), appears to be higher than that from the other sources. Too few subjects consumed yogurt in this population for meaningful analysis. For the intake of vitamin B-12 from fish, the dose-response curve is not as steep, and, for higher intakes, the 95% CI increasingly widens (Figure 2). We observed an apparent decrease in plasma vitamin B-12 for intakes of vitamin B-12 >4 μg from meat. However, the 95% CIs were very wide. The difference in plasma vitamin B-12 between those not consuming dairy products and those eating the maximum amount was ≈75 pmol/L, whereas for fish intake the respective difference was ≈35 pmol/L (*see* Supplemental Figure 2 under "Supplemental data" in the online issue).

Risk of low vitamin B-12 status according to dietary intake of vitamin B-12

Subjects with plasma vitamin B-12 <200 pmol/L (n = 291) had lower vitamin B-12 intakes and lower intakes of fish and dairy products than did those with a plasma vitamin B-12 intake >200 pmol/L ($P < 0.001$; data not shown). Logistic regression analysis showed that subjects with the highest intake of vitamin B-12 had only one-third the risk of having plasma vitamin B-12 <200 pmol/L (**Table 4**). Similarly, those with the highest intake of vitamin B-12 from milk had only one-fourth the risk of having plasma vitamin B-12 <200 pmol/L. A similar, but weaker, effect was found for high intakes of vitamin B-12 from fish but not for high intakes of vitamin B-12 from meat, eggs, and cheese. Further analysis on subjects who also had high plasma MMA (>0.27 μmol/L), consistent with impaired vitamin B-12 function, showed similar but weaker reductions in risk with a high intake. Use of vitamin B-12–containing supplements reduced the risk of plasma vitamin B-12 <200 pmol/L but not of impaired vitamin B-12 function, perhaps because of infrequent use among those with plasma vitamin B-12 <200 pmol/L (n = 18).

Separate analysis in the old group, ie, in whom a low plasma vitamin B-12 concentration is more likely to be due to malabsorption, showed that a high vitamin B-12 intake, particularly from milk, but also from fish, was associated with a reduced risk of vitamin B-12 <200 pmol/L and of impaired vitamin B-12 function. As for the total group, use of vitamin B-12–containing supplements tended to protect against plasma vitamin B-12 <200 pmol/L but not against impaired vitamin B-12 function.

DISCUSSION

In this large population-based study, we found a significant association between total dietary intake of vitamin B-12 and plasma vitamin B-12 concentrations. Notably, plasma vitamin B-12 was related to the vitamin B-12 intake from dairy products (especially from milk) and from fish, but not from meat and eggs. These findings have possible implications for nutritional guidelines.

The mean total intake (diet plus supplements) of vitamin B-12 was ≈6 μg/d, comparable with that of free-living American and northern European subjects (20, 22, 33). Only 2.3% of the subjects did not meet the Norwegian recommended intake (34) of 2.0 μg/d. The use of supplements and intake of vitamin B-12 from supplements were lower than in American studies (20, 21, 35), but were similar to those in northern European studies (22, 33). Our

