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Dietary Folate and the Risk of Depression in Finnish Middle-Aged Men

A Prospective Follow-Up Study

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Key Words

Depression · Diet · Folate · Folic acid · Kuopio Ischaemic Heart Disease Risk Factor Study

Abstract

Background: Several cross-sectional studies have focused on the low blood folate levels of depressive patients. Nevertheless, no prospective studies have been published on the association between dietary folate and depression. ***Methods:*** We studied the association between dietary folate and cobalamin and receiving a discharge diagnosis of depression in a prospective follow-up setting. Our cohort was recruited between 1984 and 1989 and followed until the end of 2000, and it consisted of 2,313 men aged between 42and 60 years from eastern Finland. ***Results:*** The mean intake of folate in the whole cohort was 256 μg/day (SD = 76). Those below the median of energy-adjusted folate intake had higher risk of getting discharge diagnosis of depression (RR 3.04, 95% CI: 1.58, 5.86) during the follow-up period than those who had a folate intake above the median. This excess risk remained significant after adjustment for current socioeconomic status, the baseline HPL depression score, the energy-adjusted daily intake of fibre and vitamin C, and the total fat intake. ***Conclusions:*** A low dietary intake of folate may be a risk factor for severe depression. This also indicates that nutrition may have a role in the prevention of depression.

Introduction

Several studies have been published on the relationship between folate and depression. Patients with major depression have had lower serum or erythrocyte levels of folate in a number of case-control studies [1–4]. Furthermore, low blood levels of folate have been linked with a poor response to antidepressant treatment [5, 6]. In a few clinical trials, augmentation of the antidepressant medication with methylfolate has resulted in better clinical and social recovery [7–9]. In some studies there has also been an inverse relationship between blood folate levels and the severity of depression [2, 5]. Bottiglieri et al. [10] detected low levels of 5-hydroxyindole acetic acid in the

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cerebrospinal fluid of depressed patients with folate deficiency, which indicates that the association between depression and folate may be mediated through monoamine synthesis. Contrary to these findings, which imply an association between a low folate level and depression, Lee et al. [11] recorded higher erythrocyte folate levels in Chinese inpatients than in controls. They suggested that culturally patterned dietary practices can influence the relationship between the folate status and depression.

Morris et al. [12] recently reported that depressed members of the general US population had lower serum and red blood cell folate concentrations. This was especially apparent among those subjects who had recently had an episode of depression. In a cross-sectional population study of middle-aged Finnish men low folate intake increased the risk of being depressed [13]. However, Penninx et al. [14] found no association between blood folate and depression among disabled, older women. Furthermore, Lindeman et al. [15] detected no such association in a general population of elderly males and females.

Although earlier cross-sectional and case-control studies and clinical trials have been reported, no studies have been published on the relationship between dietary folate and the incidence of depression. In fact, it is not known whether the association between low levels of folate and depression is caused by a low intake, poor absorption or a greater need for folate, or whether low blood levels of folate are the result of a poor appetite due to depression. Widner et al. [16] questioned whether increased oxidative stress rather than an inappropriate dietary intake of folate leads to folate deficiency.

Several studies have also been published on the association between depression and low blood levels of cobalamin (vitamin B_{12}) [6, 17, 18]. Both this association and that between depression and folate are suggested to be mediated through homocysteine metabolism or the synthesis of monoamines.

Because there have been no previous prospective studies on folate intake and the risk of depression [19], we aimed to test the hypothesis that a low folate intake among subjects initially free of depression is associated with an increased incidence of severe depression. We also examined the association between cobalamin intake and the incidence of depression.

Subjects and Methods

Participants

The Kuopio Ischaemic Heart Disease (KIHD) Study is a population-based study of risk factors for ischaemic heart disease and other outcomes among middle-aged men in the Kuopio region in Eastern Finland [20]. A total of 2,682 participants aged 42–60 years (82.9% of those eligible) were recruited for the baseline examination, which occurred between March 1984 and December 1989. Data were incomplete for 82 participants but complete data were available for the remaining 2,600 men. The study protocol was approved by the Research Ethics Committee of the University of Kuopio.

Outcomes

Data on getting discharge diagnosis of depressive disorder during the follow-up period were obtained by computer linkage to the national hospital discharge register in 2001. The average follow-up time for the cohort was 13 years. Diagnoses were made according the ICD-8 (years 1985–1986), ICD-9 (years 1987–1995) and ICD-10 (years 1996–2000).

