Reeta Rintamäki

Mood in Association with Dietary Nutrient Intakes and Sleep Length

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Department of Mental Health and Alcohol Research
National Public Health Institute, Helsinki, Finland
and
Department of Psychiatry,
University of Kuopio, Finland

Helsinki 2007

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A C A D E M I C D I S S E R T A T I O N

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Department of Mental Health and Alcohol Research,
National Public Health Institute,
Helsinki, Finland

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Department of Psychiatry,
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Kansanterveyslaitos (KTL)
Mannerheimintie 166
00300 Helsinki
Puh. vaihde (09) 474 41, faksi (09) 4744 8408

Folkhälsoinstitutet
Mannerheimvägen 166
00300 Helsingfors
Tel. växel (09) 474 41, telefax (09) 4744 8408

National Public Health Institute
Mannerheimintie 166
FI-00300 Helsinki, Finland
Telephone +358 9 474 41, telefax +358 9 4744 8408

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Supervised by:

Docent Timo Partonen, M.D., Ph.D.
Department of Mental Health and Alcohol Research
National Public Health Institute,
Helsinki, Finland

and

Docent Jukka Hintikka, M.D., Ph.D.
Department of Psychiatry,
University of Kuopio,
Kuopio, Finland

Reviewed by:

Professor Esa Leinonen, M.D., Ph.D.
Department of Psychiatry,
University of Tampere,
Tampere, Finland

and

Docent Liisa Valsta, Ph.D., M.Sc.
Department of Epidemiology and Health Promotion
National Public Health Institute,
Helsinki, Finland

Opponent:

Professor Matti Joukamaa, M.D., Ph.D.
Tampere School of Public Health,
University of Tampere,
Tampere, Finland

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Reeta Rintamäki, Ravintoaineiden ja unen pituuden yhteys mielialaan.
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TIIVISTELMÄ

Ravinnolla on tiedetty olevan vaikutuksia mielialaan, mutta vain vähän johdonmukaisia tutkimuksia on julkaistu. Tämä tutkimus mielialahäiriöiden ja ravinnon välisistä yhteyksistä perustuu kahteen aineistoon: syövänehkäisytutkimukseen (SETTI) ja bipolaarikaksostutkimukseen. Masennuksen ja ravinnon saannin välisten yhteyksien selvittämiseksi tutkittiin 29 133 keski-ikäistä suomalaista miestä, jotka tupakoivat. Miehet osallistuivat väestöpohjaiseen seurantatutkimukseen 5–8 vuoden ajan. Ravinnon saanti on laskettu ruokavaliokyselystä ja tiedot mielialasta saatiin kyselystä, jonka tutkittavat täyttivät 3 kertaa vuodessa. Vakavan masennuksen vuoksi sairaalahoitoon joutuneiden tiedot saatiin sairaaloiden hoitoilmoitusrekisteristä ja itsemurhien tiedot väestörekisteristä. Bipolaarikaksostutkimuksessa aineisto on kerätty yleisväestöstä. Henkilöt valittiin hoitoilmoitusrekisteristä, niiden joukosta joilla vuosien 1969–1991 aikana on diagnosoitu bipolaarihäiriö. Näistä potilaista on väestörekisteristä etsitty vuosina 1940–1969 syntyneet kaksoset ja heille lähetettiin kutsu tutkimukseen (n = 76). 67 tutkittavaa osallistui haastattelututkimukseen, jonka yhteydessä he täyttivät kyselyn vuodeaikavaihtelun vaikutuksesta mielialaan (SPAQ) ja myöhemmin 39 tutkittavaa täytti lisäksi ruoankäyttökyselyn (FFQ) ravinnosta ja Horne-Östbergin (MEQ) kyselylomakkeen vuorokausimieltymyksistä.

Tutkimuksessa ei löytynyt tilastollisesti merkiseviä yhteyksiä ruoasta saatujen ravintoaineiden ja mielialan väliltä. Kuitenkin terveiden ja sairaiden ravinnon saannissa oli poikkeavuuksia. Miehet, jotka olivat olleet sairaalahoidossa vakavan masennuksen vuoksi saivat ravinnostaan enemmän seriiniä ja lysiiniä. Myöskin miehet, jotka ilmoittivat masennuksen ja ahdistuksen tunteista sekä unettomuudesta käyttivät alkoholia enemmän kuin terveet henkilöt. Bipolaaripotilaat saivat ravinnostaan B_{12}-vitamiinia enemmän kuin terveet henkilöt. Myös bipolaaripotilailla oli terveitä enemmän vuodenaikavaihtelua unen pituudessa ja mielialassa. Tämän tutkimuksen tulosten mukaan ravinnon saannilla ja mielilalla ei ole voimakasta yhteyttä. Lisätutkimuksia tarvitaan selvittämään ravinnon ja mielialan välisiä yhteyksiä.

Avainsanat: masennus, bipolaarihäiriö, ravinto, uni, omega-3 rasvahapot, vitamiinit, aminohapot

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SUMMARY

Diet has an effect on mood, but few studies have examined associations between dietary intakes of nutrients and mood disorders. These associations warrant investigation. In this work, two samples of study subjects were used. For major depressive disorder we studied 29,133 men involved for five to eight years in a prospective, population-based trial in Finland (the Alpha-tocopherol, Beta-carotene (ATBC) Cancer Prevention Study). Nutrient intakes were calculated from a diet history questionnaire. Self-reports of mood symptoms were recorded three times 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. For bipolar disorder, all Finnish same-sex twins born from 1940 to 1969 were screened for a diagnosis of bipolar type I disorder (n = 76). Sixty-nine study participants filled in the Seasonal Pattern Assessment Questionnaire (SPAQ), and 39 completed the Food Frequency Questionnaire (FFQ) and Morningness-Eveningness Questionnaire (MEQ).

In present study, it found no significant associations between dietary intakes of nutrients and mood disorders in this study. However, there were some variations in intakes of food and nutrients between persons with mood disorders or mood symptoms compared with healthy individuals. Two amino acids associated with major depressive disorder. Subjects with symptoms of depression, anxiety or insomnia consumed more alcohol than healthy subjects. The dietary intake of vitamin B_{12} was greater in bipolar patients than in healthy subjects. Moreover, those with bipolar disorder had greater seasonal changes in mood and sleep length. These results do not support the view that dietary nutrient intakes have a major role in mental health. Further studies are needed to explore associations and connections between nutrient intakes and mental health.

Keywords: major depression, bipolar disorder, diet, sleep, omega-3 fatty acids, amino acids, vitamins

1 LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals I-V. In addition, some unpublished data are presented.

I. **Hakkarainen R**, Partonen T, Haukka J, Virtamo J, Albanes D, Lönnqvist J. Association of dietary amino acids with low mood. Depression and Anxiety 2003; 18: 89-94.

II. **Hakkarainen R**, Partonen T, Haukka J, Virtamo J, Albanes D, Lönnqvist J. Is low dietary intake of omega-3-fatty acids associated with depression? American Journal of Psychiatry 2004; 161: 567-569.

III. **Hakkarainen R**, Partonen T, Haukka J, Virtamo J, Albanes D, Lönnqvist J. Food and nutrient intake in relation to mental wellbeing. Nutrition Journal 2004; 3:14.

IV. **Rintamäki R**, Männistö S, Partonen T, Kieseppä T, Kaprio J, Lönnqvist J. Dietary intake, drinking and smoking in twins with bipolar disorder (submitted).

V. **Hakkarainen R**, Johansson C, Kieseppä T, Partonen T, Koskenvuo M, Kaprio J, Lönnqvist J. Seasonal changes, sleep length and circadian preference among twins with bipolar disorder. BMC Psychiatry 2003; 3: 6.

2 ABBREVIATIONS

ALA	Alpha-Linolenic Acid
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
CI	Confidence Interval
DNA	Deoxyribonucleic Acid
DHA	Docosahexaenoic Acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPA	Eicosapentaenoic Acid
FFQ	Food Frequency Questionnaire
FTCQ	Finnish Twin Cohort Questionnaire
GSS	Global Seasonality Score
GWS	Global Weather Score
HDL	High Density Lipoprotein
ICD	International Classification of Diseases
LDL	Low Density Lipoprotein
MDD	Major Depressive Disorder
MES	Morningness-Eveningness Score
MEQ	Morningness-Eveningness Questionnaire
SAD	Seasonal Affective Disorder
SPAQ	Seasonal Pattern Assessment Questionnaire

3 ABSTRACT

It is suggested that diet has an effect on mood, but only a few studies have explored associations between dietary intakes of nutrients and mood disorders. The primary aim of this study was to investigate possible associations between dietary intakes of amino acids, omega-3 fatty acids and vitamins, and mood symptoms and disorders. Another study aim was to assess circadian preference, sleep length and seasonal patterns in mood and behaviour among twins with bipolar disorder, and whether seasonal changes influence nutrient intake.

Methods

This work involved two samples of study subjects were used: one for major depressive disorder, and one for bipolar type 1 disorder. For major depressive disorder, the study population consisted of 29,133 male smokers aged 50 to 69 years who entered the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study for 5-8 years. This was a placebo-controlled trial to test whether supplementation with alpha-tocopherol or beta-carotene prevents lung cancer. At baseline 27,111 men completed a diet history questionnaire from which food and alcohol consumption and nutrient intakes were calculated. The questionnaire on background and medical history included three items on mental wellbeing, anxiety, depression and insomnia experienced in the past four months. Self-reports of mood symptoms were recorded three times 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.