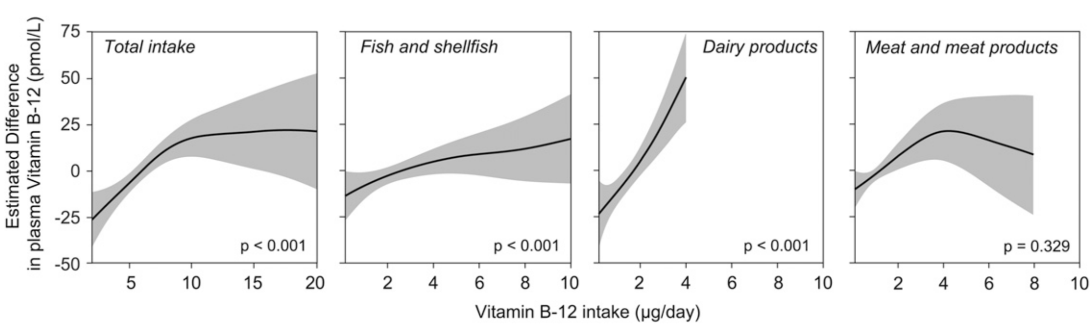

FIGURE 2. Estimated mean (and 95% CI) plasma vitamin B-12 concentrations according to the total vitamin B-12 intake and the vitamin B-12 intake from dairy products, fish and shellfish, and meat and meat products by additive Gaussian generalized regression model. Estimated plasma vitamin B-12 concentrations were adjusted for sex, age group, total energy intake, intake of supplements with B vitamins, the vitamin B-12 intake of the other 2 food items as well as the intake of vitamin B-12 from eggs. The solid lines represent the estimated dose-response curves, and the shaded areas represent the 95% CIs. P values are from the corresponding multiple linear regression analyses. The lowest and highest 2.5th percentiles of intakes are not included.

TABLE 4

Odds ratios and 95% CIs of subjects with plasma vitamin B-12 concentrations <200 pmol/L or impaired vitamin function (vitamin B-12 <200 pmol/L and methylmalonic acid >0.27 μmol/L) according to contrasting intakes of vitamin B-12 from selected food items in all and old subjects[1]

	All subjects (n = 5937)		Subjects aged 71–74 y (n = 2866)	
Dietary vitamin B-12 intake from food items	Vitamin B-12 <200 pmol/L (n = 291)	Impaired vitamin B-12 function (n = 109)	Vitamin B-12 <200 pmol/L (n = 186)	Impaired vitamin B-12 function (n = 87)
Vitamin B-12				
≤4.1 μg/d (men), ≤2.9 μg/d (women)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
4.2–12.6 μg/d (men), 3.0–9.2 μg/d (women)	0.54 (0.39, 0.75)	0.47 (0.29, 0.78)	0.58 (0.39, 0.81)	0.45 (0.26, 0.78)
>12.6 μg/d (men), ≥9.3 μg/d (women)	0.36 (0.21, 0.63)	0.41 (0.17, 0.95)	0.40 (0.20, 0.87)	0.43 (0.17, 1.08)
P for trend	0.001	0.012	0.004	0.025
Vitamin B-12 intake from dairy products[2,3]				
≤0.6 μg/d (men), ≤0.5 μg/d (women)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
0.7–2.9 μg/d (men), 0.6–2.4 μg/d (women)	0.54 (0.39, 0.74)	0.79 (0.45, 1.38)	0.63 (0.42, 0.96)	0.72 (0.33, 1.56)
≥3.0 μg/d (men), ≥2.5 μg/d (women)	0.25 (0.14, 0.45)	0.43 (0.17, 1.06)	0.41 (0.20, 0.84)	0.41 (0.16, 1.09)
P for trend	<0.001	0.074	0.008	0.089
Vitamin B-12 intake from milk[4]				
≤0.1 μg/d (men), 0.0 μg/d (women)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
0.2–2.3 μg/d (men), 1–1.8 μg/d (women)	0.48 (0.35, 0.66)	0.53 (0.31, 0.89)	0.46 (0.31, 0.69)	0.55 (0.29, 1.01)
≥2.4 μg/d (men), 1.9 μg/d (women)	0.22 90.12, 0.38)	0.25 (0.10, 0.62)	0.29 (0.15, 0.57)	0.34 (0.13, 0.88)
P for trend	<0.001	<0.001	<0.001	0.017
Vitamin B-12 intake from cheese[5]				
0.0 μg/d (men), 0.0 μg/d (women)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
0.1–0.8 μg/d (men), 0.1–0.7 μg/d (women)	0.91 (0.62, 1.34)	0.68 (0.39, 1.18)	0.98 (0.61, 1.57)	0.69 (0.38, 1.28)
≥0.9 μg/d (men), ≥0.8 μg/d (women)	0.80 (0.47, 1.36)	0.66 (0.29, 1.40)	0.99 (0.49, 1.98)	0.75 (0.29, 1.89)
P for trend	0.419	0.251	0.938	0.405
Vitamin B-12 intake from meat and meat products[6]				
≤0.4 μg/d (men), ≤0.2 μg/d (women)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
0.5–3.4 μg/d (men), 0.3–2.2 μg/d (women)	1.04 (0.72, 1.52)	0.91 (0.53, 1.56)	1.02 (0.68, 1.53)	0.87 (0.49, 1.53)
≥3.5 μg/d (men), ≥2.3 μg/d (women)	0.80 (0.47, 1.38)	0.92 (0.41, 2.08)	0.84 (0.44, 1.60)	0.82 (0.33, 2.03)
P for trend	0.450	0.775	0.705	0.588
Vitamin B-12 intake from fish and shellfish[7]				
≤1.0 μg/d (men), ≤0.7 μg/d (women)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1.1–6.6 μg/d (men), 0.8–4.6 μg/d (women)	0.57 (0.42, 0.79)	0.49 (0.29, 0.79)	0.79 (0.51, 1.24)	0.54 (0.31, 0.97)
≥6.7 μg/d (men), ≥4.7 μg/d (women)	0.40 (0.24, 0.67)	0.28 (0.12, 0.65)	0.55 (0.29, 1.07)	0.29 (0.12, 0.76)
P for trend	<0.001	<0.001	0.072	0.009
Vitamin B-12 intake from eggs[8]				
0.0 μg/d (men), 0.0 μg/d (women)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
0.1–0.4 μg/d (men), 0.1–0.3 μg/d (women)	0.73 (0.49, 1.08)	0.59 (0.34, 1.03)	0.71 (0.45, 1.11)	0.67 (0.36, 1.26)
≥0.5 μg/d (men), ≥0.4 μg/d (women)	0.59 (0.37, 0.98)	0.61 (0.29, 1.27)	0.69 (0.39, 1.25)	0.69 (0.31, 1.55)
P for trend	0.051	0.238	0.256	0.406