Assessment of Food Consumption

The dietary intake of nutrients was quantitatively assessed by means of a 4-day food recording at the KIHD baseline examination. Nutrient intake was calculated using Nutrica® software, which is mainly compiled using Finnish values for the nutrient composition of foods and takes into account the loss of vitamins during food preparation. The software has been developed at the Research Centre of the Social Insurance Institution of Finland. Intake levels of vitamins were adjusted for dietary energy intake using the residual method [21]. Energy adjustment is based on the notion that a larger, more physically active person requires a higher calorific intake, which is associated with a higher absolute intake of all nutrients. The participants were classified into two categories according to the median energy-adjusted intake of folate and cobalamin (above and below median).

Middle-aged Finnish men do not frequently take vitamin supplements. In this sample only 13% of subjects regularly used antioxidant supplements. Because commonly used supplements in the 1980s did not include folic acid, vitamin users were not excluded from the present analysis.

Assessment of Other Characteristics

Participants also completed questionnaires at baseline relating to their background, current smoking habits (yes/no), alcohol consumption (grams per week), marital status, education and adulthood socioeconomic status. A variety of indicators of adult socioeconomic status were available, including current income, current and previous occupations, the highest level of education, the perception of financial security, and housing tenure. In addition, an index of material living conditions was created by summing the number of material possessions from a list of twelve (colour television, dishwasher, car, telephone, etc). The variable was formed from these indicators. The weight and height of the participants were measured by a nurse and the body mass index (BMI) was calculated.

Exclusion Criteria

Depressive symptoms were assessed with the 18-item Human Population Laboratory Depression Scale [22]. Those who scored 5 or more at baseline were considered already depressive (n = 287) and

Table 1. Characteristics of the study population at baseline according to getting discharge diagnosis of depression in the future (mean ± SD or %)

	Subjects hospitalised due to depression (n = 47)	Subjects not hospitalised due to depression (n = 2,313)	p value for difference
Energy-adjusted folate, μg/day	233.4 (57.8)	256.0 (56.9)	0.007[a]
Total folate, μg/day	255.8 (84.5)	256.4 (75.7)	0.958[a]
Energy-adjusted cobalamin, μg/day	10.0 (15.9)	9.5 (9.1)	0.707[a]
Total cobalamin, μg/day	10.8 (16.0)	9.5 (9.3)	0.343[a]
Total energy, MJ/day	11.05 (2.94)	9.92 (2.59)	0.003[a]
Alcohol/week, g	73.0 (99.7)	72.7 (135.3)	0.761[b]
Age, years	52.2 (5.4)	53.0 (5.2)	0.190[a]
Marital status: living alone, %	12.5	12.5	0.995[c]
Education: graduated from high school, %	22.9	18.2	0.418[c]
Smoking, %	37.5	31.2	0.351[c]
HPL depression score	1.8 (1.5)	1.3 (1.3)	0.019[b]
Poor appetite, %	6.1	3.8	0.866[c]
BMI, kg/m^2	26.9 (3.3)	26.8 (3.5)	0.914[a]
Waist to hip ratio	0.93 (0.05)	0.95 (0.05)	0.100[a]

[a] Student's t test.
[b] Mann-Whitney U test.
[c] χ^2 test.

were excluded from the analysis. 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. The HPL depression scale has especially been used for screening general population samples [23, 24] and is highly correlated with the Beck Depression Inventory score [22, 25]. Cronbach's alpha for the HPL depression scale was 0.71. We also repeated the analysis excluding those participants who received a discharge diagnosis of depression during the first 2 years of follow-up.

Statistical Methods

The relative risk of depression was examined using the Cox 'proportional hazards' model adjusted for age and examination years (model 1) and for socioeconomic status, the Human Population Laboratory Depression score, the energy-adjusted daily intake of fibre and vitamin C, and the total fat intake (model 2). We used the backward stepwise method of the Cox 'proportional hazards' model to assess those covariates that had the strongest associations with depression. Because of the relatively small number of cases, the number of covariates was restricted and we chose the six covariates that had the strongest associations. The model originally included all the variables presented in table 1 except for absolute intake of the vitamins. Folate intake was allowed to compete freely with the other candidate covariates in the baseline analysis, and it had the strongest association with depression. Differences in baseline characteristics between those who received a discharge diagnosis of depression during the follow-up period and the rest of the cohort were examined using the Student t test, Mann-Whitney U test and χ^2 test.