For bipolar disorder the data were taken from a study of all Finnish same-sex twins born from 1940 to 1969 who were screened for a diagnosis of bipolar type I disorder (n= 76). The diagnosis was assessed using a structured research interview (SCID). Sixty-nine of the study participants filled in the Seasonal Pattern Assessment Questionnaire, and 39 of them later completed the Food Frequency Questionnaire and Morningness-Eveningness Questionnaire. For studying the persistence of habitual sleep and the consumption of

alcohol and smoking of tobacco, data from the Finnish Twin Cohort Questionnaire were used. Bipolar twins were compared with their healthy co-twins.

Results

There were no associations found between dietary intakes of amino acids, omega-3 fatty acids or vitamins, and mood disorders and symptoms. Only two amino acids, serine and lysine, associated with major depression, their intakes being higher higher in subjects with depressive disorder than in healthy subjects. Energy intake was higher in men who reported anxiety or depressed mood, and those reporting any such symptoms consumed more alcohol. Dietary intakes of protein and vitamin B_{12} were higher in those with bipolar disorder than in healthy individuals. Bipolar patients also experienced larger seasonal changes in sleep length and mood.

Conclusions

There was no significant association between dietary intakes of nutrients and mood disorders in this study. However, there was some variation in intakes of food and nutrients between persons with mood disorders or mood symptoms compared with healthy individuals. These results do not support the view that dietary intakes of nutrients have a major role in mental health, although more studies are needed to clarify the associations found.

4 INTRODUCTION

Mood disorders are a significant health problem throughout the world. Major depression is estimated to be the fourth most important illness causing functional disability worldwide and has been projected to become the second leading cause of disability worldwide by 2020 (Murray and Lopez, 1996; 1997). It is the fastest growing reason for early retirement and in Finland major depression is the most common reason for early disability pensions (Salminen et al. 1997; Finnish Centre for Pensions, 2005). Bipolar disorder is another serious psychiatric disorder causing great disability. It is the sixth leading cause of disability worldwide (Murray and Lopez, 1996). The estimated lifetime prevalence of major depression ranges from 10 to 30%. The lifetime prevalence of bipolar I disorder is 0.24% in Finland (Perälä et al. 2007) and varies from 0.1 to 4.8% in general populations worldwide (Rihmer and Angst, 2005).

Although there have long been suggestions that diet can have an effect on mood, very few studies have investigated associations between dietary intakes of various nutrients and mood disorders. It has been noted that there are differences in the diet of subjects with depressed mood compared to the healthy subjects. Depressed subjects consume more carbohydrates than healthy subjects and they have heightened preference for sweet carbohydrates (Christensen and Somers, 1996; Christensen, 2001).

There have also been associations notes between deficiency of specific nutrients and mood symptoms. Deficiency of certain vitamins (folate, vitamin B_{12}, and vitamin B_1) can cause depressive symptoms. It has been reported that depressed patients have low levels of folate in their serum and red blood cells (Carney et al. 1990; Fava et al. 1997; Bottiglieri et al. 2000; Lerner et al. 2006). Tryptophan is a precursor for serotonin that is known to play a key role in mood regulation. Tryptophan depletion produces depressive symptoms, especially for depressed patients with remission (Neumeister et al. 1998; Spillmann et al. 2001). Societies with a high consumption of fish appear to have a lower prevalence of depression (Hibbeln, 1998) and it has been reported that omega- 3 fatty acids may alleviate the symptoms of mood disorders (Stoll et al. 1999; Su et al. 2003). However, there are also conflicting findings (Marangell et al. 2003; Silvers et al. 2005). Against the aforementioned background, the topic of this thesis appeared to offer a fruitful opportunity for a more detailed analysis of the relationships between nutrition and mood disorders.

5 REVIEW OF THE LITERATURE

5.1 Mood disorders

Mood disorders include depressive and bipolar disorders. This study focuses on major depressive disorder (MDD) and bipolar type I disorder.

5.1.1 Major depressive disorder

Public health

Major depression forms a significant health problem in many countries. It is estimated to be the fourth most important illness to cause functional disability worldwide and has been projected to become the second leading cause of disability worldwide by 2020 (Murray and Lopez, 1996; 1997). It is the fastest growing reason for early retirement and in Finland MDD is the most common reason for early disability pensions (Salminen et al. 1997; Finnish Centre for Pensions, 2005). MDD also causes great individual harm to both patients and their relatives.

Prevalence of depression

Finland's the Health 2000 project reports the 12-month prevalence of MDD to be 4.9% (Pirkola et al. 2005). MDD is more common among women than men (6.3% vs. 3.4%). In the USA, the lifetime prevalence of MDD in the general population is 16.6% and the 12-month prevalence was 6.7 percent (Kessler et al. 2005a; 2005b).

Clinical course

MDD is characterized by severe symptoms of depression. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, MDD is defined as two or more weeks of low mood or diminished interest in usual activites, combined with four or more of the following symptoms: sleep alteration (increased or decreased), inappropriate guilt or loss

of self-esteem, altered appetite (increased or decreased), diminished energy, diminished concentration, psychomotor symptoms, or suicidal ideation (American Psychiatric Associations, 1994). There is an increased risk of suicide in patients with MDD (Harris and Barraclough, 1997). It has been estimated that lifetime risk of suicide is 6% for affective disorders (Inskip et al, 1998). The average age of onset is the mid-twenties and for most people episodes of MDD last from six to nine months. MDD may present as single or recurrent episodes. The risk of relapse over a five- year period has been estimated to be as high as 50-85% (American Psychiatric Association, 2000). An episode is considered to have ended when the full criteria for the major depressive episode have no been fulfilled for at least four consecutive months (Rush et al. 2006). Depressed patients often have somatic symptoms. It is estimated that 69% to 92% of depressed patients have somatic symptoms such as headache, chest pain, back pain and constipation (Kroenke and Price, 1993; Ebert and Martus, 1994; Simon et al. 1999; Corruble and Guelfi, 2000). Morover, 10% of patients with mood disorders have a seasonal pattern of recurrence (Faedda et al. 1993). Patients with seasonal affective disorder (SAD) have a seasonal pattern in their symptoms. Depressed episodes typically occur in autumn or winter and usually followed by recovery the following spring or summer. Fatigue, hypersomnia and increased appetite are typical symptoms of SAD.

Etiology and pathogenesis of depression

MDD is a multifactorial, heterogenous disorder with a wide range of possible etiologial factors. There are genetic, biological and environmental risk factors.

Heritability and genetic studies

MDD is a familiar disorder, with most of the familial aggregation resulting from genetic factors (Sullivan et al. 2000). A meta-analysis of five methodologically rigorous twin studies produced statistically homogeneous results and an aggregate estimate of the heritability of MDD of 37% (Sullivan et al. 2000). Kendler et al. (2006) reported that the heritability of liability to MDD was significantly higher in women (42%) than men (29%) in the Swedish National Twin Study. Recently, molecular genetic studies of MDD and gene-environmental interactions have been published. The most promising results have

been found for polymorphisms such as the serotonin transporter gene linked promoter region (HTTLPR) and brain-derived neurotrophic factor (BDNFV66M) genes in depression (Kato, 2007). Recently, it has been found in a prospective birth cohort study that a functional polymorphism of the serotonin transporter gene moderates the influence of stressful life events on depression (Caspi et al. 2003).

Neurochemistry

It has been reported that certain monoamines (noradrenaline, serotonin, and dopamine) have a role in the pathogenesis of MDD. Most of the anti-depressive medications act through an increase in serotonin neurotransmission. It has been reported that depressed subjects have reduced serotonin levels in platelets (Le Quan-Bui et al. 1984; Muck-Seler et al. 1991). Reduced serotonergic transmission is associated with the pathogenesis of depressive illness and suicidal behaviours (Åsberg et al. 1976; Doris et al. 1999; Mann, 1999). There is increased serotonin transporter activity in the brain of the depressed compared to healthy subjects (Malison et al. 1998; Reivich et al. 2004). Several studies have demonstrated reduced concentrations of dopamine metabolites both in cerebrospinal fluid and in brain in subjects with depression (Dunlop and Nemeroff, 2007). Althought the neuroimaging studies support the hypothesis that major depression is associated with a state of reduced dopamine transmission (Dunlop and Nemeroff, 2007). Traditional antidepressants also increase the concentration of noradrenaline. It has been reported that depressed subjects have altered noradrenalin receptor density, but there are also contradictory findings (Brunello et al. 2002).

Environmental risk factors

Even if heritability of liability to MDD is significant in the etiology of the disorder, environmental events account for a substantial portion of the variation in liability. There are some environmental risk factors for MDD in the general population. Subjects with stressfull and traumatic experiences, such as sexual abuse in early childhood, have increased risk of MDD disorder (Kendler et al. 2004). Lindeman et al. (2000) reported that factors associated with MDD were urban residency, smoking, alcohol intoxication, and chronic medical conditions. Long term unemployment also seems to be an important risk

factor to MDD (Hämälainen et al. 2001; 2005). Previously, unemployment was reported to associate with mental disorders in the general population (Viinamäki et al. 1995).

A recent review study reported a median prevalence of current or lifetime alcohol problems in depression were 16% (range 5-67%) and 30% (range 10-60%), respectively (Sullivan et al. 2005). It has been also reported that daily smoking is associated with MDD (Breslau et al. 1998; Ferguson et al. 2003). Psychiatric patients generally have higher rates of tobacco smoking than the general population in the USA (Hughes et al. 1986).

Deficiency of certain nutrients is another cause of depression; examples of such nutrients are deficiency of vitamin B_6, vitamin B_{12} and folate (Leklem, 1999; Scott and Weir, 1999; Reynolds, 2002).

5.1.2 Bipolar disorder

Public Health

Bipolar disorder is a serious psychiatric disorder which causes great disability. It is the sixth leading cause of disability worldwide (Murray and Lopez, 1996) and, like MDD, causes great distress and suffering to both patients and their relatives.

