

Research Article

ASSOCIATION OF DIETARY AMINO ACIDS WITH LOW MOOD

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Diet may affect mood and cognitive functions. Tryptophan and serine augmentation strategies have been applied for patients with mood or psychotic disorders. We studied the association between dietary intake of amino acids and low mood. We studied 29,133 men aged 50–69 years for 5–8 years in a population-based trial in Finland. Intake of amino acids was calculated from a diet history questionnaire completed by 27,111 men at baseline. Self-reports of depressed mood were recorded thrice a year; data on hospital treatment due to depressive disorders were derived from the national Hospital Discharge Register, and suicides were identified from death certificates. Participants were smokers at study entry. Strengths of our study include detailed data on food consumption, a substantial number of study participants, a long prospective follow-up time, and versatile data on indices of low mood. We found no association between the dietary intake of amino acids and self-report of depressed mood or risk of suicide. However, dietary intake of lysine and serine was associated with risk of hospital treatment due to major depressive disorder but these associations disappeared after excluding from analysis those who had reported depressed mood at study entry. There is no consistent association between dietary intake of amino acids and low mood. Depression and Anxiety 18:89–94, 2003. © 2003 Wiley-Liss, Inc.

Key words: proteins; amino acids; depressive disorder; diet; mood; suicide

INTRODUCTION

Diet tends to show an effect on mood and cognitive functions. A high intake of carbohydrates may result in increased uptake of tryptophan in the brain, thereby stimulating serotonin synthesis [Rogers, 2001]. This seems to lead rapidly to drowsiness in healthy subjects but to alertness in patients with seasonal affective disorder [Rosenthal et al., 1989]. A low-fat diet also may have negative effects on mood [Wells et al., 1998] and altered dietary fat intake can have acute behavioral effects independent of the level of energy consumption [Lloyd et al., 1994]. In addition, omega-3 fatty acids are claimed to benefit patients with mood disorder, schizophrenia, or dementia [Freeman, 2000]. Finally, a high intake of proteins may increase the level of alertness [Rogers, 2001], and the intake of branched-chain amino acids seems to alleviate manic symptoms acutely [Scarnà et al., 2003].

Despite this, there is still a lack of consistent data concerning nutrition and diet in individuals with

mental disorder. The aim of the present work was to study whether there are associations between intake of amino acids and low mood. The study end points were measures of varying degrees of low mood, including

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self-report of depressed mood, hospital treatment due to major depressive disorder, and suicide.

METHODS

The present study was based on the cohort of a randomized, double-blind, placebo-controlled, primary prevention trial to test whether daily supplementation with α -tocopherol, β -carotene, or both reduces the incidence of lung and other cancers [ATBC Cancer Prevention Study Group, 1994]. The present analysis was not part of the original study design a priori. Study participants were recruited from the total male population 50–69 years of age, residing in southwestern Finland ($n = 290,406$) in 1985–1988. These men were sent a questionnaire on current smoking and willingness to participate in the trial. Smokers of at least 5 cigarettes/day who were willing to participate were then sent an invitation to visit their local study center for further evaluation of their eligibility. Diagnosis of cancer, current severe angina with exertion, chronic renal insufficiency, cirrhosis of the liver, alcohol dependence, or disorder limiting participation in the long-term trial, such as mental disorder or physical disability, was reason for exclusion. Finally, 29,133 men were randomly assigned to receive supplements of α -tocopherol, β -carotene, both, or placebo in the 2×2 factorial design. The trial supplementation had no effect on main outcome measures. The ethics review boards of the participating institutions approved the study, and all subjects provided written informed consent before randomization.

At baseline, height and weight were measured. Participants completed a questionnaire with items of general background information and medical and smoking histories. Diet and alcohol consumption were assessed with a self-administered dietary history questionnaire [Pietinen et al., 1988] which assessed the frequency of consumption and usual portion size of 276 food items during the past year, using a color picture booklet as a guide for the estimation of portion size. Complete dietary data were available for 27,111 participants. Dietary nutrient data were calculated by linking the questionnaire data to the food composition database of the National Public Health Institute in Finland. Participants made three follow-up visits annually for 5–8 years. At each visit, a structured assessment of symptoms experienced in the past 4 months was made, including two items on anxiety and depression as part of a 30-item self-report questionnaire.

END POINT ASSESSMENT

Study end points were self-reported depressed mood, hospital admission due to major depressive disorder, and suicide. Subjects reporting depression were queried at baseline and each follow-up visit (3 visits/year). Follow-up continued until dropout or trial closure in

April 1993, during which 9,300 men reported depression at some point. Only the first follow-up report of depressed mood was used in analysis of the association between dietary intake of amino acids and subsequent self-reports of depressed mood.