Results

Altogether, 76 participants had a depressive disorder as a discharge diagnosis during the follow-up period, of whom 23 were excluded because of significant depressive symptoms at baseline and 8 because of later receiving a discharge diagnosis of schizophrenia, delusional psychosis or bipolar mood disorder. The remaining participants who were hospitalised and had been diagnosed as having major depression (ICD-9: 2961-, ICD-10: F32.1–3, F33.1–3; n = 31), a depressive, otherwise unspecified disorder (ICD-9: 2968A, ICD-10: F32.9, F33.9; n = 15), chronic depression (ICD-8: 300.41, ICD-9: 3004A, ICD-10: F34.1; n = 4) or adjustment disorder with depressive symptoms (ICD-9: 3090A; n = 3) during the follow-up period were categorised as having incident severe depression. As 6 participants had had several hospitalisations and diagnoses, the total number of diagnoses was 53 although the number of hospitalised participants was 47.

The baseline characteristics of the study subjects with depression and the rest of the cohort are presented in table 1. For the whole cohort, the mean intake of folate was 256 μg/day (SD: 76) and of cobalamin 9.54 μg/day (SD: 9.48). At baseline only 24.6% of the participants reached the Finnish recommended daily folate intake of

Table 2. Relative risk of depression according to energy-adjusted mean intake of folate and cobalamin B_{12}

Vitamin	Cases in lower half[a] n (%)	Cases in upper half n (%)	Relative risk model 1[b] (model 2[c])	95% CI model 1 (model 2)	p value model 1 (model 2)
Folate	35 (0.03)	12 (0.01)	3.04 (2.53)	1.58–5.86 (1.17–5.48)	<0.001 (0.019)
Cobalamin B_{12}	22 (0.02)	25 (0.02)	0.85 (0.40)	0.48–1.51 (0.43–1.39)	0.590 (0.401)

[a] According to the median.
[b] Adjusted for age and examination year.
[c] Adjusted for age and examination year, current socioeconomic status, baseline HPL depression score, and energy-adjusted daily intake of fibre and vitamin C and total fat intake.

300 µg/day [26], while 98.7% of theparticipants reached the recommended daily cobalamin intake of 2 µg/day.

Participants were divided into two groups according their median daily intake of folate. Participants in the lower (below median) folate intake group had a 3 times as high risk of getting a discharge diagnosis of depression as those in the higher (above median) folate group (RR: 3.04, 95% CI: 1.58–5.86, $p < 0.001$; table 2, model 1). In multivariate analysis adjusted for adulthood socioeconomic status, baseline HPL depression score, energy-adjusted daily intake of fibre and vitamin C, and total fat intake, the risk remained 2.5-fold higher (RR: 2.53, 95% CI: 1.17–5.48, p = 0.019; table 2, model 2). Further adjustment for marital status, education, current smoking habits and weekly alcohol consumption did not alter this association (RR: 2.51, 95% CI: 1.16–5.45, p = 0.020).

We also repeated our analysis excluding participants who had been discharged with a diagnosis of depressive disorder during the first 2 years of follow-up. This left 44 incident cases to be analysed. The relative risk of depression in the lower folate intake group remained almost the same (model 1: RR: 3.13, 95% CI: 1.58–6.19, p = 0.001; model 2: RR: 2.57, 95% CI: 1.16–5.70, p = 0.021). Furthermore, we repeated the analysis excluding those participants who had been diagnosed as having a mental disorder before the baseline. This left 40 cases to be analysed. However, the results remained significant (model 1: RR: 3.16, 95% CI: 1.54 –6.48, p = 0.002; model 2: RR: 2.53, 95% CI:1.17–5.48, p = 0.019). There was a significant difference in total energy intake between the depressed and the other participants (table 1). However, adjustment for the total energy intake had little effect on the association between folate intake and the incidence of depression (model 1: RR: 3.01, 95% CI: 1.56–5.82, p = 0.001). In order to eliminate the possible bias of other folate-related diseases causing depression, we repeated the analyses excluding those participants who had history of cancer or cardiovascular disease (n = 846), which left 35 cases to be analysed, but it had little effect on the results (model 1: RR: 2.82, 95% CI: 1.35–5.89, p = 0.006; model 2: RR: 2.51, 95% CI: 1.06–5.95, p = 0.036).

Participants were also divided into two groups according to the median daily intake of cobalamin. However, the intake of cobalamin and the incidence of depression were not associated (RR: 0.85, 95% CI: 0.48–1.51, p = 0.59; table 2, model 1). Furthermore, splitting the cohort into tertiles or quartiles still revealed no association between cobalamin intake and an increased risk of depression.

Discussion

In our study, participants with a low dietary folate intake had a 3-fold as high risk of getting a discharge diagnosis of depressive disorder during the follow-up period as those in the higher folate intake group. The relationship remained significant and independent even after adjustment for several confounding risk factors for depression and low vitamin intake.

