Dietary Folate and Depressive Symptoms Are Associated in Middle-Aged Finnish Men[1]

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ABSTRACT Several cross-sectional studies have focused on the low blood folate levels of depressed patients. However, no published studies have examined the association between dietary folate and current symptoms of depression in a general population. We investigated the association between dietary folate, cobalamin, pyridoxine and riboflavin and current symptoms of depression in a cross-sectional general population study. We recruited 2682 men aged between 42 and 60 y from eastern Finland. Those who had a previous history of psychiatric disorder were excluded (n = 146, 5.6% of the cohort). Depressive symptoms were assessed with the 18-item Human Population Laboratory Depression Scale. Those who scored 5 or more at baseline were considered to have elevated depressive symptoms (n = 228, 9.3% of the cohort). The participants were grouped into thirds according to their dietary folate intake. Those in the lowest third of energy-adjusted folate intake had a higher risk of being depressed [odds ratio (OR) 1.67, 95% CI = 1.19–2.35, P = 0.003] than those in the highest folate intake third. This increased risk remained significant after adjustment for smoking habits, alcohol consumption, appetite, BMI, marital status, education, adulthood socioeconomic status and total fat consumption (OR = 1.46, 95% CI = 1.01–2.12, P = 0.044). There were no associations between the intake of cobalamin, pyridoxine or riboflavin, and depression. These results indicate that nutrition may have a role in the prevention of depression. J. Nutr. 133: 3233–3236, 2003.

KEY WORDS: • depression • diet • folate • folic acid • Kuopio Ischemic Heart Disease Risk Factor study

Previous studies published on the relationship between folate and depression investigated mainly heterogeneous groups of psychiatric patients. A number of case-control studies recorded low serum or erythrocyte levels of folate in psychiatric patients with major depression (1–4). Low blood levels of folate were associated with a poor response to treatment with antidepressants (5,6). Antidepressant medication was successfully augmented with methylfolate or folinic acid in three clinical trials (7–9), and some studies reported a negative correlation between blood folate levels and the severity of depression (2,5).

Few reports have been published on the association between folate and depression in general populations. Recently, Morris and co-workers (10) reported that depressed subjects in the U.S. population, especially those who had recently had an episode of depression, had lower folate concentrations in serum and RBC. However, Lindeman et al. (11) and Pennix et al. (12) found no significant associations between blood folate and depression in aging populations.

Several studies have also been published on the association between depression and cobalamin (vitamin B-12) (6,13,14), riboflavin (vitamin B-2) (15,16) and pyridoxine (vitamin B-6) (16,17). The associations between these vitamins and depression may be mediated through homocysteine or the synthesis of monoamines in brain.

Although earlier cross-sectional and case-control studies as well as clinical trials have been reported, no published studies have examined the relationship between dietary folate and current depressive symptoms in a general population. On the basis of previous studies, which utilized different study designs, we hypothesized that a low folate intake is associated with depression, and tested this hypothesis in a sample of middle-aged men from a general population.

We also investigated whether there were associations between the intake of cobalamin, riboflavin and pyridoxine and the risk of depression, because these vitamins may also have associations with depression, possibly through mechanisms similar to those of folate.

SUBJECTS AND METHODS

Subjects. The Kuopio Ischemic Heart Disease Risk Factor study is a population-based study of risk factors for ischemic heart disease and other outcomes among middle-aged men in the Kuopio region of eastern Finland (18). A total of 2682 participants aged 42–60 y (82.9% of those eligible) were recruited for the baseline examination, which occurred between March 1984 and December 1989. Those who reported having previously been diagnosed with a psychiatric disorder were excluded (n = 146, 5.6% of the cohort). Data were incomplete for 93 participants; thus, complete data were available for 2443 men. The study protocol was approved by the Research Ethics Committee of the University of Kuopio.

Assessment of depressive symptoms. Depressive symptoms were assessed with the 18-item Human Population Laboratory Depression

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Scale (HPL depression scale).[3] The scale consists of items dealing with mood disturbance, a negative self-concept, loss of energy, problems with eating and sleeping, trouble with concentration, and psychomotor retardation or agitation. A cut-off score ≥ 5 was used earlier to define elevated depressive symptoms; therefore we used the same cut-off point in this study (19). In this article we call those subjects "depressed." The HPL depression scale was developed especially for screening general population samples (20,21) and is highly correlated with the Beck Depression Inventory score (19,22). In our sample, 9.3% of participants were considered to be depressed (n = 228). Cronbach's α for the HPL depression scale was 0.71. Those who marked "incorrect" for the statement "I have a good appetite" on the HPL depression scale were considered to have a poor appetite.