Prevalence and epidemiology of bipolar disorder

The Health 2000 project reports that the lifetime prevalence of bipolar I disorder in Finland is 0.24% (Perälä et al. 2007). The estimated incidence of bipolar I disorder in the Finnish population in the period 1970-1991 was 5.8 per 100,000 population (Kieseppä et al. 2000). In other countries the lifetime prevalence has varied from 0.1 to 4.8% in general populations (Rihmer and Angst, 2005). The lifetime prevalence of bipolar disorder in the USA was 2.6% in general population.

Clinical course

Bipolar disorder is characterized by mood swings that alternate between periods of mania and periods of depression. According to DSM-IV (American Psychiatric Association, 1994), mania is defined as a distinct change in mood and functioning lasting at least one week, and is characterized by a euphoric or irritable mood accompanied by symptoms such as increased energy, decreased need for sleep, rapid thinking and speech, grandiosity, poor judgement and impulsivity, and in some cases, psychotic symptoms. For patients with bipolar disorder, episodes of mania are often followed by periods of MDD. Patients may also have mixed mood states, in which the symptoms of mania and depression occur simultaneously, or rapid cycling, where continuous or frequently shifting mood states occur.

Seasonal recurrences have been found in 10% of patients with mood disorders (Faedda et al. 1993). Shin et al. (2005) reported that subjects with bipolar disorder have as much seasonal fluctuation as subjects with seasonal depression. However, there are also contradictory findings. Partonen and Lönnqvist (1996) reported that there was no seasonal variation among all hospital admissions in subjects with bipolar disorder.

Bipolar disorder tends to affect men and women equally. The average age of first manic episode is the early twenties. Even in patients with continued adherence to medication regimens, the risk of relapse over a five-year period has been estimated to be as high as 73% (Gitlin et al. 1995). The estimated lifetime risk of suicide is 6% for all affective disorders in general (Inskip et al. 1998).

Etiology and pathogenesis of bipolar disorder

The etiology of bipolar disorder is multifactorial and still poorly understood. Biological and especially genetic factors seem to be important for the vulnerability, and environmental factors increase the risk.

Heritability and genetic studies

A meta-analysis of 18 family studies arrived at a recurrence risk of bipolar disorder for first-degree relatives of bipolar probands of 8.7% and a risk for unipolar depression of 14.1% (Smoller and Finn, 2003). It has been suggested that familial aggregation is due predominantly to genetic factors, with heritability estimates in the range of 60 to 85% (Smoller and Finn, 2003). Kieseppä et al (2004) reported a high heritability (93%) of bipolar disorder in a nationwide population-based twin study. Numerous studies have attempted to localize susceptibility genes for bipolar disorder, but still have not led to a consensus about any particular predisposing locus to bipolar disorder. Bipolar disorder is a multigenetic disorder determined by several genes. Based on numerous linkage studies some chromosomal regions are associated with bipolar disorder (Craddock et al. 2005). Also, it has been reported that two genes, D-amino-acid oxidase activator (DAOA) and brain derived neurotrophic factor (BDNF), maybe associate with bipolar disorder (Craddock et al. 2005). In a recent meta-analysis the polymorphism in serotonin transporter gene (5-HTT) showed significant association with bipolar disorder (Lasky-Su et al. 2005).

Neurochemistry

It has been reported that serotonin has a role in the pathogenesis of bipolar disorder. Serotonergic abnormalities have been reported in bipolar disorder, e.g. increased serotonin receptors in platelets, a lower maximal velocity of serotonin platelet uptake, and decreased brain serotonin neurotransmitter activity (Marazzitti et al. 1991; Prange et al. 1974; Price et al. 1990; Pandey et al. 2003). Recently, Oquendo and co-workers (2007) reported that patients with bipolar disorder had 16% to 26% lower serotonin transporter bingin potential in brain using positron emission tomography compared to healthy controls.

Sleep and circadian rhythms

Disturbances of the sleep-wake cycle and circadian rhythms are prevalent in bipolar disorder. Changes in the sleep-wake cycle can trigger manic episodes in bipolar disorder (Wehr et al. 1987). Experimentally induced sleep deprivation was associated with the onset of hypomania or mania in a study of depressed patients (Wu and Bunney, 1990). A recent

systematic review study established that sleep disturbance was the most common prodrome of mania and the sixth most common prodrome of bipolar disorder (Jackson et al. 2003). Harvey et al. (2005) reported that euthymic patients with bipolar disorder also have clinically significant sleep disturbance. Moreover, it has been suggested that children of bipolar parents have dysregulation of sleep, which may be an early marker of bipolar disorder (Jones et al. 2006). It has been hypothesized that bipolar disorder patients have a genetic diathesis that may take the form of circadian rhythm instability. Accordingly, it has been reported that sleep deprivation changes the expression of several genes in the cerebral cortex of rat's brains (Terao et al. 2006).

Twin studies suggest a genetic susceptibility to seasonal changes (Madden et al. 1996; Jang et al.1997). It has been hypothesized that mutation in circadian rhythm-related genes can cause bipolar disorder, which has strong heritability, but more studies are needed (Benedetti et al. 2003; Mansour et al. 2006; Nievergelt et al. 2006). The protein products of circadian genes are necessary for the generation and regulation of circadian rhythms (Ko and Takahashi, 2006). There is also some evidence that bipolar disorder is associated with some circadian rhythm-related genes, with the strongest evidence for the aryl hydrocarbon receptor nuclear translocator-like (ARNTL) gene, but more large studies are needed to confirm these findings (Benedetti et al. 2003; Mansour et al. 2006; Nievergelt et al. 2006).

Environmental risk factors

There are some environmental risk factors which affect bipolar disorder, but the findings are still unclear. Stressful life-events later in life may predispose to mania or depression in bipolar patients, but their association with the onset of the first episode remains controversial (Ambelans, 1987; Ellicot et al. 1990; Scalre and Creed, 1990). An association between childhood physical abuse and mania has also been reported (Levitan et al. 1998).
The lifetime prevalence of alcohol abuse or dependence in patients with bipolar disorder has been reported to be 46.2% and 39.2%, respectively (Regier et al. 1990). In addition, patients with alcohol dependence tend to have a heightened risk for a lifetime diagnosis of co-morbid mania (Helzer and Pryzbeck, 1988). Smoking incidence is high, over 50%, in patients with bipolar disorder (Gonzale-Pinto et al. 1998). However, excessive smoking is

associated with psychotic disorders in general rather than bipolar disorder specifically (Corvin et al. 2001).

There is no evidence that deficiency of specific nutrients can cause bipolar disorder, but omega-3 fatty reportedly alleviate the symptoms (Stoll et al. 1999).

5.2 Mood and food

Food habits have changed in Finland over the past decades and nowadays resemble those of a typical European diet in many ways. Earlier the Finnish diet was largely based on grains, milk products, and potatoes. The consumption of grain and starch products has since declined, while animal products have increased. Vegetables and fruit consumption has also increased steadily (Pietinen et al. 2001). The intake of vitamins and minerals is generally adequate (Männistö et al. 2003).

There was a shortage of studies on relationships between dietary intakes and mood prior to the start of the studies presented herein. However, recent years have seen a growing interest in exploring these associations and the findings of several studies are presented here. Mostly of the studies have attempted to clarify the association between fish consumption and depression.

It has been reported that people with a high consumption of fish appear to have a lower prevalence of depression (Hibbeln 1998; Tanskanen et al. 2001a; 2001b, Silvers and Scott 2002; Timonen et al. 2004). Hibbeln (1998) found that greater seafood consumption was related to lower life-time prevalence rates of MDD across nine countries. In two Finnish studies a significant reverse association between consumption of fish and depression was observed only for females (Tanskanen et al. 2001b; Timonen et al. 2004). It has been also reported that increased fish intake in people without depressive symptoms had no substantial effect on mood (Woo et al. 2002; Ness et al. 2003). Noaghiul and Hibbeln (2003) reported that greater rates of seafood consumption were associated with lower prevalence rates of bipolar disorder in cross-national comparisons across 12 countries. The results of the fish studies are seen in Table 1.

Hintikka et al. (2005) recently reported that daily tea drinking was associated with a low level of depressive symptoms in the Finnish general population. None of those whose daily tea intake was five cups or more had depression. Individuals drinking regular coffee with caffeine were reported to have decreased total sleep time and sleep quality, and increased sleep latency (Shilo et al. 2002). Also, caffeine administration can increase anxiety and alertness (Brice and Smith, 2002).

Table 1. The Associations between the intake of fish/seafood and mood disorders

Study subjects	**N**	**Intake of omega 3-fatty acids/fish**	**Findings**	**Authors**
25-64 year-old Finnish adults	1 772	High consumption / low consumption of fish*	Fish↓ mood↓ Association founded only in women.	Tanskanen et al. 2001
25-64 year-old Finnish adults	3 204	High consumption / low consumption of fish*	Fish ↑ mood↑	Tanskanen , 2001
70 year-old and over Chinese elderly	2 032	Infrequent, occasional and daily consumption	Fish ↑ mood↔	Woo et al. 2002
Over 15 years old New Zealander adults	4 644	Non-fish consumers/ Fish consumers	Fish ↑ mood↑	Silvers and Scott, 2002
37-70 year-old UK men	377	Fish advice: EPA 8.8 mg/d No fish adivice: EPA 8.7 mg/d	Fish ↑ mood↔	Ness et al. 2003
31 year-old Finnish adults (birth cohort)	5 689	Regular fish eaters/ Rare fish eaters**	Fish↓ mood↓ Association founded only in women.	Timonen et al. 2004
Cross-national comparison			Fish ↑ depression↓	Hibbeln, 1998
Cross-national comparison			Fish ↑ bipolar disorder↓	Noahghiul and Hibbeln, 2003

* Fish were consumed twice a week or more often vs less than twice a month
** eat fish weekly or more often vs eat fish monthly or more seldom
↓ = low consumption, worsened of mood, ↔ = no effects on mood , ↑ = high consumption, improved of mood

5.3 Mood and nutrients

5.3.1 Macronutrients

The macronutrients sources of energy are carbohydrates, fats and proteins. Carbohydrates are compounds made up of sugars. They are classified by their number of sugar units: monosaccharides (such as glucose and fructose), disaccharides (such as lactose and sucrose) and bigger molecules, oligo- and polysaccharides. Carbohydrates are the most common source of energy, but they are not essential nutrients.