Several studies have linked cobalamin and folate because they are suggested to have the same type of association with depression [6, 17, 18]. They are involved in single carbon transfer methylation reactions connected with the synthesis of serotonin and other monoamine neurotransmitters and catecholamines [17]. Folate and cobalamin deficiency additionally results in the accumulation of methylmalonic acid and homocysteine, which have also been suggested to aggravate depression [27, 28]. Bottiglieri et al. [10] found high levels of homocysteine in 52% of depressed inpatients.

In our study there was no relationship between the intake of the cobalamin and depression. This is probably

because the diet in Finland typically contains a high proportion of dairy products and meat, which are rich sources of cobalamin. However, many Finns eat relatively few green vegetables and other sources of folate. In our sample only 25% of the participants reached the recommended daily intake of folate, but 99% reached the recommended intake of cobalamin [26]. Lee et al. [11] suggested that Chinese people in Hong Kong obtain so much folate from their diet that even in those who have the lowest levels of folate it does not aggravate depressive symptoms. While an adequate intake of folate is typical in Hong Kong, a low folate intake in the ageing male population of eastern Finland seems to be quite common. It is also notable that the recommended daily folate intake of 300 μg/day in Finland is lower than in many other countries.

Depressed participants had a higher total energy intake than the others. However, there was no difference in appetite, BMI or waist to hip ratio between the groups. Morris et al. [12] did not find appetite loss, weight loss or being underweight to be related to blood folate levels, but being overweight was more common among the depressed participants. This could imply that other factors in the diet are also associated with depression. An increased appetite, weight gain and increased eating, especially a craving for starch and sugar, are associated with an atypical subtype of depression. An increased BMI has also been associated with depression in some studies [29]. Unfortunately, we were unable to investigate any of these possible underlying mechanisms in our material.

Unlike the food frequency method, food records are based on the actual intake of foods. A major strength of the food record method is that it does not rely on memory. In the KIHD Study, food records are collected for 4 consecutive days. One of our qualified nutritionists provides the necessary instructions and checks the completed food records with the study subject. The weakness of the food record method is that day-to-day intake of foods is highly variable for many individuals. Although undereating could occur during record-keeping days, we believe that 4 consecutive days are enough to reliably detect differences in energy intake between depressed and non-depressed subjects.

Our study had some limitations. First, we could not fully exclude the possibility that the relationship between depression and dietary folate is explained by other health features of a folate-rich diet. It could also be that poor eating habits, low physical activity, smoking and excess alcohol consumption cluster in same people, who would in any case be at risk of mental health problems, either because of their lifestyle or despite it. However, adjustment for the intake of total fat, fibre and vitamin C, and several possible risk factors associated with lifestyle did not alter the main results in our study.

Changes in eating habits during the follow-up period could also have biased our results. However, earlier studies on this material have shown eating habits to remain relatively stable. Unpublished follow-up data for 440 of these men revealed that the average daily folate intake had decreased by 7.1% (from 268 to 248 μg/day) during 11 years of follow-up. Because our study is a prospective population study it is more easily generalised to the general population than case-control studies. Naturally, however, we cannot generalise our findings to men in all age groups. However, the intake of folate seems to change quite slowly in the Finnish population in relation to age.

Depression in Finland, as in many other countries, is more common among women [30], which makes the generalisation of the findings to women difficult in a sample consisting only of men. However, the homogeneity of our sample improves the possibility of identifying associations between depression and background variables, because the etiology of depression is considered to be multifactorial.

Unfortunately, Finland has no national register of outpatients with depression, and the total number of cases of depression could not therefore be included in our analysis. Furthermore, many depressed people do not seek treatment for their problems. For this reason we limited our analysis to severe depression requiring hospitalisation. This restriction and the exclusion of participants with depressive symptoms at baseline also strengthens the probability that a low dietary folate intake is a cause of depression rather than a consequence of it. In other words, this also eliminates the bias of poor appetite as a symptom of depression affecting dietary habits. Furthermore, poor appetite was quite rare in both hospitalised and non-hospitalised subject groups (6.1 vs. 3.8%), and there was no significant difference between them. Repeating the analysis and excluding those who were hospitalised during the first 2 years of follow-up should also minimise bias due to depression causing poor dietary habits.

Conclusion

Taken together, low dietary folate may be associated with an increased risk of severe depression, at least in middle-aged men living in eastern Finland. However, this

association may only be present in populations with a generally low intake of folate. Further studies are therefore needed to verify these findings, and also to evaluate the possibility of preventing depression by improving dietary habits.

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