Assessment of diet consumption. The dietary intake of nutrients was assessed quantitatively by 4-d food recording during the baseline examination. Nutrient intake was calculated using Nutrica software (The Social Insurance Institution of Finland), which was compiled mainly from Finnish values for the nutrient composition of foods, and takes into account the loss of vitamins during food preparation. The software was developed at the Research Centre of the Social Insurance Institution of Finland. The nutrient composition of foods in version 2.5 of the Nutrica software was obtained mainly from analyses carried out in the 1990s. The latest data on the vitamin contents of fruits and vegetables are incorporated. Nutrica contains a large database comprising 1300 food items and dishes and 30 nutrients, including dietary folate and group B vitamins.

Vitamin intake was adjusted for dietary energy intake using the residual method (23). Energy adjustment is based on the assumption that a larger, more physically active person requires a greater energy intake, which is also associated with a greater absolute intake of all other nutrients. The participants were grouped into tertiles according to their energy-adjusted and absolute intakes of folate and cobalamin, pyridoxine and riboflavin.

Other subject characteristics. Participants also completed questionnaires at baseline relating to their sociodemographic background, current smoking habits (yes/no), alcohol consumption (g/wk), marital status and education. Marital status was changed into a variable "living alone" (living in marriage or in common law marriage/living alone). The weight and height of the participants were measured by a nurse and the BMI was calculated.

Statistics. Differences in the characteristics between depressed participants and the rest of the cohort were examined using the Student's t test, Mann-Whitney U-test and χ^2 test. Participants were divided into thirds according to the energy-adjusted intakes of the vitamins. We used Cronbach's α as a measure of the internal consistency of the HPL-depression scale. The odds ratio (OR) for depression was examined using the logistic regression model adjusted for age and examination years (Model 1) and for smoking habits, consumption of alcohol, appetite, BMI, living alone, education, adulthood socioeconomic status and total fat consumption (Model 2). Values in the text are mean ± SD.

RESULTS

The characteristics of the middle-aged men with current depressive symptoms and the rest of the cohort are presented in **Table 1**. Depressed men lived alone more often than the others. They had a lower daily energy intake, more frequently reported a poor appetite and also drank more alcohol.

Depressed men had a lower absolute daily intake of folate and pyridoxine than the others. Only 23.6% of the men consumed the recommended dietary allowance (RDA) of 300 μg/d of folate, whereas 100% of the cohort reached the RDA of the other B vitamins (**Table 2**) (24). The vitamin intakes of the whole cohort were 253.9 μg/d for folate, 9.5 μg/d for cobalamin, 1.9 mg/d for pyridoxine and 2.2 mg/d for riboflavin.

[3] Abbreviations used: CSF, cerebrospinal fluid; HPL depression scale, Human Population Laboratory Depression scale; OR, odds ratio; RDA, recommended dietary allowances; SAM, *S*-adenosylmethionine.

TABLE 1

Characteristics of the study population of middle-aged men stratified by the presence (HPL ≥ 5) or absence (HPL < 5) of current depressive symptoms[1,2]

	(HPL ≥ 5)	(HPL < 5)	*P*-value[3]
n	228	2215	
Age, *y*	53.8 ± 4.5	53.0 ± 5.2	0.014*
BMI, *kg/m²*	26.9 ± 4.0	26.8 ± 3.5	0.659*
Waist-to-hip ratio	0.96 ± 0.06	0.95 ± 0.06	0.049*
Alcohol intake, *g/wk*	96.6 ± 134.9	72.4 ± 134.6	0.003#
Energy intake, *MJ/d*	9.53 ± 2.54	9.95 ± 2.62	0.020*
Fat intake, *g/d*	100.7 ± 35.2	101.8 ± 33.7	0.639*
Education			
Graduated from high school, %	18.7	18.3	0.87†
Marital status			
Living alone, %	17.8	12.1	0.012†
Poor appetite, %	18.3	3.6	<0.0001†
Smoking, %	33.8	31.2	0.426†

[1] Values are means ± SD or %.
[2] HPL is the Human Population Laboratory Depression Scale.
[3] Significance of the difference between groups was assessed by * Student's t test; # Mann-Whitney U-test; † χ^2 test.

The men were grouped into thirds according to their daily intakes of folate, cobalamin, pyridoxine and riboflavin. In the lowest third of folate intake, 11.5% of men were depressed and in the highest third, 7.2%. Respective figures for the other vitamins were 8.8 and 10.0% for cobalamin, 8.4 and 9.4% for pyridoxine and 9.1 and 8.8% for riboflavin (**Table 3**). Folate intakes were 201.9 ± 52.0 μg/d in the lowest third, 243.6 ± 47.8 μg/d in the middle third and 315.9 ± 70.9 μg/d in the highest third.