Fats consist of a glycerol molecule with three fatty acids attached. They are a concentrated source of energy, 38 kJ/g (9 kcal/g). Fats are essential nutrients because they include essential fatty acids. Fat also is needed to carry and store the essential fat-soluble vitamins, like vitamin D.

Proteins are made up of 20 amino acids, each with different metabolic fates in the body. The amino acids that the body cannot manufacture must be supplied in the diet and are known as essential amino acids. Sources and recommended intakes of macronutrients are seen in Table 2. In Finland the recommended total energy intake for adult malesis 10.4-12 MJ /day, depending on physical activity (National Nutrition Council, 2005). Carbohydrates should supply 50 to 60% of the total energy intake, protein should provide 10 to 20%, and fat approximately 30 to 35% (National Nutrition Council, 2005). There few studies of associations between macronutrients and mood are presented here.

Carbohydrates

Subjects with MDD tend to consume more carbohydrates in their diets than non-depressed individuals (Christensen and Somers, 1996), and they show heightened preference for sweet carbohydrate or fat- rich foods during depressive episodes (Christensen, 2001). High carbohydrate intakes increase brain uptake of the amino acids tryptophan, which in turn stimulates the synthesis of serotonin (Rogers, 2001.) This seems, for example, to rapidly lead to drowsiness in healthy subjects but to alertness in patients with SAD (Rosenthal et al. 1989). A detailed study of the lifestyle of 89 bipolar patients and 445 age- and sex-matched controls showed that total daily sucrose intake, %age of energy from carbohydrate, and consumption of sweetened drinks were higher in bipolar patients (Elmslie et al. 2001). Westover and Marangell (2002) reported a highly significant

correlation between sugar consumption and annual rates of depression in a cross-national study involving six countries.

Fats and proteins

In general, a low-fat diet may have negative effects on mood (Wells et al. 1998), and altered dietary fat intake can lead to acute behavioural effects such as drowsiness, independent of energy consumption, in healthy subjects (Lloyd et al. 1994). The intake of branched-chain amino acids may acutely alleviate manic symptoms in patients with adequate drug treatment (Scarnà et al. 2003), and a high intake of proteins also seems to increase alertness (Rogers, 2001).

Table 2. Food sources of nutrients and recommended intakes.		
	Sources	**Recommendations**
Carbohydrates	bread and cereals, fruits and berries [a*]	50-60% of the total energy intake [c]
Fats	fat spreads and oils, meat dishes, meat products, milk products [a*]	approximately 30% of the total energy intake [c]
Proteins	meat dishes and products, milk products, eggs [a*]	10-20% of the total energy intake [c]
Omega-3 fatty acids		1% of the total energy intake [c]
ALA	vegetable oils; canola-, soybean-, flaxseed oils, leafy green vegetables, nuts, flaxseeds [a*]	
Long-chain omega-3 fatty acids	fatty fish; salmon, tuna, sardine, herring and mackerel [a*]	
Amino Acids	meat, cheese, fish and offal [a*]	
Tryptophan	reindeer meat, liver, cheese, tuna, nuts, soybean, sunflower seed, poppy seeds [b**]	4-6 mg/kg/day [d]
Serine	salmon, cheese, eggs, pork, cattle, soybeans, nuts, sunflower seed, poppy seeds [b**]	no recommendations
Lysine	cheese, cattle, pork, chicken, sardine, tuna, pearch, salmon, cod, carp, lens, soybeans, sunflower seeds [b**]	12-30 mg/kg/day [d]
Vitamins		
Folate	whole grain products, fresh vegetables, fruits, meat and eggs [a*]	300 µg/day for men and older women 400 µg/day for young women [c]
Vitamin B_{12}, Cobalamin	animal products such as meat, fish and dairy products [a*]	2.0 µg/day [c]
Vitamin B_1 , Thiamine	whole grain products, meat products and eggs [a*]	1.0-1.5 mg/day [c]
Vitamin B_2, Riboflavin	dairy products, meat and egg products [a*]	1.2 -1.7 mg/day [c]
Vitamin B_6, Pyridoxine	meat and egg products, whole grain products and fruits and berries [a*]	1.2-1.6 mg/day [c]
Vitamin D	fish products, milk and margarine [a*]	7.5 -10 µg /day [c]
[a] (Männistö et al. 2003), [b](Souci et al. 1994; Salo-Väänänen, 1996), [c] (National Nutrition Council, 2005), [d] (Matthews, 1999), * Sources in the Finnish diet, **High content / 100 g of food		

5.3.2 Amino acids

The 20 or so amino acids that make up the body's proteins each have different metabolic fates. Amino acids are joined together in long strings by peptide bonds to form proteins of differing shapes and sizes. There are eight (nine in infants) essential amino acids for the human body: isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine and histine. In this present study, tryptophan, lysine and serine were the main focus of investigated.

Tryptophan

Tryptophan is essential amino acid. It is a precursor for serotonin synthesis. Free tryptophan is transported into the brain across the blood-brain barrier by an active protein shuttle for which five other large neutral amino acids (valine, leucine, isoleleucine, phenyalanine and tyrosine) also compete. In the brain serotonin is synthesized from tryptophan. It is first converted into 5-hydroxytryptophan by the enzyme tryptophan hydroxylase; 5-hydroxytryptophan is then decarboxylated by the enzyme aromatic acid decarboxylase to serotonin. Serotonin is stored in synaptic vesicles where it stays until released by a neuronal impulse. Serotonin is stored in synaptic vesicles where it stays until released by a neuronal impulse. Serotonin is destroyed by the enzyme monoamine oxidase and converted into an inactivate metabolite, 5-hydroxyindoleaceticacid (Cooper et al. 1996). Serotonin can also be converted to melatonin in the pineal gland at night. Melatonin influences the circadian rhythms.

Dietary protein and carbohydrate content can specifically influence brain tryptophan and serotonin levels by effects on plasma amino acids patterns. Carbohydrate in the diet increases secretion of insulin, which raises the plasma concentration of tryptophan and decreases the concentrations of other large neutral amino acids. This leads to increased tryptophan and thus raises serotonin concentrations in the brain (Fernström and Wurtman, 1971a; 1971b). Sources and recommended intakes of tryptophan are seen in Table 2.

Tryptophan and mood

Tryptophan is a precursor for serotonin that is known to play a key role in many brain functions, such as mood regulation. A number of studies has shown that acute tryptophan depletion produces depressive symptoms and results in worsening of mood (Neumeister et al. 1998; Spillmann et al. 2001). The results of the most important studies of tryptophan depletion in depressed and healthy subjects are seen in Table 3.

There have been a few studies of tryptophan depletion in patients with bipolar disorder. Cappiello et al. (1997) reported increased manic symptoms after tryptophan depletion in recently recovered patients. However, in three other studies there were no effects of tryptophan depletion in patients treated with lithium (Benkelfat et al. 1995; Cassidy et al. 1998; Hughes et al. 2000). The results of the most important studies of tryptophan depletion in subjects with bipolar disorder are seen in Table 4.

A number of negative studies have been published recently, suggesting that the effects of tryptophan depletion on mood are less consistent in psychiatric patients and healthy volunteers (Bell et al. 2001; Van der Does, 2001). The rationale for augmentation has now been challenged (Nelson, 2000). Bell et al. (2001) reported in their review article that in patients with depression tryptophan depletion tends to result in no worsening of depression in untreated subjects but a relapse in those who have responded to antidepressants. In addition, Van der Does (2001) found that tryptophan depletion has a mood lowering effect only in subgroups of recovered depressed patients, patients with SAD and vulnerable healthy subjects.

There are several reports that plasma tryptophan is significantly lower in patients with MDD than in normal controls (Coppen et al. 1973; Cowen et al. 1989). Recently, Hoekstra et al. (2006) reported that bipolar disorder patients had a decreased tryptophan plasma levels compared to normal controls. Because tryptophan is a precursor for serotonin, tryptophan supplementation has been applied to the treatment of patients with SAD (Lam et al. 1997). Lam (1997) has been reported that tryptophan may be an effective augmentation strategy for those patients with SAD who show limited or poor response to bright ligh therapy.

Table 3. Effects of tryptophan depletion in depressed and healthy subjects.

Study subjects	N	Findings	Authors
Depressed patients (untreated)	43	Mood↔	Delgado et al. 1994
Depressed patients (untreated),	22	Mood↔	Price et al. 1997
Depressed patients (untreated)	38	Mood↔	Price et al. 1998
Depressed patients (remitted),	21	11/21 relapsed	Delgado et al. 1990
Depressed patients (remitted)	21	7/21 relapsed	Bremner et al. 1997
Depressed patients (remitted)	14	Mood↔	Leyton et al. 1997
Depressed patients (remitted)	20	5/12 relapsed with TRP depletion 0/8 relapsed with no TRP depletion	Åberg-Wistedt et al. 1998
Depressed patients (remitted)	24	Mood↓ Mood↔ controls	Moreno et al. 1999
Depressed patients (remitted)	22	Mood↔	Neumeister et al. 1998
Depressed patients (remitted)	30	1/15 relapsed with fluoxamine 8/15 relapsed with desipramine	Delgado et al. 1999
Depressed patients (remitted)	10	5/7 relapsed 1/3 relapsed with placebo	Spillmann et al. 2001
Depressed patients (remitted)	41 women, 18 men	women mood↓ men mood ↔	Moreno et al. 2006
SAD* patients, remission	10	8/10 relapsed	Lam et al. 1996
Healthy subjects women	12	Mood↔	Oldman et al. 1994
Healthy subjects	12	Mood↔	Smith et al. 1997a,b
Healthy subjects men	10	Mood↔	Bhatti et al. 1998

SAD* = Seasonal Affective Disorder, ↓ = Worsened of mood, ↔ = No effects on mood,
↑ = Improved of mood

Table 4. Effects of tryptophan depletion in bipolar disorder.

