Article

Vitamin B_{12} Deficiency and Depression in Physically Disabled Older Women: Epidemiologic Evidence From the Women's Health and Aging Study

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Objective: It has been hypothesized that adequate concentrations of vitamin B_{12} and folate are essential to maintain the integrity of the neurological systems involved in mood regulation, but epidemiologic evidence for such a link in the general population is unavailable. This study examined whether community-dwelling older women with metabolically significant vitamin B_{12} or folate deficiency are particularly prone to depression.

Method: Serum levels of vitamin B_{12}, folate, methylmalonic acid, and total homocysteine were assayed in 700 disabled, nondemented women aged 65 years and over living in the community. Depressive symptoms were measured by means of the Geriatric Depression Scale and categorized as no depression, mild depression, and severe depression.

Results: Serum homocysteine levels, serum folate levels, and the prevalences of folate deficiency and anemia were not associated with depression status. The depressed subjects, especially those with severe depression, had a significantly higher serum methylmalonic acid level and a nonsignificantly lower serum vitamin B_{12} level than the nondepressed subjects. Metabolically significant vitamin B_{12} deficiency was present in 14.9% of the 478 nondepressed subjects, 17.0% of the 100 mildly depressed subjects, and 27.0% of the 122 severely depressed women. After adjustment for sociodemographic characteristics and health status, the subjects with vitamin B_{12} deficiency were 2.05 times as likely to be severely depressed as were nondeficient subjects.

Conclusions: In community-dwelling older women, metabolically significant vitamin B_{12} deficiency is associated with a twofold risk of severe depression.

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Vitamin B_{12} (cobalamin) and folate are essential in several metabolic pathways in the central nervous system, and their metabolism is intimately connected (1, 2). Both are involved in single-carbon transfer (methylation) reactions necessary for the production of monoamine neurotransmitters, phospholipids, and nucleotides. A deficiency of either vitamin may cause an impaired methylation in the central nervous system and may result in neurological and/or psychiatric disease that becomes irreversible if not treated properly (3, 4). This connection is supported by findings that psychiatric patients, especially depressed patients, frequently are found to have abnormalities in vitamin B_{12} and folate status (5–7). Furthermore, both folate and vitamin B_{12} replacement therapy in patients with major depression appear to produce substantial affective improvements (8–12). However, since the studies thus far have been restricted to psychiatric patients, it is unknown whether vitamin B_{12} and folate deficiencies affect depressed mood in the general, community-dwelling population.

Low serum vitamin B_{12} and folate levels are not very specific and have low sensitivity in diagnosing tissue deficiency (13, 14). Therefore, in the present study the definitions of vitamin B_{12} and folate deficiency were based on both low levels of these vitamins and high levels of the specific metabolites methylmalonic acid and total homocysteine, respectively (15–17). In the present study we examined whether these assessments of vitamin B_{12} and folate deficiency were associated with depression in a community-dwelling, representative sample of disabled older women.

Method

Study Sample

In this study we used data from the baseline assessment of the Women's Health and Aging Study, a prospective cohort study of the causes and course of physical disability in a representative sample of physically disabled older women without severe cognitive impairment living in the community. The study design and characteristics of the study sample have been described in detail elsewhere (18). Briefly, an age-stratified random sample of 6,521 community-dwelling women aged 65 years and older was selected from the Health Care Financing Administration's Medicare enrollees living in the Baltimore area. After exclusion of those who had died, were institutionalized, or had moved from the area,

5,316 were eligible for screening, and 4,137 consented to a screening interview. The criteria for study eligibility were a Mini-Mental State score of 18 or higher (19) and reported difficulty in performing tasks in at least two of four domains: mobility/exercise tolerance, upper-extremity abilities, higher-function tasks of independent living, and basic self-care. Overall, 1,409 women were eligible, of whom 1,002 (71.1%) participated in the full baseline interview and, 1 to 2 weeks later, an in-home comprehensive examination. The respondents' written informed consent to participation was obtained after complete description of the study.