Participants in the lowest tertile of folate intake had a 67% higher risk of being depressed than those in highest third (**Table 4**, Model 1). When adjusted for age, examination years, smoking habits, consumption of alcohol, appetite, BMI, living alone, education, adulthood socioeconomic status and total fat consumption, the risk remained significant (Table 4, Model 2). Among participants in the lowest third of cobalamin, pyridoxine and riboflavin intakes, the risk of being depressed did not differ from that among men in the highest third.

DISCUSSION

In our study, participants with a dietary folate intake in the lowest tertile had a 67% greater risk of having elevated depressive symptoms than those in the highest tertile. Multivariate analysis supported the existence of an independent relationship between dietary folate intake and current depression.

A deficiency of folate and cobalamin results in the accumulation of homocysteine, which has been suggested to aggravate depression (25,26). Methylfolate supplies methyl groups in the synthesis of methionine from homocysteine, whereas cobalamin and pyridoxine serve as cofactors or substrates for enzymes involved in homocysteine metabolism. Methionine is a precursor of *S*-adenosylmethionine (SAM), which serves as a methyl donor in many methylation reactions in the brain, and is reported to have antidepressant properties (13,27). Dietary intake of folate has been strongly associated with levels of homocysteine in the blood (28,29). Low levels of riboflavin may also lead to the accumulation of homocysteine in people who have a low folate status (30).

TABLE 2

Daily intake of B-vitamins in middle-aged men stratified by the presence (HPL ≥ 5) or absence (HPL < 5) of current depressive symptoms[1,2]

	HPL ≥ 5 (n = 228)	HPL ≤ 5 (n = 2215)	Finnish RDA[3]	Subjects consuming the RDA, %	P-value[4]
Folate, *μg/d*	236.0 ± 69.1	256.2 ± 74.7	300	23.6	<0.001
Cobalamin, *μg/d*	9.3 ± 8.4	9.6 ± 9.6	2.0	100.0	0.666
Pyridoxine, *mg/d*	1.8 ± 0.5	1.9 ± 0.5	1.5	100.0	0.025
Riboflavin, *mg/d*	2.1 ± 0.8	2.2 ± 0.8	1.6	100.0	0.110

[1] Values are means ± SD or %.
[2] HPL is the Human Population Laboratory Depression Scale.
[3] RDA, recommended dietary allowance; see (24).
[4] Significance of the difference between groups.

Folate and cobalamin are also involved in single-carbon transfer methylation reactions connected with the synthesis of serotonin and other monoamine neurotransmitters and catecholamines (13). Bottiglieri et al. (27) found that over half of their severely depressed inpatients had raised total plasma homocysteine. Patients with raised total plasma homocysteine had significant lowering of serum, RBC and cerebrospinal fluid (CSF) folate, CSF SAM and CSF monoamine metabolites. According to Bottiglieri and co-workers, this might indicate that there exists a biological subgroup of depressed individuals among patients with severe depression characterized by folate deficiency, and impaired methylation and monoamine neurotransmitter metabolism.

In our study, there was no relationship between cobalamin intake and depression, even though some earlier cross-sectional studies reported low blood levels of cobalamin in depressed patients (4). The diet in Finland is quite high in dairy products and meat, which are rich sources of cobalamin, but many Finns eat relatively few green vegetables and other sources of folate (24). Accordingly, in our cohort, only 24% of the participants reached the RDA for folate, but 99% reached the recommended intake of cobalamin. The Finnish RDA of 300 μg/d for folate is also lower than that, for example, in the United States (400 μg/d). Even the mean intake in the highest tertile was low (317.7 μg/d) compared with these higher recommendations. All of the participants had an adequate intake of pyridoxine and riboflavin. There was a slight difference between depressed and other participants in the absolute intake of pyridoxine (P = 0.025), but this association was not significant in the logistic regression model using the energy-adjusted intake of pyridoxine. Lee et al. (31) suggested that Chinese people in Hong Kong obtain so much folate from their vegetable-rich diet that even in those who have the lowest blood levels of folate, depressive symptoms are not aggravated. The association between folate intake and depression may therefore be determined by culturally patterned eating habits.

The total energy intake of the depressed participants was significantly lower than that of the other participants. This may be because of poor appetite or neglect of well-being resulting from depression.