Study subjects	N	Findings	Authors
BD patients in remission, men	10	Mood↔	Benkelfat et al. 1995
BD patients, recently recovered	7	Manic symptoms↑	Cappielo et al. 1997
BD patients	4	Mood↔	Cassidy et al. 1998
BD patients, in remission	19	Mood↔	Hughes et al. 2000
First-degree relatives of BD patients and controls	30	Relatives+ controls mood↓	Sobczak et al. 2002

BD = Bipolar disorder, ↓ = Worsened of mood, ↔ = No effects on mood, ↑ = Symptoms increased

Serine

Serine it is not an essential amino acids in the human diet. It is produced from hydroxypyryvate derived either from glucose or from glycerol. Serine is then used as a precursor for glycine through a process that transfers a methylene group to tetrahydrofolate (Matthews, 1999). It is precursor for glysine. Sources of serine are seen in Table 2.

Serine and mood

Serine acts 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). Previously, 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), but there are also reports of low serine plasma levels in psychotic depressive disorder (Fekkes et al. 1994; Maes et al. 1998). Sumiyoshi et al. (2004) recently reported that patients with schizophrenia and also those with MDD had increased plasma serine levels compared to normal controls.

Lysine

Lysine, an essential amino acids for humans, acts as a precursor for the carnitine, which is involved in lipid metabolism. Acetylincarnitine is synthesized from carnitine too, and also plays a part in lipid metabolism (Pettegrew et al. 2000). Sources and recommended intakes of lysine are seen in Table 2.

Lysine and mood

Currently, there are no data regarding the impact of lysine on brain functions or mental disorder. In one study lycine fortification of wheat reduced anxiety and stress among an economically disadvantaged population in Syria (Smriga et al. 2004).

5.3.3 Omega-3 fatty acids

Omega-3 fatty acids are polyunsaturated fatty acids. The omega number indicates the number of carbon atoms from the methyl end of the acyl chain to the first double bond. The first double bond in an omega-3 fatty acid is three carbons from the methyl end of the molecule. Alpha linolenic acid (ALA, 18:3n-3) is an essential fatty acid for humans (Jones and Kubow, 1999). ALA can be converted to the longer-chain omega-3 fatty acid, eicosapentaenoic acid (EPA, 20:5n-3). EPA can elongated to docosapentaenoic acid (22:5:n-3), and then further extended, desaturated, and beta-oxidized to produce decosahexaenoic acid (DHA, 22:6n-3) (Jones and Kubow, 1999).

While ALA is the precursor for longer omega-3 fatty acids, EPA acts as the precursor for certain eicosanoids, such as prostaglandins, thromboxane, and leukotriens. Eicosanoids play a large role in modulating cardiovascular, pulmonary, immune, reproductive, and various secretory functions (Jones and Kubow, 1999). EPA also affects lipoprotein metabolism and decreases the production of other compounds, including cytokines, interleukin 1b, and tumornecrosis factor α. The pro-inflammatory cellular activities exerted by these compounds include stimulating the production of collagenase and increasing the expression of adhesion molecules necessary for leukocyte extravasation (James et al. 2000). DHA (22:6n-3), one of the main structural lipids in the mammalian brain, plays

crucial roles in the development and function of brain neurons. It is also concentrated in the retina and testes (Jones and Kubow, 1999).

Sources and recommended intakes of omega-3 fatty acids are seen in Table 2. The intake of the combined essential fatty acid (omega-3 plus omega-6) should form at least 3% of total energy, including approximately 1% from omega-3 fatty acids (Table 2). If the daily energy intake is 8368 kJ (2000 kcal), this means 2-3 g of omega-3 fatty acids per day (National Nutrition Council, 2005).

Population based studies

Societies with a high consumption of fish appear to have a lower prevalence of depression Hibbeln 1998; Tanskanen et al. 2001a; 2001b, Silvers and Scott 2002; Timonen et al. 2004). However, the dietary intake of omega-3 fatty acids did not associate with depression in a study of a community sample of Australian women (Jacka et al. 2004). The dietary intake of total omega fatty acids and ALA associated inversely with depression, but the intakes of EPA and DHA and also of fish consumption, did not associate with depression in Japanese lung cancer patients (Suzuki et al. 2004). Noaghiul and Hibbeln (2003) founded a robust correlational relationship between greater seafood consumption and lower prevalence rates of bipolar disorder in a comparison across 12 countries. Recently, Appleton et al. (2007) founded that higher omega-3 fatty acids intakes from fish associated with lower levels of depressed mood, but the association disappeared after adjustment for age and social deprivation.

Concentration studies

There is evidence that people with MDD have significantly lower omega-3 levels in red cell membranes (Edwards et al. 1998; Peet et al. 1998), in serum cholesteryl esters (Maes et al. 1999), and in plasma phospholipids (Tiemeier et al. 2003; Frasure-Smith et al. 2004) compared to controls. It has also been reported that depressed subjects have lower omega-3 fatty acid levels in adipose tissue compared to healthy controls (Mamalakis et al. 2004). Low EPA levels in red cells have been found in patients with suicide attempts (Huan et al.

2004). Green et al. (2006) also reported decreased levels of omega-3 in red blood cells membrane in patients with social anxiety disorder.

De Vriese et al. (2004) reported seasonal variation in polyunsaturated fatty acid levels in humans. EPA and DHA levels are lower in winter. They suggested that this seasonality may be related to the incidence of violent suicide. They also suggested that annual variations of essential fatty acids are related to the expression of the serotonin markers, such as the Bmax [3H]-paroxetine binding to platelets.

Supplemental studies

Results of some supplement-based trials are seen in Table 5. A placebo-controlled, double blind trial with 28 depressed patients found that omega-3 fatty supplements (9.6 g/day for 8 weeks) alleviated the effects of depressive symptoms (Su et al. 2003). However, a double blind, placebo-controlled trial of DHA (2g/day for 6 weeks) in a sample of 36 clinically depressed patients demonstrated no significant improvements in the treatment group compared to controls (Marangell et al. 2003). Silvers et al. (2005) reported that fish oil (3g/d omega-3 for 12 weeks) treatment did not improve mood when compared to the placebo oil in depressed patients. Two clinical studies have used doses of 1 to 2 g per day of EPA ethyl ester to successfully treat patients with depression. Nemets et al (2002) reported that in a double blind, placebo-controlled trial with 20 MDD patients who responded only partially to standard antidepressant treatment, EPA ethyl ester supplements (2g/d for 4 weeks) alleviated depressed symptoms. Also, a double blind, placebo-controlled trial with 52 depressed patients with antidepressant treatment showed that an EPA ethyl ester supplements (1g/day/12 weeks) was effective in treating depression in patients who remained depressed despite adequate drug treatment (Peet and Horrobin, 2002). However in this study, only a dosage of 1 g/day showed efficacy compared to 2-4 g/day dosages. A randomized, placebo-controlled, adjunctive trial of EPA (6 g/day for 4 months) in the treatment of bipolar depression and rapid cycling bipolar disorder did not find overall evidence of efficacy for adjunctive treatment (Keck et al. 2006). In a recent double blind, placebo-controlled trial on 231 young adult prisoners, antisocial behaviour as measured by the number of their disciplinary offences before and during the

supplementation, was reduced by the supplementation of vitamins, minerals and essential fatty acids (Gesch et al. 2002).

A placebo-controlled trial with 30 patients found that omega-3 fatty acid pharmacological dose supplements (9.6g/day for 4 months) alleviated symptoms of depression in patients with bipolar disorder (Stoll et al. 1999). They also had longer periods of remission than the placebo group. Treatment of bipolar disorder with adjunctive EPA (1 to 2 g/day for 12 weeks) resulted in improved clinical outcomes compared with placebo in terms of scores on the Hamilton Rating Scale for Depression and the Young Mania Rating Scale (Frangou et al. 2006).

Table 5. Associations between dietary intake or supplemental use of omega 3 –fatty acids and mood.