(Continued)

TABLE 4 (*Continued*)

Dietary vitamin B-12 intake from food items	All subjects (n = 5937)		Subjects aged 71–74 y (n = 2866)	
	Vitamin B-12 <200 pmol/L (n = 291)	Impaired vitamin B-12 function (n = 109)	Vitamin B-12 <200 pmol/L (n = 186)	Impaired vitamin B-12 function (n = 87)
Vitamin B-12 from supplements				
Nonsupplement users	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
0.3–2.0 μg/d	0.75 (0.38, 1.48)	0.77 (0.24, 2.45)	0.93 (0.37, 2.34)	0.79 (0.19, 3.26)
>2.0 μg/d	0.51 (0.26, 0.99)	0.46 (0.15, 1.48)	0.44 (0.18, 1.10)	0.38 (0.10, 1.56)
P for trend	0.034	0.172	0.080	0.168

[1] Values adjusted for age (except for the 71–74-y-old subjects), sex, energy intake, and creatinine. Except for supplement use, the categories were chosen so that the reference (ref) group included the lowest 12.5th percentile of intake, whereas the high intake group included the top 12.5th percentile of intake based on the total population. The 3 categories of each food group were ranked according to sex.
[2] Includes milk, yogurt, cheese, cream, and ice cream.
[3] Also adjusted for total intakes of fish, meat, and eggs.
[4] Also adjusted for total intakes of fish, meat, cheese, and eggs.
[5] Also adjusted for total intakes of fish, meat, milk, and eggs.
[6] Also adjusted for total intakes of fish, dairy products, and eggs.
[7] Also adjusted for total intakes of dairy products, meat, and eggs.
[8] Also adjusted for total intakes of fish, meat, and dairy products.

findings also showed a higher consumption of fish and dairy products than in other northern European and American studies (36, 37). The high intake of these food items probably contributes to the low prevalence of vitamin B-12 deficiency observed.

In agreement with other studies (20–22, 33), we showed that plasma vitamin B-12 was positively associated with total vitamin B-12 intake. This association was also present in older subjects, in whom vitamin B-12 deficiency is more prevalent. Moreover, our data imply that the increase in plasma vitamin B-12 reaches a plateau when vitamin B-12 intake exceeds 10 μg/d, similar to finding from the Framingham Offspring Study (20) but somewhat higher than the saturation intakes of 7 μg/d in Hispanic subjects (21) and of 6 μg/d in Danish women (22).