At the time of the examination each participant was asked whether she was willing to give a blood sample, which was collected by a phlebotomist at the third home visit. A separate informed consent statement was signed for this procedure. Approximately 75% of the participants completed the phlebotomy at baseline. For this report we used the data on the 700 women for whom all laboratory test results needed to classify vitamin deficiency status were available. These women, as compared to those for whom blood results were not available, were significantly younger (mean age, 77.3 [SD=7.8] versus 80.7 [SD=8.2] years) ($t=6.2$, $df=1000$, $p<0.001$) and somewhat less disabled in self-care tasks but were not significantly different in terms of race, education, or depressive symptoms (mean score on Geriatric Depression Scale [20], 7.9 [SD=5.4] versus 8.2 [SD=5.7]) ($t=0.6$, $df=1000$, $p=0.53$).

Determination of Vitamin Deficiency

Low serum vitamin B_{12} and folate levels are not specific in diagnosing tissue deficiency. A substantial proportion of persons with low serum vitamin B_{12} and folate levels do not appear to have tissue deficiencies of these vitamins (21). Moreover, the serum vitamin level may be low normal despite a tissue deficiency (8). The measurement of two metabolites of vitamin-dependent conversions, in combination with serum vitamin levels, provides more valid evidence for the presence of tissue vitamin deficiency (15, 16). Vitamin B_{12} deficiency reduces the enzymatic conversion of L-methylmalonyl-CoA to succinyl-CoA and, consequently, increases the conversion of D-methylmalonyl-CoA to methylmalonic acid. Both folate and vitamin B_{12} deficiency limit the methylation of homocysteine to methionine. For this study, the presence of high levels of serum methylmalonic acid and homocysteine in combination with low serum vitamin B_{12} and folate levels were used to determine tissue vitamin deficiency.

The serum samples were processed and aliquoted in the Core Genetics Laboratory of the Johns Hopkins University School of Medicine. The samples were shipped on dry ice to the University of Colorado Health Sciences Center for metabolite assays. Methylmalonic acid, homocysteine, and total 2-methylcitric acid were assayed by using stable isotope dilution and gas chromatography/mass spectrometry with selected ion monitoring. The normal ranges for the serum metabolites had been previously determined from 60 normal blood donors aged 18–65 years with a male-female ratio of 1:1 and were defined as two standard deviations above and below the mean after log normalization to correct for skewness of the data. The normal ranges were as follows: homocysteine, 5.4–13.9 μmol/liter; methylmalonic acid, 73–271 nmol/liter; and total 2-methylcitric acid, 60–228 nmol/liter. Serum vitamin B_{12} and folate levels were measured by competitive protein binding assays in the central laboratory of Corning Clinical Laboratories in Teterboro, N.J., by using intrinsic factor and folate-binding protein according to the method of Ciba-Corning Diagnostics Corporation (Medfield, Mass.). The normal ranges specified by the laboratory for vitamin B_{12} and folate were 148–664 pmol/liter and 6.8–36.0 nmol/liter, respectively.

As in an earlier report (22), vitamin B_{12} deficiency was defined according to two classifications, using a high and a low cutoff, in order to explore the existence of a dose-response relationship. High-cutoff vitamin B_{12} deficiency is present when the serum vitamin B_{12} level is less than 258 pmol/liter, the methylmalonic acid level is higher than 271 nmol/liter, and the methylmalonic acid level is higher than the total 2-methylcitric acid level. A low-cutoff vitamin B_{12} deficiency is present when the serum vitamin B_{12} level is less than 148 pmol/liter, the methylmalonic acid level is higher than 271 nmol/liter, and the methylmalonic acid level is higher than the total 2-methylcitric acid level. Folate deficiency is present when the serum folate level is less than 11.4 nmol/liter and the homocysteine level is higher than 13.9 μmol/liter. This broad definition of folate deficiency might overlap with vitamin B_{12} deficiency, since elevated homocysteine levels could be from vitamin B_{12} deficiency alone. A second, more specific definition avoids this overlap by defining folate deficiency as a serum folate level less than 11.4 nmol/liter, a homocysteine level higher than 13.9 μmol/liter, and a methylmalonic acid level of 271 nmol/liter or less.