Study Subjects	N	The intake of omega-3 fatty acids (g/day)	Findings	Authors
23-97 year-old Australian women	755	Total omega-3 fatty acids: 0.11 g/day	Mood ↔	Jacka at al. 2004
Japanese lung cancer patients	771	Total omega intake was 1.52 g/d for subjects without depression and 1.43g/d for depressed subjects	Fish: Mood↔ Total omega -3 fatty acids: mood↑	Suzuki et al. 2004
General population (UK)	2982	Total omega intake was 1.6 g/day, intake of omega-3 fatty acids from fish was 0.6 mg/day	Omega-3 fatty acids from fish associated with lower levels of depressed mood, but the association disappeared after adjusting for age and social deprivation.	Appleton et al. 2007
18-70 year-old depressed patients (UK)	70	E- EPA 1, 2 or 4 g/day, or placebo	1 g/d mood↑ 2.4 g/d mood↔	Peet et al. 2002
28-73 year-old depressed patients (Israel)	20	E-EPA 2g/day, or placebo	Mood↑	Nemets et al. 2002
18-60 year-old depressed patients (Taiwan)	22	EPA + DHA 9.6 g/d, or placebo	Mood↑	Su et al. 2003
18-65 year-old depressed patients (USA)	35	DHA 2 g/d, or placebo	Mood↔	Marangell et al. 2003
18-65 year-old depressed patients (New Zealand)	59	EPA + DHA 3g/d, or placebo	Mood ↔	Silvers et al. 2005
Young adult prisoners (UK)	231	EPA+ DHA 1.24 g/d, +omega-6 fatty acids 1.42 g/d, or placebo	Reduced antisocial behaviour	Gesch et al. 2002
18-65 year-old patients with bipolar disorder (USA)	30	9.6 g/d omega-3 fatty acids, or placebo	Remission ↑	Stoll et al. 1999
18-70 year-old patients with bipolar disorder (UK)	75	1 g/d or 2 g/d E-EPA, or placebo	Mood↔ HRDS↓* CGI↓**	Frangou et al. 2006
20-73 year-old patients with bipolar disorder (USA)	116	E-EPA 6g/day, or placebo	Mood↔	Keck et al. 2006

* HRDS = Hamilton Rating Scale for Depression, ** CGI = Clinical Global Impression Scale
↓ = Worsening of mood, ↔ = No effects on mood, ↑ = Improvement of mood

5.3.4 Vitamins

Folate

Folate belongs to the group of water-soluble B vitamins. There are over 100 different forms of folate in diet. Folate acid is the synthetic form of folate. They are essential for humans like all vitamins. Folate acts as coenzyme in numerous metabolic pathways in the body. It is required for the synthesis of thymidylate and thus for deoxyribonucleic acid (DNA). Folate is also necessary in protein synthesis and is especially important during periods of rapid cell division and growth, such as infancy and pregnancy (Herbert, 1999).

One possible manifestation of folate deficiency is megaloblastic anaemia is a, which results from decreased synthesis of DNA and ribonucleic acid. Folate deficiency is characterized by weakness, dyspnea, diarrhea, weight loss, and neurological symptoms. Folate deficiency is associated with a high frequency of irritability, forgetfulness, and hostile and paranoid behaviour (Herbert, 1999). Sources and recommended intakes of folate are seen in Table 2. In addition, deficiencies of folic acid as well as pyridoxine (B_6) and vitamin B_{12} , can lead to high homocysteine levels as a consequence of their involvement in homocysteine metabolism (Miller et al. 1994). Homocysteine is a sulphur-containing amino acid formed from the essential amino acid methionine. A high blood level of homocysteine is associated with hightened risk of ischaemic heart disease and stroke risk (Homocysteine Studies Collaboration, 2002).

Folate and mood

Folate deficiency has been known to be linked to depressive disorder, and it has particular effects on mood, and on cognitive as well as social function (Bottiglieri, 1996; Alpert and Fava, 1997; Reynolds 2002). Depressed patients have been shown to have low levels of folate in their serum and red blood cells (Carney et al. 1990; Fava et al. 1997; Bottiglieri et al. 2000; Lerner et al. 2006). Findings of folate and vitamin B_{12} studies are seen in Table 6. It has been also reported that patients with low folate status have been weaker treatment response to antidepressants (Abou-Saleh and Coppen, 1989; Carney et al. 1990; Fava et

al.1997), and folate replacement therapy in patients with MDD appears to produce substantial affective improvements (Godfrey et al. 1990; Mischoulon 1996; Coppen and Bailey, 2000). It has been reported that depressed individuals in the general US population had lower serum and red blood cell folate concentrations (Morris et al. 2003). Low serum folate also associated with an increased severity of depressive symptoms in a epidemiological sample of middle-age individuals in Australia (Sachdev et al. 2005) However, Penninx et al. (2000) did not find an association between blood folate and depression among disabled older women, although Ramos et al (2004) reported that low folate status was associated with depressive symptoms in elderly Latino women, but not elderly Latino men. Other findings suggest that folate deficiency is not independently related to the depressive disorders (Tiemeier et al. 2002), and low plasma folate levels are not significantly related to depression in a general population in Norway (Bjelland et al. 2003). Recently, it have been reported that low levels of dietary folic acid are associated with elevated depressive symptoms and MDD in middle-aged men (Tolmunen et al. 2003; 2004a). The data regarding an association between folate and mania are scarce, but red blood cell folate levels in patients with mania have been reported (Hasanah et al. 1997).

Recently, several studies have shown that total plasma homocysteine is a sensitive marker of functional deficiency of either folic acid or vitamin B_{12}. The synthesis of methionine from homocysteine requires a supply of methyl groups from methyl folate, and also vitamin B_{12} as a cofactor. Thus functional deficiency of either vitamin results in raised plasma levels of homocysteine (Lindenbaum et al. 1988; Stabler et al. 1988), and a high-folate diet decreases plasma homocysteine concentration (de Bree et al. 2001a; Silaste et al. 2003). It has been reported that depressed patients had raised plasma homocysteine (Lindenbaum et al. 1988; Bottiglieri et al. 2000; Bjelland et al. 2003), but not all studies have found this association (Fava et al. 1997; Pennincx et al. 2000; Tiemeier et al. 2002). Recently, Tolmunen et al. (2004b) reported that high serum concentrations of homocysteine associated with depression in middle-aged men. Smoking is also known to be associated with an increased plasma homocysteine level and reduced of levels of folate, vitamin B_{12} and vitamin B_6 (de Bree et al. 2001b; O'Callaghan et al. 2002).

Table 6. Association between serum folate, vitamins B, and mood disorders.

Study subjects	N	Blood fragment	Findings	Authors
Elderly Dutch people	694	Plasma concentration	Folate↓ Mood↔ Vitamin B_{12}↓ Mood↓	Tiemeier et al. 2002
English inpatients (MDD), the mean age 34 years	84	Plasma concentration	Folate↓ Mood↔ Homocysteine ↑→ Folate↓ Mood ↓ Vitamin B_{12}↓ Mood↔	Bottiglieri et al. 2000
46- 49 and 70-74 year-old Norwegian adults	5 948	Plasma concentration	Folate↓ Mood↔ (Middle- aged women Folate↓ Mood ↓) Vitamin B_{12}↓ Mood↔	Bjelland et al. 2003
Depressed patients (the mean age 59.5) and normal controls (the mean age 44.7)	155	Red blood cell concentrations	Folate↓ Mood↓	Abou-Saleh and Coppen, 1989
English depressed patients	285	Red blood cell concentrations	Folate↓ Mood↓ Vitamin B_{12}↓ Mood↔	Carney et al. 1990
American patients (MDD), the mean age 39.9 years	213	Serum concentrations	Folate↓ Mood ↓ Vitamin B_{12}↓ Mood↔	Fava et al. 1997
15-39 year-old US population	2 948	Serum concentrations	Folate↓ Mood↓ Vitamin B_{12}↓ Mood↔	Morris et al. 2003
Elderly Latinos, > 60 year-old	1 463	Plasma concentrations	Folate↓ Mood↓ women Folate↓ Mood↔ men Vitamin B_{12}↓ Mood↔	Ramos et al. 2004
60-64 year-old Australian adults	412	Serum concentrations	Folate↓ Mood↓ Vitamin B_{12}↓ Mood↔	Sachdev et al. 2005
Israeli psychiatric patients (MDD), the mean age 39.4 years	224	Serum concentration	Folate↓ Mood ↓ Vitamin B_{12}↓ Mood↔	Lerner et al. 2006
Manic hospitalised patients and normal controls from Malaysia	78	Serum concentrations and red-cell concentrations	Folate↓ (red-cell) Mood↓	Hasanah et al. 1997
Elderly Dutch women, > 65 years-old	700	Serum concentrations	Vitamin B_{12}↓ Mood↓ Folate↓ Mood↔	Penninx et al. 2000
21-69 year-old Finnish outpatients (MDD)	115	Red blood cell concentrations	Vitamin B_{12}↑ → good treatment outcome Folate ↑Mood↔	Hintikka et al. 2003
19-92 year-old Danish adults	140	Plasma concentrations	Vitamin B_6↓Mood↓ Folate↓ Mood↔ Vitamin B_{12}↓ Mood↔	Hvas et al. 2004a

↓ = Worsened mood, low levels of vitamin, ↔ = No effects on mood, ↑ = improved mood, high levels of vitamin

Vitamin B_{12} (Cobalamin)

Vitamin B_{12}, also known as cobalamin, belongs to the group of water-soluble B vitamins, all of which are essential for humans. Vitamin B_{12} is a coenzyme in two metabolic reactions. The methylcobalamin form is needed as one of the coenzymes involved in the synthesis of methionine from homocysteine. It is necessary in small amounts for the formation of proteins and red blood cells, and for the function of the central nervous system and maintenance of the inner lining of the intestinal tract. One clinical manifestation of vitamin B_{12} deficiency is megaloblastic anaemia. It can also cause paresthesia, constipation, peripheral neuropathy, depressive symptoms and dementia (Scott and Weir, 1999). Sources and recommended intakes of vitamin B_{12} are seen in Table 2.

Vitamin B_{12} and mood

Vitamin B_{12} deficiency has been linked to various neuropsychiatric disorders including affective illness (Hector and Burton 1988; Lindenbaum et al. 1988; Healton et al. 1991). It has been reported that depressed subjects have low serum vitamin B_{12} levels (Pennincx et al. 2000, Tiemeier et al. 2002), but there are also contradictory findings (Fava et al. 1997; de Jong et al. 2001). Recent population-based studies have not found an association between vitamin B_{12} levels and symptoms of depression (Bjelland et al. 2003; Morris et al. 2003; Sachdev et al. 2005) It has been reported that high levels of vitamin B_{12} are associated with good treatment outcome in patients with MDD (Hintikka et al. 2003). In a study of Hvas et al. (2004a) supplemental vitamin B_{12} treatment did not improve cognitive function or symptoms of depression within the three-month study period. The results vitamin B_{12} studies are seen in Table 6.