Data on hospital admissions for depressive disorders were derived from the National Hospital Discharge Register, which covers in-patient admissions to all medical and psychiatric hospital beds in Finland. Accuracy of the register compared with medical records is excellent, with data being identical in about 95% of primary diagnoses [Keskimäki and Aro, 1991]. The diagnoses were coded according to the International Classification of Diseases [ICD-8; World Health Organization, 1968] up to the end of 1986, and according to the Diagnostic and Statistical Manual of Mental Disorders [DSM-III-R; American Psychiatric Association, 1987] thereafter. Two hundred eighty men were hospitalized at least once for major depressive disorder by the end of 1994. In analysis of the association between the dietary intake of amino acids and subsequent hospital admission due to major depressive disorder, the first admission with this diagnosis was used. Information about hospital admissions for depressive disorders was available for active participants and dropouts alike.

Follow-up of survival extended to the end of 1994. Data on deaths were derived from the Central Population Register, and cause of death was reviewed from death certificates. We considered suicide assigned as cause of death to be the third study end point, with 102 suicides committed during follow-up. Figure 1 shows cross-categorization of participants according to the three study end points.

STATISTICS

We used Cox proportional hazards regression models to analyze the relations between baseline dietary intake of amino acids and first occurrence of self-reported depressed mood, first hospital admission period due to major depressive disorder, and suicide.

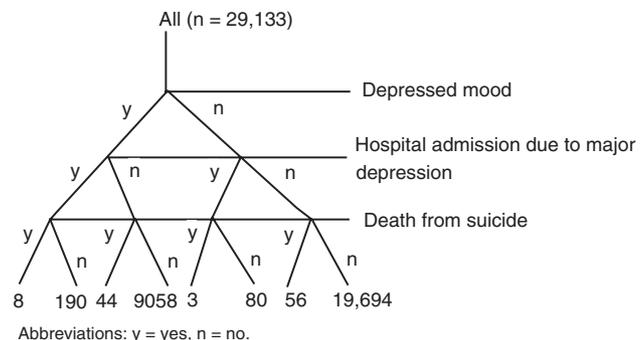


Figure 1. Number of subjects divided by subgroups of self-reported depressed mood, hospital admission due to major depression, and suicide.

Intake of amino acids was included in the models as tertile categories. We also compared the highest decile and the lowest decile with the middle category. To limit the effect of confounding factors, we repeated analyses by excluding those who had given a self-report of depressed mood at study entry.

Known important risk factors for major depressive disorder and suicide, including age, body mass index (BMI), energy intake, serum total cholesterol, high-density lipoprotein cholesterol, consumption of alcohol, education, marriage, self-reported depression, self-reported anxiety, and smoking, were entered into the models as covariates. Estimated relative risks and

95% confidence intervals (CIs) were calculated. Dietary factors were adjusted for energy intake in the models [Willett, 1990].

RESULTS

Table 1 lists baseline characteristics by study end point status; intake of dietary amino acids is listed in Table 2. On average, intake was similar in all groups. There were no significant associations between intake of amino acids and risk of self-reported depressed mood during follow-up (Table 3).

TABLE 1. Baseline characteristics of subjects by end point and in whole cohort

Characteristics	Self-reported depressed mood		Hospital admission		Suicide		Whole cohort	
N	8,612		246		102		27,111	
Age (yr)	57.6	5.1	56.7	5.1	57.4	4.92	57.7	5.1
BMI (kg/m ²)	26.3	3.8	26.3	4.2	25.6	3.64	26.3	3.8
Serum total cholesterol (mmol/l)	6.22	1.19	6.09	1.24	5.90	1.17	6.24	1.17
HDL cholesterol (mmol/l)	1.23	0.34	1.21	0.32	1.31	0.37	1.23	0.34
Cigarettes smoked/day	21.1	9.1	22.10	9.8	22.4	8.8	20.4	8.8
Consumption of alcohol (g/day)	20.1	23.8	19.3	23.6	19.1	25.1	18.0	21.6
Weight (kg)	79.2	12.9	79.7	13.8	76.1	11.1	79.4	12.8
Married (%)	79.3		72.8		67.6		81.2	
Education more than elementary school (%)	23.8		32.5		16.6		21.7	
Self-reported depression (%)	34.5		48.4		37.3		14.6	
Self-reported anxiety (%)	41.8		50.4		44.1		22.0	

Values are expressed as mean and *sd*, or proportion.