Measurement of Depression

Depressive symptoms were measured by means of the 30-item Geriatric Depression Scale (20). The Geriatric Depression Scale has been shown to be a reliable and valid measure for older persons (20, 23). Scores can range from 0 to 30, with high scores indicating high levels of depressive symptoms. By using generally accepted cutoff scores (23, 24), the respondents were categorized as having no depression (score≤9), mild depression (score=10–13), or severe depression (score≥14). It should be emphasized that the Geriatric Depression Scale measures depressive symptoms and does not make a clinical diagnosis of depression. Nevertheless, the criterion validity of its cutoff points for clinical depression is good (for mild and severe cutoff points, respectively: sensitivity, 89% and 78%; specificity, 73% and 86%) (23).

Covariates

The sociodemographic variables included age, race, years of education completed, and household income. Alcohol intake was classified as an average consumption of less than one versus one or more alcoholic drinks per day. Body mass index was calculated by dividing the measured weight in kilograms by the square of the height in meters. Since impaired renal function may elevate serum metabolite levels independent of vitamin level, the serum creatinine level (assayed with sodium picrate according to the Ciba-Corning creatinine procedure) was used to indicate possible presence of renal failure. The participants were requested to display the containers for all prescription and nonprescription medication (including vitamin preparations) taken in the past 2 weeks. The interviewers recorded medication name, form, strength, and dose. The presence of 17 major chronic diseases was determined by using standardized algorithms incorporating participant self-reports, physical examination findings, medication use, physicians' reports, and review of medical records (18). Self-reported disability was categorized into three levels: receipt of help from a person to perform one or more basic activities of daily living (bathing, dressing, eating, using the toilet, getting in or out of bed or chairs), no receipt of help but difficulty with one or more activities of daily living, and moderate disability (meeting the study inclusion criteria but not involving difficulties with activities of daily living).

Data Analyses

Chi-square statistics for trend and analysis of variance were used to assess differences in proportions and means, respectively, between the nondepressed, mildly depressed, and severely depressed women. Polychotomous logistic regression models, computed with the procedure Catmod of the SAS program (25), were used to assess the association of vitamin deficiency and the three-

TABLE 1. Characteristics of 700 Physically Disabled Older Women in an Epidemiologic Study of Depression[a] and Levels of Vitamin B_{12} and Folate

Characteristic	No Depression (N=478)		Mild Depression (N=100)		Severe Depression (N=122)		Analysis	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*F (df=2, 697)*	*p*
Age (years)	77.3	7.7	77.4	8.0	77.2	7.9	0.0	0.97
Body mass index (kg/m^2)	28.9	6.8	28.7	6.7	28.9	7.2	0.1	0.95
Serum creatinine level (mg/dl)	1.1	0.5	1.1	0.5	1.1	0.4	0.2	0.80
Number of chronic diseases	2.4	1.5	2.5	1.6	3.1	1.5	10.1	<0.001
	N	*%*	*N*	*%*	*N*	*%*	*χ^2 (df=1)*	*p*
Education ≥12 years	183	38.3	33	33.3	34	27.9	4.9	0.03
Annual income (dollars)[b]							2.6	0.11
<8,000	151	36.0	28	33.3	45	41.7		
8,000–24,999	189	45.0	42	50.0	51	47.2		
≥25,000	80	19.0	14	16.7	12	11.1		
Black race	145	30.3	26	26.0	25	20.5	4.8	0.03
Alcohol use ≥1 drink/day	32	6.7	5	5.0	8	6.6	0.1	0.82
Serum creatinine level ≥1.3 mg/dl[b]	65	13.9	15	15.3	14	11.5	0.3	0.60
Disability in activities of daily living							22.9	<0.001
No	194	40.6	30	30.0	30	24.6		
Yes, receives no help	226	47.3	53	53.0	57	46.7		
Yes, receives help	58	12.1	17	17.0	35	28.7		
Use of vitamin preparations								
Any	111	23.2	26	26.0	22	18.0	0.9	0.34
Vitamin B complex	7	1.5	2	2.0	2	1.6	0.1	0.82
Vitamin B_{12}	11	2.3	2	2.0	2	1.6	0.2	0.64
Folate	7	1.5	1	1.0	1	0.8	0.4	0.54
Multivitamin	97	20.3	22	22.0	18	14.8	1.3	0.25

[a] Depression status was determined with the Geriatric Depression Scale. No depression: score≤9; mild depression: score=10–13; severe depression: score≥14.
[b] Numbers do not total 700 because of missing data.

category depression variable. Unadjusted and adjusted odds ratios and 95% confidence intervals (CIs) were calculated.