The relationship between dietary folate and depression could be explained by other beneficial components of a folate-rich diet. However, if this was true, there might also be an association between depression and the dietary intake of certain other B vitamins that are available in food also commonly considered to be healthy. We found no significant associations in our cohort between the energy-adjusted daily intake of cobalamin, pyridoxine or riboflavin and depression. It could also be that poor eating habits and many other risk factors for depression cluster in the same people. However, adjustment for several possible risk factors associated with lifestyle in our study did not affect the main results.

We did not use structured diagnostic interviews to diagnose depression, which may be considered a limitation. Lindeman et al. (32) found the prevalence of a major depressive episode to be 7.2% in a large random sample of Finnish men aged 15–75 y. In our sample, the prevalence of depressive symptoms was similar (9.2%). Nevertheless, our sample may have included some cases of minor depressive disorders and dysthymia as well as major depressive disorders.

An association between the intake of folate and depression has been suggested to be most clearly apparent in aging populations (33). In our sample, the mean age was only 53 y; therefore the association between the folate intake and depression may have been stronger if we had selected an older population. Our sample also included only men, whereas previous studies have detected an association between folate levels and depression in both men and women (8,10,30).

A low dietary folate intake could be a consequence, rather than a cause of depression. This possible bias is difficult to eliminate in a cross-sectional study. There might also exist a vicious cycle in which folate deficiency aggravates depression, which has poor appetite as a symptom, and this in turn further

TABLE 3

Numbers and proportions of depressed middle-aged men in the tertiles of vitamin intakes[1]

Vitamin	Lowest third	Middle third	Highest third	P-value for linear trend[2]
Folate, *n (%)*	93 (11.5)	76 (9.1)	59 (7.2)	0.002
Intake, *μg/d*	45.4–226.0	226.8–269.1	269.3–587.5	
Cobalamin *n (%)*	73 (8.8)	74 (9.0)	81 (10.0)	0.442
Intake, *μg/d*	2.2–5.9	5.9–8.7	8.7–136.0	
Pyridoxine *n (%)*	68 (8.4)	82 (10.0)	78 (9.4)	0.503
Intake, *mg/d*	0.3–1.7	1.7–2.1	2.1–4.4	
Riboflavin, *n (%)*	75 (9.1)	81 (9.9)	72 (8.8)	0.866
Intake, *mg/d*	0.4–1.9	1.9–2.4	2.4–5.3	

[1] Values are n (%) of men in the third that have current depressive symptoms, and the range of vitamin intakes in thirds of 2443 middle-aged Finnish men.
[2] χ^2 test.

TABLE 4

Odds ratios (OR) of depression in middle-aged men according to intakes of vitamins

Vitamin	Lowest third Model 1[1] [(Model 2[2])] OR (95% CI)	Middle third Model 1[1] [Model 2[2]] OR (95% CI)	Highest third OR	*P*-value[3] Model 1 [Model 2]
Folate	1.67 (1.19–2.35)	1.30 (0.91–1.86)	1.0 (ref.)	0.003
	[1.46 (1.01–2.12)]	[1.23 (0.85–1.79)]		[0.044]
Cobalamin (B-12)	0.88 (0.63–1.23)	0.89 (0.64–1.24)	1.0 (ref.)	0.445
	[0.79 (0.56–1.13)]	[0.82 (0.58–1.16)]		[0.196]
Pyridoxine (B-6)	0.88 (0.62–1.27)	1.07 (0.77–1.48)	1.0 (ref.)	0.446
	[0.79 (0.55–1.13)]	[1.04 (0.74–1.47)]		[0.189]
Riboflavin (B-2)	1.06 (0.75–1.48)	1.14 (0.82–1.60)	1.0 (ref.)	0.757
	[1.24 (0.87–1.78)]	[1.23 (0.87–1.74)]		[0.237]

[1] Logistic regression adjusted for age and examination years.
[2] Logistic regression adjusted for age, years of study, smoking habits, consumption of alcohol, appetite, BMI, living alone, education, adulthood socioeconomic status and total fat consumption.
[3] Significance of difference between lowest and highest tertiles.

lowers the folate intake and furthermore aggravates folate deficiency. However, the main results remained significant after adjustment for poor appetite, even though a poor appetite was significantly more common among the depressed participants. We excluded participants who had a previous psychiatric history; this also reduced the possible bias of the residual symptoms of depression or other psychiatric disorders affecting eating habits. For example, depressed subjects may omit fruits or juices as snack, a practice that could lead to our findings. It is also possible that depressed subjects do not complete their food records as carefully as others, which could have affected our results.

Low dietary folate is associated with elevated depressive symptoms, at least in middle-aged men living in eastern Finland, and is also common among these men. Further studies are warranted to determine whether this association also exists in populations in which an adequate intake of folate is common.

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