Folate and vitamin B_{12} deficiency may be caused by a number of factors including dietary deficiency, malabsorption, and increased requirement for these vitamins during stress (Abou-Saleh and Coppen, 1986). Both folate and vitamin B_{12} are essential in several metabolic pathways in the central nervous system, and their metabolism is intimately connected (Abou-Saleh and Coppen 1986; Chanarin et al. 1989). A deficiency of either vitamin causes impaired methylation in the central nervous system and may result in neurological and psychiatric disease that becomes irreversible if not treated properly

(Hector and Burton, 1988). Also, vitamin B_{12} has been reported to modulate human melatonin secretion (Yamazaki et al. 1991). Intravenous administration of vitamin B_{12} increased rectal temperature in the later hours the daytime (Uchiyama et al. 1995). In the study of Hashimoto et al. (1996) light exposure phase-advanced the melatonin rhythm in the vitamin B12-receiving group but not in the placebo group. Thus, vitamin B_{12} seems to enhance the light-induced phase-shift in the human circadian rhythm. As circadian rhythms are disturbed in depression and in mania, similar mechanisms could also take place in the association between vitamin B_{12} and depression. However, these connections have been studied only in healthy volunteers.

Vitamin B_1 (Thiamine)

Vitamin B_1, also known as thiamine, is another water-soluble B vitamin essential for humans. Vitamin B_1 serves biochemically as the coenzyme of a-keto acid decarboxylation and transketolation. It is needed in the body cells to convert carbohydrates, proteins and fats into energy. Vitamin B_1 also has a role in neurophysiology. It is concentrated in nerve cell membranes and also in muscle cells. It facilitates impulse conduction in peripheral nerves. Vitamin B_1 deficiency, which is common in alcoholism, can produce confusion and psychotic symptoms, in addition to neurological signs (Petrie and Ban, 1985). Deficiency of vitamin B_1 can cause two clinical manifestations: beriberi and Wernicke-Korsakoff syndrome. Wernicke-Korsakoff syndrome is cause by chronic alcohol abuse. Wernicke-Korsakoff syndrome causes a derangement of mental function and it can also lead to psychosis. Vitamin B_1 by injection and perorally are used to prevent Wernicke-Korsakoff syndrome. Other symptoms of deficiency of vitamin B_1 are cardiac failure, muscle weakness, peripheral and central neuropathy, and gastrointestinal malfunctions (Tanphaichitr, 1999). Vitamin B_1 supplementation had reported to improve general well-being in elderly women (Smidt et al. 1991). Sources and recommended intakes of vitamin B_1 are seen in Table 2.

Vitamin B_2 (Riboflavin)

Vitamin B_2, is also known as riboflavin. It participates in oxidation-reduction reactions in numerous metabolic pathways and in energy production via the respiratory chain. It is vital for body growth and red blood cell production and is also involved in the release of energy from carbohydrates. Deficiency of vitamin B_2 is characterized by sore throat, hyperaemia, and oedema of pharyngeal and oral mucous membranes, cheilosis, and normochromic, normocytic anaemia (McCormic, 1999). Sources and recommended intakes of vitamin B_2 are seen in Table 2. Vitamin B_2 also plays a role in thyroxine metabolism, and deficiency may contribute to the pathophysiology of mental disorders via this route (Bell et al. 1992).

Vitamin B_6 (Pyridoxine)

Vitamin B_6 exists in three major chemical forms: pyridoxine, pyridoxal, and pyridoxamine all of which are essential water-soluble vitamins. Vitamin B_6 functions as a cofactor to numerous enzymes in metabolic pathways. It is a coenzyme for reactions that to synthesize several neurotransmitters, including serotonin, dopamine, and nerepinephrine. Vitamin B_6 is involved in gluconeogenesis via its role in transaminations and in the action of glycogen phosphorylase. Also, it has a significant impact on immune function and red cell metabolism. Deficiency of vitamin B_6 can cause depression, confusion, irritability, stomatitis, cheilosis and glossitis (Leklem, 1999). Sources and recommended intakes of vitamin B_6 are seen in Table 2.

Vitamin B_6 is involved in the same metabolic pathways in the central nervous system as vitamin B_{12} and folate. Hvas et al. (2004b) found a low level of plasma vitamin B_6 associated with symptoms of depression. It has also been reported in two studies that vitamin B_6 supplementation has positive effects on memory performance, but not on mood (Deijen et al. 1992; Bryan et al. 2002).

Vitamin D

Vitamin D is a fat-soluble vitamin. It is found in food, and also the human body makes it when exposed to ultraviolet B rays from the sun. Vitamin D exists in several forms, each with a different level of activity. Calciferol is the most active form of vitamin D, other versions being relatively inactive in the body. The liver and kidney help convert vitamin D to its active hormone state (van den Berg, 1997). Once vitamin D is produced in the skin or consumed in food, it requires hydroxylation in both liver and kidney to 1.25 dihydroxyvitamin D, the physiologically active form. Active vitamin D functions as a hormone because it sends a message to the intestines to increase the absorption of calcium and phosphorus (van den Berg, 1997).

The principal physiologic function of vitamin D is to maintain serum calcium and phosphorus concentrations in a range that supports cellular processes, neuromuscular function, and bone ossification. Experimentally, vitamin D suppresses the proliferation of normal and malignant cells and induces differentiation and apoptosis (Ylikomi et al. 2002). Vitamin D deficiency can cause rickets in children and osteomalacia in adults. The symptoms are muscular weakness in addition to weak bones.

Sources and recommended intakes of vitamin D are seen in Table 2. Ultraviolet B rays from the sun trigger vitamin D synthesis in the skin (Holick et al. 1994; 2002). Season, latitude, time of day, cloud cover, smog, and sunscreen all affect ultraviolet B ray exposure and vitamin D synthesis (Wharton et al. 2003). At northern latitudes there are marked seasonal fluctuations in serum 25-hydroxyvitamin D levels the serum concentrations being high during summer and low during winter due to the marked difference in sunlight exposure (Tjellesen and Christiansen 1983; Lamberg-Allardt 1984; Hine and Roberts 1994; Davies et al. 1999). In Finland, a northern European country, there is no short-wavelength ultraviolet light reaching the ground in wintertime. Since the synthesis of vitamin D in the skin is therefore reduced, dietary vitamin D is important for maintaining a normal vitamin D status at the northernmost latitudes throughout the year (Lamberg-Allardt et al. 1983; Webb et al. 1988; Holick 1995).

Vitamin D and mood

Vitamin D supplementation during winter also seems to improve mood in healthy volunteers (Lansdowne and Provost, 1998). One possible mechanism of action is that serum 1,25-dihydroxyvitamin D levels affect the levels of serotonin in the hypothalamus (Privette et al. 1991) and thereby enhance the synthesis and transmission of serotonin, leading to improvement in mood. However, Dumville and co-workers (2006) recently reported that daily supplementation of vitamin D did not improve the mental well-being of elderly women during winter months.

5.4 Relevance of this study

In summary, there are no consistent findings of associations between nutrition and mood, although some specific nutrients have been suggested to relate to mood. Tryptophan has slight effects on mood, mostly in depressed patients. Tryptophan depletion studies have noted effects on mood, mainly in depressed subjects or those with vulnerability to depression. There are no relevant data about effects of other amino acids on mood. There is conflicting evidence on whether omega-3 fatty acids can be used in the treatment of mood disorders. Also, only a few studies have found an association between dietary intake of fish, a major source of long chain omega-3 fatty acids, and mood. Folate deficiency causes depressed symptoms and there are differences in folate status in depressed patients. Deficiency of folate mainly appears to affect mood in older people or subjects with depression. The evidence on the effects of vitamin B_{12} on mood is conflicting. The role of other vitamins (B_1, B_2, B_6, D) in mood regulation is still unclear. There are no previous studies of dietary intake in subjects with bipolar disorder.

Because of the shortage of previous reports and lack of evidence, the topic of this thesis provided a useful opportunity to make a more detailed analysis of the relationships between nutrition and mood disorders. The focus of the study is on the specific nutrients which are suggested to relate to mood and mood disorders.

6 AIMS OF THE STUDY

The primary aim was to analyse whether there were significant associations of dietary intakes of nutrients with mood disorders (I, II, III, IV).

Another aim was to study whether seasonal changes in mood and circadian preferencefor activities had significant relations to diet (IV, V).

A third aim was to elucidate whether insomnia, sleep debt or seasonal changes in sleep duration, i.e. length of sleep, were linked to dietary intakes in mood disorders (III, IV, V).

To answers these questions, the specific aims were formulated as follows.

I. To study associations between dietary intake of amino acids and low mood, depression, and suicide.
The main question was: Is the intake of tryptophan related to depression?
(Study I)

II. To study associations between dietary intake of omega-3 fatty acids and low mood, depression, and suicide. Consumption of fish rich in long-chain omega-3 fatty acids, specifically, was assessed.
The main question was: Is the intake of omega-3 fatty acids related to depression?
(Study II)

III. To study whether food consumption and intake of nutrients in subjects with depressed mood, anxiety and insomnia differed from those in subjects without any such symptoms.
The main question was: How does mood affect eating habits? (Study III)

IV. To study the intake of nutrients and consumption of food items among twins with bipolar disorder, and also to study the consumption of alcohol and cigarette smoking. In addition, to elucidate the influence of seasonal changes in mood and behaviour on nutrient intake.
The main question was: How does bipolar disorder affect eating habits?
(Study IV)

V. To study seasonal variations in hospital admission and self-reported well-being in twins with bipolar disorder. Another aim was to study the effect of natural light exposure on mood. Another aim was to assess circadian preference, sleep length and seasonal patterns in mood and behaviour among twins with bipolar disorder. *The main question was: How does bipolar disorder affect seasonal changes in mood and behaviour, and especially sleep? (Study V)*

7 SUBJECTS AND METHODS

In the present work two samples of study subjects were used: one for studies of major depressive disorder, another for studies of bipolar type 1 disorder.