Results

The mean age of the study sample was 77.3 years (range=65–100, SD=7.8), 28.0% were black, and 64.2% had less than 12 years of education. Of the 700 participants, 478 (68.3%) were not depressed, 100 (14.3%) were mildly depressed, and 122 (17.4%) were severely depressed. Table 1 shows the demographic characteristics, disease status, and multivitamin use of the study sample according to depression status. Compared to the nondepressed subjects, the depressed women had less education, were more likely to be white, and had more chronic diseases and disability in activities of daily living. No differences were found with respect to age, income, body mass index, alcohol use, and use of vitamin preparations.

The prevalence of vitamin B_{12} deficiency defined according to the high cutoff (i.e., serum vitamin B_{12} level less than 258 pmol/liter plus an elevated serum methylmalonic acid level) was 17.3% (N=121). Of these women, 32 (4.6% of total sample) qualified for the lower, conventional cutoff for vitamin B_{12} deficiency, that is, a serum vitamin B_{12} level below 148 pmol/liter plus an elevated serum methylmalonic acid level. Folate deficiency was found in 7.1% (N=50) of the participants. According to the more specific definition (which avoids overlap with vitamin B_{12} deficiency), 3.1% (N=22) had folate deficiency. Only 18 (2.6 %) of the women had both vitamin B_{12} and folate deficiency.

Table 2 shows the serum vitamin and metabolite concentrations and the vitamin deficiency prevalences by depression status. The mildly and severely depressed women tended to have lower vitamin B_{12} levels than the nondepressed women, but this difference was not statistically significant. Forty percent of the depressed women scored below the vitamin B_{12} cutoff of 258 pmol/liter, which was significantly higher than the 31.6% among the nondepressed. Even more profound differences between the nondepressed and depressed subjects were found for the serum methylmalonic acid concentration. Of the severely depressed women, 43.4% had elevated methylmalonic acid levels, whereas the rates were 35.0% and 30.1% among the mildly depressed and nondepressed subjects, respectively. Serum folate and homocysteine concentrations did not differ according to depression status.

Vitamin B_{12} deficiency was present significantly more often among the severely depressed and mildly depressed subjects than among the nondepressed women (Table 2). This pattern was also observed when the low cutoff was used to define vitamin B_{12} deficiency. Folate deficiency, defined by either the broad or the strict criteria, was not associated with depression status. Other serum metabolites related to vitamin B_{12} and/or folate metabolism were assayed, and there were no significant differences in me-

TABLE 2. Relation of Depression Status[a] to Serum Levels of Vitamin B_{12}, Folate, and Metabolites and to Deficiency Rates in 700 Physically Disabled Older Women

	No Depression (N=478)				Mild Depression (N=100)				Severe Depression (N=122)				Analysis[b]	
Variable	Mean	SD	N	%	Mean	SD	N	%	Mean	SD	N	%	χ^2 or F	p
Serum levels of vitamins and metabolites														
Vitamin B_{12}														
Level (pmol/liter)	502	277			463	224			446	230			2.6	0.07
Subjects with levels <258			151	31.6			40	40.0			49	40.2	4.3	0.04
Subjects with levels <148			29	6.1			6	6.0			12	9.8	1.8	0.18
Folate														
Level (nmol/liter)	12.3	16.1			12.8	10.0			9.9	6.1			1.6	0.21
Subjects with levels <11.4			68	14.2			16	16.0			14	11.5	0.3	0.56
Homocysteine														
Level (µmol/liter)	11.4	4.9			11.6	7.8			12.3	5.6				0.25
Subjects with levels >13.9			99	20.7			20	20.0			34	27.9	2.2	0.13
Methylmalonic acid														
Level (nmol/liter)	258	193			299	311			311	249			3.4	0.03
Subjects with levels >271			144	30.1			35	35.0			53	43.4	7.8	0.005
Rates of vitamin deficiencies														
Vitamin B_{12} deficiency[c]														
High cutoff			71	14.9			17	17.0			33	27.0	9.2	0.002
Low cutoff			18	3.8			4	4.0			10	8.2	3.7	0.05
Folate deficiency[d]														
Broad definition			35	7.3			5	5.0			10	8.2	0.9	0.94
Strict definition			15	3.1			4	4.0			3	2.5	0.4	0.81
B_{12} or folate deficiency			92	19.2			22	22.0			39	32.0	8.6	0.003