TABLE 2. Daily intake of energy (kcal), proteins (g), and amino acids (g) at baseline by end point and in whole cohort

Intake	Self-reported depressed mood		Hospital admission		Suicide		Whole cohort	
N	8,612		246		102		27,111	
Energy intake	2,858	791	2,809	838	2,868	839	2,815	787
Protein	104.4	29.7	104.6	31.4	104.2	29.9	103.2	29.5
Alanine	3.88	1.128	3.91	1.150	3.87	1.149	3.84	1.117
Arginine	5.34	1.549	5.37	1.621	5.30	1.589	5.27	1.532
Asparagine-aspartate	7.34	2.103	7.40	2.165	7.35	2.156	7.27	2.080
Cysteine	1.41	0.417	1.41	0.429	1.41	0.405	1.40	0.411
Glutamate-glutamine	18.21	5.425	18.16	5.817	18.18	5.400	18.05	5.369
Glycine	3.43	1.036	3.44	1.047	3.40	1.059	3.39	1.026
Histidine	2.87	0.842	2.89	0.876	2.84	0.836	2.84	0.836
Isoleucine	3.87	1.145	3.90	1.208	3.88	1.159	3.83	1.134
Leucine	7.39	2.211	7.44	2.350	7.43	2.236	7.31	2.191
Lysine	6.40	1.914	6.47	2.020	6.42	1.946	6.34	1.898
Methionine	2.08	0.632	2.10	0.674	2.09	0.642	2.06	0.626
Phenylalanine	4.21	1.249	4.23	1.324	4.23	1.262	4.17	1.238
Proline	7.90	2.498	7.87	2.715	7.95	2.513	7.85	2.473
Serine	4.25	1.272	4.27	1.350	4.30	1.309	4.20	1.258
Threonine	3.48	1.019	3.50	1.071	3.50	1.037	3.44	1.008
Tryptophan	1.28	0.373	1.29	0.388	1.29	0.375	1.27	0.370
Tyrosine	3.48	1.067	3.51	1.139	3.52	1.089	3.45	1.056
Valine	4.79	1.427	4.83	1.511	4.81	1.442	4.74	1.414

Values are expressed as mean and *sd*.

TABLE 3. Relative risk and 95% confidence interval of self-reported depression, hospital admission due to major depression, and suicide, by baseline intake of amino acids[†]