We observed significant differences in plasma vitamin B-12, depending on the food source. Milk provides the most bioavailable vitamin B-12, even in older subjects with a low vitamin B-12 status. The Framingham Offspring Study (20) first observed that vitamin B-12 from milk was better absorbed than that from meat. An earlier study in vegetarians (19) supported the beneficial effects of dairy products on vitamin B-12 status. However, a study in Hispanic elderly did not find an association, possibly because of their low dairy intake (21).

Although the vitamin B-12 content of various types of milk is not high (0.2–0.4 μg/100 g) (31), milk is a significant contributor to vitamin B-12 intake, because the consumption of milk is high in this population, as in most Scandinavian countries (38, 39). Appreciable losses of vitamin B-12 have been reported during the processing of milk; boiling for 2–5 min resulted in a 30% loss (23). However, milk in Norway is primarily consumed raw and with meals. When radioactive vitamin B-12 dissolved in milk was administered to human subjects, the mean absorption was 55% (40). The high bioavailability from dairy products may also explain the adequate vitamin B-12 status observed in most lactoovovegetarians compared with vegans (41, 42). About 20–60% of vitamin B-12 originally found in milk is recovered in various cheeses (43), which may explain the associations detected after adjustments.

Our results suggest that the bioavailability of vitamin B-12 from meat is lower than previously indicated (23). At least 2 other studies found a weak association between meat and vitamin B-12 status (19, 20). Meat and meat products are rich sources of vitamin B-12 but are consumed after cooking, which subjects the vitamin to significant losses (≈33%) (23). This lack of association may also be explained by the differences in the absorption and release of protein-bound vitamin B-12. Persons with decreased gastric secretion often have difficulty digesting collagen, a major constituent of meat that is primarily digested by pepsin (44), which could prevent the release of vitamin B-12 from proteins. Another possible explanation is that the absorption efficiency of vitamin B-12 from meat might be low partly because of its high vitamin B-12 content, eg, absorption from liver is estimated to be 11% (23). Because the intrinsic factor–mediated intestinal absorption system is saturated at ≈1.5–2.0 μg of vitamin B-12 per meal, vitamin B-12 bioavailability significantly decreases with higher intakes of vitamin B-12 per meal (23, 45).

We found an association between plasma vitamin B-12 and intake of fish. There is a high consumption of fish in this population (46). Although fish consumed in Norway is usually cooked, the loss of vitamin B-12 in fish from cooking is not high

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(23). In the Norwegian food database, vitamin B-12 contents of certain fish are high (2.1–12.7 μg/100 g) (31).

In the Framingham Offspring Study (20) and in a study of Hispanic elderly (21), intake of supplements was associated with increased vitamin B-12 status. In our study, vitamin B-12 intake from supplements (>2 μg/d) in subjects with plasma vitamin B-12 <200 pmol/L improved their vitamin B-12 status, but not in the elderly. This may have been due to the low dose in the supplements and to the fact that few subjects used them, which made it difficult to detect associations.

Our findings may have implications for guidelines for the maintenance of a good vitamin B-12 status. Whereas supplementation is recommended for those at immediate risk of deficiency, the options for increasing the overall vitamin B-12 status of the population are either fortification or targeted dietary recommendations. Our confirmation that dairy foods provide a highly bioavailable source of vitamin B-12 and that increased milk intake can raise plasma concentrations within the normal range suggests that the promotion of a high intake of dairy products would be a good strategy. It would avoid potential pitfalls of fortification and could be applied in less-developed regions. By increasing the overall vitamin B-12 status of a large portion of the population vulnerable to vitamin B-12 deficiency without malabsorption (elderly, pregnant and lactating women, infants, vegetarians, and persons from parts of the world with a low intake of animal-derived products), not only could morbidities associated with overt deficiency be prevented, but so too could the proposed subtle harmful effects attributable to low-normal concentrations of vitamin B-12 in persons with adequate vitamin B-12 absorption. Although the proportional increase in mean plasma vitamin B-12 concentrations was modest at ≈14.4% (48 pmol/L) from the bottom to the top quartile of dairy product intake (Table 3), such an increase would be beneficial in subjects with low-normal concentrations of vitamin B-12. Furthermore, correction of an imbalance between folate and vitamin B-12 (47), as may occur in countries that have fortified flour with folic acid (15), or in vegetarians (48) may possibly be achieved by this nutritional strategy.