[a] Depression status was determined with the Geriatric Depression Scale. No depression: score≤9; mild depression: score=10–13; severe depression: score≥14.
[b] Chi-square tests for linear trend (df=1) were used for categorical variables. Analyses of variance (df=2, 697) were used for continuous variables.
[c] See Method section of text for definitions of cutoff levels.
[d] See Method section of text. The broad definition of folate deficiency may include persons with vitamin B_{12} deficiency; the strict definition avoids overlap with vitamin B_{12} deficiency by additionally excluding subjects with high concentrations of methylmalonic acid.

thionine, methylglycine, dimethylglycine, cystathionine, and 2-methylcitric acid across depression status.

The mean corpuscular volume did not significantly differ between the subjects with a high-cutoff vitamin B_{12} deficiency (93.5 fl, SD=7.5) and those without a deficiency (93.3 fl, SD=6.5). Likewise, serum hematocrit levels did not significantly differ between the subjects with vitamin B_{12} deficiency (mean=39.9 mg/dl, SD=4.7) and nondeficient persons (mean=39.9 mg/dl, SD=4.2). Anemia (defined as a serum hematocrit less than 35.0 mg/dl) was somewhat more common in the subjects with vitamin B_{12} deficiency (17.4%) than in nondeficient subjects (11.0%) (χ^2=3.9, df=1, p=0.05). Anemia was not associated with depression status (χ^2=1.7, df=1, p=0.40).

As compared to those without a high-cutoff vitamin B_{12} deficiency, the deficient subjects were more likely to have congestive heart failure (16.5% versus 9.3%) (χ^2=5.5, df=1, p=0.02) or cancer (21.5% versus 14.2%) (χ^2=4.1, df=1, p=0.04) but less likely to have diabetes (8.3% versus 19.2%) (χ^2=8.3, df=1, p=0.004). Multivariate analyses were subsequently adjusted for the presence of these three diseases. The prevalences of other diseases (e.g., disc disease, spinal stenosis, arthritis, myocardial infarction, angina, pulmonary disease, and stroke) were not significantly associated with vitamin B_{12} deficiency. Also, there was no association between vitamin B_{12} deficiency and cognitive function. The percentage of persons with scores on the Mini-Mental State between 18 (study inclusion criterion) and 23 (indicative of mild cognitive impairment) did not significantly differ (χ^2=0.0, df=1, p=0.84) between those with vitamin B_{12} deficiency (17.4%) and nondeficient persons (16.6%).

Polychotomous logistic regression models were calculated to assess the associations of vitamin B_{12} deficiency and folate deficiency with the three-category depression variable (Table 3). Adjustment was made for age, race, education, income, body mass index, serum creatinine level, disability in activities of daily living, and the presence of diabetes, cancer, and congestive heart failure. For mild depression, no associations with vitamin B_{12} or folate deficiency were found. However, for severe depression, strong associations with vitamin B_{12} deficiency were found. Women with a high-cutoff vitamin B_{12} deficiency were 2.13 times as likely to be severely depressed. After adjustment for all covariates, the odds ratio became 2.05. When we used the more stringent, low-cutoff definition of vitamin B_{12} deficiency, the odds ratios were somewhat higher (unadjusted odds ratio=2.28, adjusted odds ratio=2.09). Folate deficiency was not associated with severe depression.