Amino acid intake (in tertiles)*	g/day	Self-reported depressed mood		Hospital admission		Suicide	
Alanine	<3.3	1.00		1.00		1.00	
	3.3–4.2	1.04	0.99–1.10	1.07	0.77–1.48	1.38	0.86–2.21
	>4.2	1.04	0.99–1.10	1.32	0.96–1.80	1.03	0.62–1.72
Arginine	<4.5	1.00		1.00		1.00	
	4.5–5.7	0.98	0.93–1.03	0.88	0.63–1.22	0.96	0.60–1.54
	>5.7	1.01	0.96–1.07	1.27	0.93–1.72	0.89	0.54–1.45
Asparagine–Aspartate	<6.2	1.00		1.00		1.00	
	6.2–7.9	0.98	0.93–1.03	1.05	0.76–1.45	1.30	0.82–2.06
	>7.9	1.02	0.97–1.07	1.28	0.93–1.74	0.92	0.55–1.54
Cysteine	<1.2	1.00		1.00		1.00	
	1.2–1.5	0.90	0.85–0.95	0.85	0.61–1.17	1.33	0.83–2.12
	>1.5	1.01	0.96–1.07	1.09	0.79–1.49	0.87	0.51–1.48
Glutamate–Glutamine	<15.3	1.00		1.00		1.00	
	15.3–19.7	0.92	0.87–0.97	1.19	0.86–1.64	1.64	1.03–2.61
	>19.7	0.95	0.90–1.01	1.13	0.81–1.57	0.78	0.44–1.37
Glycine	<2.9	1.00		1.00		1.00	
	2.9–3.7	1.06	1.01–1.12	1.10	0.80–1.52	0.65	0.40–1.06
	>3.7	1.04	0.98–1.09	1.26	0.92–1.72	0.84	0.53–1.34
Histidine	<2.4	1.00		1.00		1.00	
	2.4–3.1	1.01	0.96–1.07	1.10	0.79–1.52	1.16	0.72–1.86
	>3.1	1.00	0.95–1.06	1.36	0.99–1.86	1.00	0.61–1.65
Isoleucine	<3.3	1.00		1.00		1.00	
	3.3–4.2	1.01	0.95–1.06	1.16	0.84–1.60	1.09	0.67–1.77
	>4.2	1.01	0.96–1.07	1.30	0.94–1.78	1.16	0.71–1.90
Leucine	<6.2	1.00		1.00		1.00	
	6.2–8.0	0.98	0.93–1.04	1.21	0.88–1.66	1.29	0.79–2.08
	>8.0	1.00	0.95–1.05	1.26	0.92–1.74	1.15	0.70–1.91
Lysine	<5.4	1.00		1.00		1.00	
	5.4–6.9	1.01	0.96–1.07	1.17	0.85–1.62	0.94	0.58–1.54
	>6.9	1.01	0.96–1.06	1.40	1.02–1.93	1.16	0.72–1.86
Methionine	<1.8	1.00		1.00		1.00	
	1.8–2.2	1.00	0.95–1.06	1.22	0.89–1.68	1.36	0.85–2.18
	>2.2	1.02	0.97–1.08	1.27	0.92–1.75	1.08	0.65–1.79
Phenylalanine	<3.6	1.00		1.00		1.00	
	3.6–4.5	0.93	0.89–0.98	1.17	0.85–1.62	1.62	1.00–2.61
	>4.5	0.99	0.94–1.04	1.29	0.94–1.78	1.10	0.65–1.88
Proline	<6.6	1.00		1.00		1.00	
	6.6–8.6	0.92	0.87–0.97	1.13	0.81–1.56	1.25	0.77–2.01
	>8.6	0.92	0.87–0.97	1.23	0.89–1.70	0.96	0.57–1.62
Serine	<3.6	1.00		1.00		1.00	
	3.6–4.6	0.96	0.91–1.01	1.17	0.84–1.62	1.36	0.84–2.19
	>4.6	1.01	0.96–1.07	1.38	1.00–1.90	1.06	0.64–1.78
Threonine	<2.9	1.00		1.00		1.00	
	2.9–3.7	0.99	0.94–1.04	1.03	0.74–1.42	1.34	0.83–2.15
	>3.7	1.02	0.97–1.08	1.30	0.95–1.78	1.07	0.64–1.79

TABLE 3 (continued)

Amino acid intake (in tertiles)*	g/day	Self-reported depressed mood		Hospital admission		Suicide	
Tryptophan	<1.1	1.00		1.00		1.00	
	1.1–1.4	0.98	0.93–1.03	1.25	0.91–1.72	1.34	0.84–2.14
	>1.4	1.00	0.95–1.06	1.26	0.92–1.75	0.98	0.59–1.65
Tyrosine	<2.9	1.00		1.00		1.00	
	2.9–3.8	0.99	0.94–1.04	1.16	0.84–1.60	1.26	0.77–2.04
	>3.8	1.00	0.95–1.05	1.34	0.98–1.84	1.19	0.72–1.96
Valine	<4.0	1.00		1.00		1.00	
	4.0–5.2	0.98	0.93–1.03	1.17	0.85–1.61	1.21	0.75–1.97
	>5.2	1.00	0.95–1.06	1.30	0.95–1.79	1.12	0.68–1.84

$n = 27,111$.

[†]Relative risk was adjusted for baseline age, body mass index, energy intake, serum total cholesterol, high-density lipoprotein cholesterol, consumption of alcohol, education, marriage, self-reported anxiety, self-reported depression, and smoking.

*Lowest intake tertile as reference.

Two amino acids were associated with subsequent hospital admissions due to major depressive disorder: Relative risk (95% CI) was 1.40 (1.02–1.93) for lysine and 1.38 (1.00–1.90) for serine in the highest tertile, respectively, compared with the lowest tertile (Table 3). However, these associations disappeared after excluding subjects with self-report of depressed mood at study entry. Then, the relative risk (95% CI) was 0.87 (0.24–1.50) for lysine and 1.10 (0.42–1.76) for serine in the highest tertile, respectively, compared with the lowest tertile.

There were no significant associations between intake of amino acids and risk of suicide during follow-up (Table 3). We also compared the highest decile and lowest decile with the middle tertile of dietary intake of amino acids for each study end point, but there was no significant difference (data not shown).

DISCUSSION

Intake of two amino acids, serine and lysine, was associated with increased risk of hospital treatment due to major depressive disorder. That the high intake of serine or lysine was not linked to heightened risk as assessed with all three study end points may reflect the diversity in mood regulation processes and our study end points (Fig. 1).