Advantages of our study include its large study population and the use of a validated FFQ, which provides information about nutrient intake over a period of a year (49), although we recognize its limitations (50). Another weakness in our study relates to the inability to include the preparation losses of vitamin B-12 from food items. Inclusion of an estimate of losses did not change the overall results, but modestly reduced total vitamin B-12 intake. Although the content of vitamin B-12 was not measured using the same method for all the food items, the vitamin B-12 values in our food-composition table are similar to those reported by other national sources. In our population, we had no data on atrophic gastritis or the chronic use of medications that affect absorption. Nevertheless, plasma MMA was measured and we were able to identify subjects with functional vitamin B-12 deficiency.

In conclusion, we suggest that, even in a well-nourished population, dietary intake is an important contributor to plasma vitamin B-12. It appears that vitamin B-12 in meat is less bioavailable than is that in milk and fish, which may have implications for recommendations about how to maintain a good vitamin B-12 status. On the basis of our observations and of previously published findings (20, 22), it seems that daily dietary vitamin B-12 intakes between 6 and 10 μg ensures the maximal plasma vitamin B-12 concentration in persons with adequate vitamin B-12 absorption. This amount is considerably larger than the current recommended daily intakes. We suggest that the guidelines for improving vitamin B-12 status should focus on the intake of dairy products, particularly milk, because vitamin B-12 appears to be more bioavailable from these sources.

We thank Kari Juul and Elfrid Blomdal for help with setting up the data files and with literature support. Kari Solvoll, Elin Bjørge Løken, and Gunnar H Åmlid are gratefully acknowledged for their work with the food frequency questionnaires.

The authors' responsibilities were as follows—HR, SEV, and GST: participated in the study design and organization of data collection; CAD: assessed food intakes and helped develop the food-frequency questionnaire; AV and HR: developed the concept, conducted the statistical analysis, and wrote the first draft of the manuscript; PB: contributed to the calculation of food intakes; and AV, EN, PB, CAD, HR, ADS, GST, PMU, and SEV: interpreted the results and contributed to the study design and critical revision of the manuscript. None of the authors reported a conflict of interest.