Discussion

To our knowledge, this is the first study examining the relationship between vitamin B_{12} deficiency and depression in a community-based population. We found that community-dwelling older physically disabled women with metabolically significant vitamin B_{12} deficiency had a risk of depression that was more than twice as high as that of women without vitamin B_{12} deficiency. The higher risk

TABLE 3. Polychotomous Logistic Regression Model Relating Vitamin B_{12} and Folate Deficiency to Mild and Severe Depression in 700 Physically Disabled Older Women

Type of Vitamin Deficiency	Mild Depression Versus No Depression				Severe Depression Versus No Depression			
	Odds Ratio	95% CI	χ^2 (df=2)	p	Odds Ratio	95% CI	χ^2 (df=2)	p
Vitamin B_{12} deficiency[a]								
High cutoff								
Unadjusted	1.17	0.66–2.10	0.3	n.s.	2.13	1.33–3.41	9.8	0.002
Adjusted[b]	1.03	0.56–1.93	0.0	n.s.	2.05	1.22–3.44	7.3	0.007
Low cutoff								
Unadjusted	1.06	0.35–3.22	0.0	n.s.	2.28	1.03–5.08	4.1	0.04
Adjusted[b]	1.00	0.32–3.12	0.0	n.s.	2.09	0.89–4.91	2.9	0.09
Folate deficiency[c]								
Broad definition								
Unadjusted	0.67	0.25–1.74	0.7	n.s.	1.13	0.54–2.35	0.1	n.s.
Adjusted[b]	0.67	0.25–1.78	0.6	n.s.	1.20	0.56–2.60	0.2	n.s.
Strict definition								
Unadjusted	1.29	0.42–4.01	0.2	n.s.	0.78	0.22–2.73	0.2	n.s.
Adjusted[b]	1.35	0.43–4.33	0.3	n.s.	0.90	0.24–3.36	0.0	n.s.

[a] See Method section of text for definitions of cutoff levels.
[b] Adjusted for age, race, education, income, body mass index, serum creatinine level, congestive heart failure, cancer, diabetes, and disability in activities of daily living.
[c] See Method section of text. The broad definition of folate deficiency may include persons with vitamin B_{12} deficiency; the strict definition avoids overlap with vitamin B_{12} deficiency by additionally excluding subjects with high concentrations of methylmalonic acid.

was apparent for severe depression but not for mild depression. No association with depression was found for metabolically significant folate deficiency.

If vitamin B_{12} deficiency is truly associated with depression, what are the potential mechanisms? Vitamin B_{12} deficiency significantly reduces the reactions promoted by two B_{12}-dependent enzymes: L-methylmalonyl-CoA mutase and methionine synthase. There is a resulting accumulation of methylmalonic acid and homocysteine, respectively. The serum vitamin B_{12} levels in our sample were indeed strongly, inversely correlated with serum levels of homocysteine and methylmalonic acid (21). Various neurotoxic mechanisms involving the homocysteine metabolism pathway have been suggested; these include a buildup of *S*-adenosylhomocysteine and an increased metabolism of homocysteic acid that may become neurotoxic through activation of *N*-methyl-D-aspartate receptors (26). However, the association between homocysteine and depression was not very strong in our study, whereas the association with the other metabolite, methylmalonic acid, was markedly stronger: the depressed subjects had significantly higher methylmalonic acid levels than the nondepressed subjects. Methylmalonic acid levels can be elevated in subjects with renal insufficiency, but this did not play a role in our study since the serum creatinine levels and the proportions with elevated creatinine levels were similar in the depressed and nondepressed subjects. To our knowledge, detrimental effects on mood due to actions in the methylmalonic acid metabolism pathway have not been extensively examined and described before. Our findings should encourage further research efforts in this area.

Some other psychobiological explanations for the link between vitamin B_{12} deficiency and depression have been suggested as well. Vitamin B_{12} is required for the synthesis of *S*-adenosylmethionine, which is the major methyl donor in many important methylation reactions in the brain. Since *S*-adenosylmethionine has antidepressant properties (27), inhibited synthesis may cause depression. However, in our study, *N*-methylglycine and methionine concentrations, which should be low in the case of *S*-adenosylmethionine deficiency, were normal in women who were severely depressed (mean=1.5 μmol/liter, SD=5.9, and mean=20.8 μmol/liter, SD=0.6, respectively) and were not significantly different from the levels in the subjects with no or mild depression. Consequently, it is not very likely that the effect of vitamin B_{12} deficiency on depression operates through inhibited *S*-adenosylmethionine synthesis. Another explanation may be that vitamin B_{12} deficiency affects serotonin and catecholamine synthesis, which may result in depressive illnesses (27, 28). Finally, vitamin B_{12} deficiency has been shown to cause demyelination of the spinal cord and the brain (4, 11) and consequently may result in neuropsychiatric disorders.