Because these two associations attenuated after exclusion of subjects who at study entry had reported depressed mood during the preceding 4 months, subjects at risk for severe forms of major depression may tend to eat more protein-rich foods. Alternatively, positive associations between serine and lysine intake levels and risk of major depressive disorder may have occurred by chance owing only to multiple comparisons.

High serine plasma concentrations have been suggested to be a potential marker for psychotic disorder in general, and for depressive disorder with psychotic symptoms in particular [Waziri et al., 1984; Baruah et al., 1991; Mauri et al., 1998]. However, there are also

reports of low serine plasma levels in psychotic depressive disorder [Fekkes et al., 1994; Maes et al., 1998]. Serine seems to act as a partial agonist at the glycine modulation site of the glutamate receptor in the brain, and therefore tends to affect brain functions [Watson et al., 1990]. Currently, there are no data regarding the impact of lysine on brain functions or mental disorder. However, lysine is an essential amino acid and is, for instance, an elementary part in the cascade of carnitine metabolism [Jacob and Belleville, 1992]. This particular role of lysine is worth studying in more depth in future.

Unexpectedly, we found no association between intake of tryptophan and our study end points. Tryptophan is a precursor for serotonin that is known to have a key role in many brain functions: for example, in mood regulation. Studies have shown that acute tryptophan depletion produces depressive symptoms and results in worsening of mood [Neumeister et al., 1998; Spillman et al., 2001]. For this reason, tryptophan supplementation has been applied for the treatment of depressed patients [Lam et al., 1997].

Interestingly, negative studies have been published recently suggesting that the effects of tryptophan depletion on mood are not consistent [Bell et al., 2001, Van der Does, 2001], and the rationale for augmentation has been challenged [Nelson, 2000]. Our results agree with these recent findings in that the effect of tryptophan on mood may be less robust than has been assumed earlier. Furthermore, there are no data showing whether serum serine or lysine concentrations can affect brain tryptophan uptake.

LIMITATIONS

Limitations of our study are that participants were solely men, of a restricted age cohort, and all were smokers at study entry. However, there are no data about the effect of smoking on amino acid metabolism. Our exclusion criteria limit the generalizability of our

findings, but the study still provides valid and reliable data on a community-based, homogeneous sample of older men. In our study, dietary intake of protein and essential amino acids exceeded recommended daily intake values for men [Matthews, 1999]. This may explain the lack of the association between low intake of amino acids and self-report of low mood. There was no evidence of any protective action of high levels of dietary protein or amino acids against low mood, either.

On the other hand, strengths of our study include a combination of detailed data on food use and versatile data on indices of low mood for a substantial number of subjects during a long prospective follow-up. Diet and alcohol consumption were assessed with a validated food use questionnaire to measure habitual intake over the previous year. For most nutrients, the reproducibility of this method is 0.6–0.7 and the validity 0.6–0.7 [Pietinen et al., 1988]. In addition, we collected versatile data on depression, which increases the validity and reliability of the assessment. However, the assessment of self-reported depression was based on a single item, which might have compromised the specificity but not the sensitivity. Here, the number of items as such may not be crucial for detecting probable cases of major depression because, for example, two questions only may be equal to many for identifying the disorder [Whooley et al., 1997].

In conclusion, we did find no consistent association between intake of amino acids and low mood. Tryptophan intake was not linked to any measure of depression in this study.