REFERENCES

1. Vogiatzoglou A, Refsum H, Johnston C, et al. Vitamin B12 status and rate of brain volume loss in community-dwelling elderly. Neurology 2008;71:826–32.
2. Lindenbaum J, Healton EB, Savage DG, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med 1988;318:1720–8.
3. Selhub J, Bagley LC, Miller J, Rosenberg IH. B vitamins, homocysteine, and neurocognitive function in the elderly. Am J Clin Nutr 2000;71: 614S–20S.
4. Hin H, Clarke R, Sherliker P, et al. Clinical relevance of low serum vitamin B12 concentrations in older people: the Banbury B12 study. Age Ageing 2006;35:416–22.
5. Weikert C, Dierkes J, Hoffmann K, et al. B vitamin plasma levels and the risk of ischemic stroke and transient ischemic attack in a German cohort. Stroke 2007;38:2912–8.
6. Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Yoon JS. Predictive value of folate, vitamin B12 and homocysteine levels in late-life depression. Br J Psychiatry 2008;192:268–74.
7. Dror DK, Allen LH. Effect of vitamin B12 deficiency on neurodevelopment in infants: current knowledge and possible mechanisms. Nutr Rev 2008;66:250–5.
8. Pennypacker LC, Allen RH, Kelly JP, et al. High prevalence of cobalamin deficiency in elderly outpatients. J Am Geriatr Soc 1992;40: 1197–204.
9. Lindenbaum J, Rosenberg IH, Wilson PW, Stabler SP, Allen RH. Prevalence of cobalamin deficiency in the Framingham elderly population. Am J Clin Nutr 1994;60:2–11.
10. Joosten E, van den Berg A, Riezler R, et al. Metabolic evidence that deficiencies of vitamin B-12 (cobalamin), folate, and vitamin B-6 occur commonly in elderly people. Am J Clin Nutr 1993;58:468–76.
11. Baik HW, Russell RM. Vitamin B12 deficiency in the elderly. Annu Rev Nutr 1999;19:357–77.
12. Clarke R, Grimley Evans J, Schneede J, et al. Vitamin B12 and folate deficiency in later life. Age Ageing 2004;33:34–41.
13. Karnaze DS, Carmel R. Neurologic and evoked potential abnormalities in subtle cobalamin deficiency states, including deficiency without anemia and with normal absorption of free cobalamin. Arch Neurol 1990;47:1008–12.
14. Refsum H, Smith AD. Low vitamin B-12 status in confirmed Alzheimer's disease as revealed by serum holotranscobalamin. J Neurol Neurosurg Psychiatry 2003;74:959–61.
15. Morris MS, Jacques PF, Rosenberg IH, Selhub J. Folate and vitamin B-12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. Am J Clin Nutr 2007;85:193–200.
16. Carmel R. Prevalence of undiagnosed pernicious anemia in the elderly. Arch Intern Med 1996;156:1097–100.