Some alternative, nonpsychobiological explanations should be given as well. Depression itself could cause low vitamin B_{12} levels through decreased appetite and resultant decreased food intake (29). This is unlikely in our sample, as body mass index and the percentage of subjects who reported weight loss during the previous year (23.8%) did not differ across depression status. Also, serum folate level, which is sensitive to dietary intake, did not differ across depression groups. However, we do not have information on specific nutrient intake in this study. In addition, malabsorption of vitamins and increased utilization of vitamin B_{12} among depressed patients have been suggested to play roles (30). These possibilities cannot be directly addressed by our data and require further examination. It has also been suggested that estrogen use has an effect on vitamin B_{12} level. However, the relation of estrogen use and vitamin B_{12} level was examined in a study of elderly women by Carmel et al. (31), and no link was

found. Also, in our sample, estrogen use (by 9.3% of the subjects) was not associated with vitamin B_{12} level or with depression status, indicating that estrogen use did not play any role in the link between vitamin B_{12} deficiency and depression. Finally, our results could be explained by serious undiagnosed illnesses leading to both malnutrition and depression. This is unlikely, however, since the Women's Health and Aging Study used a very rich source of information concerning diseases, disability, and health status. Adjustment for these variables did not affect the findings.

We did not find an association between depression and folate deficiency. This result is inconsistent with findings from some earlier studies of depressed psychiatric inpatients, in which there was an inverse relationship between folate status and severity of depression: depressed patients with folate in the deficient range had more severe depression than those with folate in the normal range (5, 6). The discrepancy between our and others' results may be due to the fact that the earlier studies used only serum folate level to diagnose folate deficiency and did not use serum metabolites to confirm the true presence. Serum folate levels are rapidly affected by fluctuations in daily dietary intake and may obscure the true folate status. Consequently, associations between depression and serum folate level that are not metabolically confirmed may be more likely to be due to decreased appetite and lower resultant food intake in the most severely depressed patients. Further, the subjects of our study were members of the community-dwelling older population, whereas earlier studies all focused on depressed patients in institutions. The prevalence of folate deficiency in our community-dwelling sample was lower than prevalences found in studies of depressed psychiatric inpatients, even though those studies used lower cutoffs for serum folate to define deficiency. Although the severity of depression appears to be associated with abnormally low folate levels among patients with a psychiatric diagnosis of depression, our study suggests that an association between folate deficiency and depression is absent in the population of community-dwelling older disabled women.

Our study had some limitations. The analyses presented here are cross-sectional; thus, cause-and-effect relationships cannot be proven. Longitudinal data are necessary to further examine the causal pathway in the link between vitamin B_{12} deficiency and depression. Other factors—such as the duration of the vitamin deficiency, the duration of the depressive symptoms, associated metabolic disorders, and genetic predisposition—may also determine whether an affective disorder will occur. We did not have data about these aspects. Finally, our results apply to disabled women only. Exploration of possible sex differences and generalization of our findings to healthier populations will be necessary in further studies.

The prevalence of depression in our sample was high (31.7%) and higher than in similarly aged samples of (less disabled) women (around 20%) (32). Vitamin B_{12} deficiency is rather common among older persons. In our study sample of physically disabled older women, 17.3% had a confirmed tissue deficiency of vitamin B_{12}, which is slightly higher than the 12% to 15% reported in other (less disabled) older populations (33, 34). In line with findings in other studies (8, 21), our data showed that only a small proportion (17.4%) of the B_{12}-deficient subjects had megaloblastic anemia. Clinicians and other health care providers need to be aware of the high prevalence of vitamin B_{12} deficiency in disabled older women, and they need to screen and treat appropriately, irrespective of the presence of anemia. Our findings show, apparently for the first time, that vitamin B_{12} deficiency and depression are associated in a community-based population of disabled older women.

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