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REFERENCES

- American Psychiatric Association. 1987. Diagnostic and statistical manual of mental disorder 3rd ed., revised (DSM-III-R). Washington, DC: APA.
- ATBC Cancer Prevention Study Group. 1994. The alpha-tocopherol, beta-carotene lung cancer prevention study: Design, methods, participant characteristics, and compliance. *Ann Epidemiol* 4:1–10.
- Baruah S, Waziri R, Hegwood TS, Mallis LM. 1991. Plasma serine in schizophrenics and controls measured by gas chromatography-mass spectrometry. *Psychiatry Res* 37:261–270.
- Bell C, Abrams J, Nutt D. 2001. Tryptophan depletion and its implications for psychiatry. *Br J Psychiatry* 178:399–405.
- Fekkes D, Peplinkhuizen L, Verheij R, Bruinvels J. 1994. Abnormal plasma levels of serine, methionine, and taurine in transient acute polymorphic psychosis. *Psychiatry Res* 51:11–18.
- Freeman MP. 2000. Omega-3 fatty acids in psychiatry: A review. *Ann Clin Psychiatry* 12:159–165.
- Jacob C, Belleville F. 1992. L-carnitine: Metabolism, functions and value in pathology. *Pathol Biol (Paris)* 40:910–919.
- Keskimäki I, Aro S. 1991. Accuracy of data on diagnoses, procedures and accidents in the Finnish Hospital Discharge Register. *Int J Health Sci* 2:15–21.
- Lam RW, Levitan RD, Tam EM, Yathan LN, Lamoureux S, Zis AP. 1997. L-Tryptophan augmentation of light therapy in patients with seasonal affective disorder. *Can J Psychiatry* 42:303–306.
- Lloyd HM, Green MW, Rogers PJ. 1994. Mood and cognitive performance effects of isocaloric lunches differing in fat and carbohydrate content. *Physiol Behav* 56:51–57.
- Maes M, Verkerk R, Vandoolaeghe E, Lin A, Scharpè S. 1998. Serum levels of excitatory amino acids, serine, glycine, histidine, threonine, taurine, alanine and arginine in treatment-resistant depression: Modulation by treatment with antidepressants and prediction of clinical responsiveness. *Acta Psychiatr Scand* 97:302–308.
- Matthews DE. 1999. Proteins and amino acids. In: Maurice ME, Olson JA, Shike M, Ross AC, editors. *Modern nutrition in health and disease*. 9th ed. Baltimore: Williams & Wilkins. p 41–43.
- Mauri MC, Ferrara A, Boscati L, Bravin S, Zamberlan F, Alecci M, Invernizzi G. 1998. Plasma and platelet amino acids concentrations in patients affected by major depression and under fluvoxamine treatment. *Neuropsychobiology* 37:124–129.
- Nelson JG. 2000. Augmentation strategies in depression 2000. *J Clin Psychiatry* 61(Suppl. 2):13–19.
- Neumeister A, Praschak-Rieder N, Hesselmann B, Vitouch O, Rauh M, Barocka A, Kasper S. 1998. Effects of tryptophan depletion in fully remitted patients with seasonal affective disorder during summer. *Psychol Med* 28:257–264.
- Pietinen P, Hartman AM, Haapa E, Räsänen L, Haapakoski J, Palmgren J, Demetrius A, Virtamo J, Huttunen JK. 1988. Reproducibility and validity of dietary assessment instruments. *Am J Epidemiol* 128:655–666.
- Rogers PJ. 2001. A healthy body, a healthy mind: A long-term impact of diet on mood and cognitive function. *Proc Nutr Soc* 60:135–143.
- Rosenthal NE, Genhart MJ, Caballero B, Jacobsen FM, Skwerer RG, Coursey RD, Rogers S, Spring BJ. 1989. Psychobiological effects of carbohydrate- and protein-rich meals in patients with seasonal affective disorder and normal controls. *Biol Psychiatry* 25:1029–1040.
- Scarnà A, Gijsman HJ, McTavish SFB, Harmer CJ, Cowen PJ, Goodwin GM. 2003. Effects of a branched-chain amino acid drink in mania. *Br J Psychiatry* 182:210–213.
- Spillman MK, Van der Does AJW, Rankin MA, Vuolo RD, Alpert JE, Nierenberg AA, Rosenbaum JF, Hayden D, Schoenfeld D, Fava M. 2001. Tryptophan depletion in SSRI-recovered depressed outpatients. *Psychopharmacology* 155:123–127.
- Van der Does AJW. 2001. The effects of tryptophan depletion on mood and psychiatric symptoms. *J Affect Disord* 64:107–119.
- Watson GB, Bolanowski MA, Baganoff MP, Deppeler CL, Lanthorn TH. 1990. D-Cycloserine acts as a partial agonist at the glycine modulatory site of the NMDA receptor expressed in *Xenopus* oocytes. *Brain Res* 510:158–160.
- Waziri R, Wilcox J, Sherman AD, Mott J. 1984. Serine metabolism and psychosis. *Psychiatry Res* 12:121–136.
- Wells AS, Read NW, Laugharne JDE, Ahluwalia NS. 1998. Alterations in mood after changing to a low-fat diet. *Br J Nutr* 79:23–30.
- Whooley MA, Avins AL, Miranda J, Browner WS. 1997. Case-finding instruments for depression: Two questions are as good as many. *J Gen Intern Med* 12:439–445.
- Willet W. 1990. *Nutritional epidemiology*. New York: Oxford University Press.
- World Health Organization. 1968. Eighth revision of the International Classification of Diseases (ICD-8). Geneva: WHO.