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17. Howard JM, Azen C, Jacobsen DW, Green R, Carmel R. Dietary intake of cobalamin in elderly people who have abnormal serum cobalamin, methylmalonic acid and homocysteine levels. Eur J Clin Nutr 1998;52:582–7.
18. Institute of Medicine. Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington, DC: National Academies Press, 1998:306–56.
19. Miller DR, Specker BL, Ho ML, Norman EJ. Vitamin B-12 status in a macrobiotic community. Am J Clin Nutr 1991;53:524–9.
20. Tucker KL, Rich S, Rosenberg I, et al. Plasma vitamin B-12 concentrations relate to intake source in the Framingham Offspring study. Am J Clin Nutr 2000;71:514–22.
21. Kwan LL, Bermudez OI, Tucker KL. Low vitamin B-12 intake and status are more prevalent in Hispanic older adults of Caribbean origin than in neighborhood-matched non-Hispanic whites. J Nutr 2002;132:2059–64.
22. Bor MV, Lydeking-Olsen E, Moller J, Nexo E. A daily intake of approximately 6 microg vitamin B-12 appears to saturate all the vitamin B-12-related variables in Danish postmenopausal women. Am J Clin Nutr 2006;83:52–8.
23. Watanabe F. Vitamin B12 sources and bioavailability. Exp Biol Med (Maywood) 2007;232:1266–74.
24. Konstantinova SV, Vollset SE, Berstad P, et al. Dietary predictors of plasma total homocysteine in the Hordaland Homocysteine Study. Br J Nutr 2007;98:201–10.
25. Refsum H, Nurk E, Smith AD, et al. The Hordaland Homocysteine Study: a community-based study of homocysteine, its determinants, and associations with disease. J Nutr 2006;136:1731S–40S.
26. Fiskerstrand T, Refsum H, Kvalheim G, Ueland PM. Homocysteine and other thiols in plasma and urine: automated determination and sample stability. Clin Chem 1993;39:263–71.
27. Molloy AM, Scott JM. Microbiological assay for serum, plasma, and red cell folate using cryopreserved, microtiter plate method. Methods Enzymol 1997;281:43–53.
28. Kelleher BP, Broin SD. Microbiological assay for vitamin B12 performed in 96-well microtitre plates. J Clin Pathol 1991;44:592–5.
29. Husek P. Simultaneous profile analysis of plasma amino and organic acids by capillary gas chromatography. J Chromatogr B: Biomed Sci Appl 1995;669:352–7.
30. Andersen LF, Solvoll K, Johansson LR, Salminen I, Aro A, Drevon CA. Evaluation of a food frequency questionnaire with weighed records, fatty acids, and alpha-tocopherol in adipose tissue and serum. Am J Epidemiol 1999;150:75–87.
31. Rimestad AH, Borgejordet Å, Vesterhus KN, et al. Den store matvaretabellen. [The Norwegian food composition table.] Oslo, Norway: National Nutrition Council, 2001 (in Norwegian).
32. Lindgren A. Elevated serum methylmalonic acid: how much comes from cobalamin deficiency and how much comes from the kidneys? Scand J Clin Lab Invest 2002;62:15–20.
33. van Asselt DZ, de Groot LC, van Staveren WA, et al. Role of cobalamin intake and atrophic gastritis in mild cobalamin deficiency in older Dutch subjects. Am J Clin Nutr 1998;68:328–34.
34. Becker W, Lyhne N, Pedersen AN, et al. Nordic nutrition recommendations 2004—integrating nutrition and physical activity. Scand J Nutr 2004;48:178–87.
35. Garry PJ, Goodwin JS, Hunt WC. Folate and vitamin B12 status in a healthy elderly population. J Am Geriatr Soc 1984;32:719–26.
36. Haveman-Nies A, Tucker KL, de Groot LC, Wilson PW, van Staveren WA. Evaluation of dietary quality in relationship to nutritional and lifestyle factors in elderly people of the US Framingham Heart Study and the European SENECA Study. Eur J Clin Nutr 2001;55:870–80.
37. Ranganathan R, Nicklas TA, Yang SJ, Berenson GS. The nutritional impact of dairy product consumption on dietary intakes of adults (1995–1996): the Bogalusa Heart Study. J Am Diet Assoc 2005;105:1391–400.
38. Hjartaker A. Consumption of dairy products in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort: data from 35 955 24-hour dietary recalls in 10 European countries. Public Health Nutr 2002;5:1259–71.
39. Johansson L, Solvoll K, Bjørneboe G-EA, Drevon CA. Dietary habits among Norwegian men and women. Scand J Nutr 1997;41:63–70.
40. Russell RM, Baik H, Kehayias JJ. Older men and women efficiently absorb vitamin B-12 from milk and fortified bread. J Nutr 2001;131:291–3.
41. Millet P, Guilland JC, Fuchs F, Klepping J. Nutrient intake and vitamin status of healthy French vegetarians and nonvegetarians. Am J Clin Nutr 1989;50:718–27.
42. Krajcovicová-Kudlácková M, Blazicek P, Kopcova J, Bederova A, Babinska K. Homocysteine levels in vegetarians versus omnivores. Ann Nutr Metab 2000;44:135–8.
43. Arkbage K, Witthoft C, Fonden R, Jagerstad M. Retention of vitamin B12 during manufacture of six fermented dairy products using a validated radio protein-binding assay. Int Dairy J 2003;13:101–9.
44. Guyton A, Hall J. Digestion and absorption in the gastrointestinal tract. In: Belfus L, ed. Textbook of medical physiology. 11th ed. Philadelphia, PA: Elsevier Saunders, 2006:809–10.
45. Scott JM. Bioavailability of vitamin B12. Eur J Clin Nutr 1997;51(suppl 1):S49–53.
46. Nurk E, Drevon CA, Refsum H, et al. Cognitive performance among the elderly and dietary fish intake: the Hordaland Health Study. Am J Clin Nutr 2007;86:1470–8.
47. Smith AD. Folic acid fortification: the good, the bad, and the puzzle of vitamin B-12. Am J Clin Nutr 2007;85:3–5.
48. Yajnik CS, Deshpande SS, Jackson AA, et al. Vitamin B12 and folate concentrations during pregnancy and insulin resistance in the offspring: the Pune Maternal Nutrition Study. Diabetologia 2008;51:29–38.
49. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–26 (discussion 1127–36).
50. Flood VM, Smith WT, Webb KL, Mitchell P. Issues in assessing the validity of nutrient data obtained from a food-frequency questionnaire: folate and vitamin B12 examples. Public Health Nutr 2004;7:751–6.