7.1 The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Cancer Prevention study) (I, II, III)

The Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study was a double-blind, placebo-controlled, randomized primary prevention trial testing the hypothesis that daily supplementation with α-tocopherol or β-carotene reduces the incidence of lung and other cancers (ATBC Cancer Prevention Study Group, 1994).

7.1.1 Study subjects

The study participants were recruited between 1985 and 1988 from the total male population 50-69 years of age residing in southwestern Finland (n=290,406). These men were sent a questionnaire on current smoking status and willingness to participate in the trial. Smokers of at least five cigarettes per day and who were willing to participate were then invited to visit their local study center for further evaluation of their eligibility. A previous cancer diagnosis, current severe angina with exertion, chronic renal insufficiency, cirrhosis of the liver, alcohol dependence, or a disorder limiting participation in the long-term trial, such as mental disorder or physical disability, were reasons for exclusion. A total of 29,133 men were randomly assigned to receive supplements of either α-tocopherol, β-carotene, both, or placebo, in a 2x2 factorial design. The ethics review boards of the participating institutions approved the study, and all subjects provided written informed consent prior to randomization.

7.1.2 Follow-up

Active intervention continued for all participants through April 1993 and ranged from five to eight years (median 6.1 years).

7.1.3 Assessment of mood and behaviour

Data on hospital admissions for MDD and mania were derived from the National Hospital Discharge Register, which covers in-patient admissions to all medical and psychiatric hospital beds in Finland. The accuracy of the register compared with medical records is excellent, with data being identical in about 95% of the 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. Later diagnoses, after 1995, were coded according to the ICD-10. A total of 280 men were hospitalized at least once for MDD (included MDD and depressive disorder NOS) by the end of 1994.

In a new analysis (unpublished data) a total of 247 men were hospitalized at least once for MDD (including only MDD, not depressive disorder NOS) by the end of May 2001. A total of 48 men were hospitalized due to manic episodes at least once by the end of May 2001.

Data on deaths were derived from the Central Population Register, and the cause of death was reviewed from the death certificates. A total of 102 men committed suicide during the follow-up. The follow-up of survival extended to the end of 1994.

At baseline, subjects completed a questionnaire on their medical history, including three questions on mental wellbeing. These items concerned anxiety, depressed mood and insomnia experienced in the past three months (Have you felt feelings of depression in the last three months? Have you felt feelings of anxiety in the last three months? Have you had insomnia in the last three months?).

The trial involved three follow-up visits annually. At each follow-up visit the participants were asked whether they had felt anxiety, depression, or insomnia since the preceding visit. To identify subjects who suffered chronically from these symptoms, those reported throughout the first follow-up year were taken into account, i.e. at baseline and the three follow-up visits (4 months, 8 months and 12 months). Men reporting anxiety, depression, insomnia, or all these symptoms at all four visits were considered as cases and those without symptoms as controls in these analyses (Study III).

7.1.4 Assessment of food consumption

Diet and alcohol consumption were assessed from a self-administered dietary history questionnaire (Pietinen et al. 1988), which asked the frequency of consumption and the usual portion size of 276 food items during the past year. In the questionnaire there was a photographic picture booklet with 122 food items and mixed dishes to help in estimating portion sizes (Haapa et al. 1985). Complete dietary data were available for 27,111 participants. Dietary nutrient data were analyzed by linking the questionnaire data to the food composition database of the National Public Health Institute, Finland.

7.1.5 Assessment of other characteristics

At baseline, subjects completed a questionnaire about their general background and medical and smoking histories. Height and weight were also measured, and a blood sample was drawn for determining serum total and high-density lipoprotein (HDL) cholesterol concentrations. Concentrations of cholesterols were assessed using an enzymatic method.

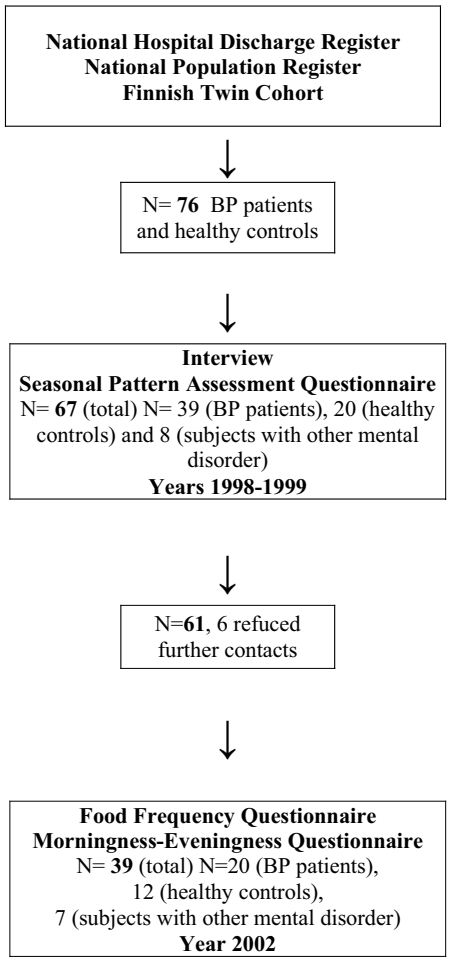
7.2 Twin Study (IV, V)

7.2.1 Study subjects

Study participants were searched from the National Hospital Discharge Register of Finland to identify all patients with at least one of the ICD-8 codes 296.10 or 296.30 in 1969–86 (World Health Organization, 1967), or DSM-III-R codes 296.4, 296.5 or 296.6 in 1987–91 (American Psychiatric Association, 1987). Dates for each admission were recorded. The National Population Register was thereafter used to locate twins born between 1940 and 1969. Also, the Finnish Twin Cohorts were checked to identify any additional twins (Kaprio et al. 1990). One twin pair with no history of mental illness was included to increase the number of healthy controls. All the 76 participants identified were sent an invitation to participate with their co-twin in the study (See in Figure 1).

The twin study was approved by the Ethics Committee of the National Public Health Institute, and by the Ministry of Social Affairs and Health. Written informed consent was obtained from all subjects after they received a complete description of the study.

Figure 1. Study sample of the Twin Study



Abbreviations: BP= bipolar disorder

7.2.2 Diagnostic assessment

All the probands and co-twins (n=67) were interviewed by one of the investigator (T.K) to confirm diagnosis of the probands and to assess any mental disorders of the co-twins by using the Structured Clinical Interview for DSM-IV Disorders (SCID) (Spitzer et al. 1997). Interviews were made blind to zygosity. The zygosity determination was based on genetic marker analysis, and on questionnaires on resemblance during childhood (Sarna et al. 1987).

7.2.3 Assessment of seasonal changes in mood and behaviour

First, 67 participants filled in the Seasonal Pattern Assessment Questionnaire (SPAQ; Rosenthal et al. 1984) and they were then invited to research interviews that took place from November 1998 to December 1999. Thirty-nine of them had bipolar disorder, with mean age 44.3 years (range 29-57), and 20 were assessed as healthy (no mental disorder), with mean age 44.7 years (range 33-57). In addition, eight had a mental disorder other than bipolar disorder, and were excluded from further analysis. There was a greater proportion of men among the bipolar twins than healthy twins, but no difference in the affection status by zygosity. The number of discordant pairs was 15.

SPAQ was used for the assessment of seasonal variation in length of sleep, social activity, mood, weight, appetite, and energy level (Rosenthal et al. 1984). The sum of these six scales yields the Global Seasonality Score (GSS), which can range from 0 (no change) to 24 (extremely marked change). This questionnaire also investigated the changes in wellbeing caused by local weather conditions. The sum of these ten scales (cold weather, hot weather, humid weather, sunny days, dry days, long days, grey cloudy days, high pollen count, foggy smoggy days, and short days) yields a global score, designated here as the Global Weather Score (GWS), which can range from -30 to + 30. Negative scores indicate negative effects and positive scores indicate positive effects of changes in weather conditions on feelings of wellbeing. In addition, two new variables were made from the SPAQ, and coded and analysed separately: light exposure (the sum of sunny days, and long days) and grey, cloudy days (the sum of grey cloudy days, foggy smoggy days, and short days).

7.2.4 Assessment of food consumption

Six twins refused any further contact early on, and 61 twins were finally sent the Food Frequency Questionnaire (FFQ) and the Morningness-Eveningness Questionnaire (MEQ) (Horne and Östberg, 1975) in January 2002 (See Figure 1). The response rate was 67% (41 out of 61). An additional two participants were excluded at baseline because of incompletely filled FFQs. Of the 39 respondents, 20 had bipolar disorder, with mean age

46.6 years (range 32-60), and 12 were assessed as healthy (no mental disorder), with mean age 46 (range 33-58). In addition, seven had mental disorder other than bipolar disorder, and were excluded from further analysis. Diagnoses of other mental disorders were schizoaffective disorder, recurrent MDD, schizophrenia, and alcohol abuse.

The FFQ is a validated questionnaire (Paalanen et al. 2006) that was used in the Health 2000 Survey. It is a modified and updated version of two Finnish questionnaires used in earlier studies, the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (Pietinen et al. 1988) and the Kuopio Breast Cancer Study (Männistö et al. 1996). The FFQ is designed to cover the whole diet over the preceding 12 months, and the main purpose is to rank individuals according to their average food consumption and nutrient intake. The 128 food items are presented under 12 subgroups, e.g. dairy products, vegetables and fruits and berries. After each subgroup there are empty lines for subjects to add foods not listed in the questionnaire. The portion sizes are fixed and, if possible, specified using natural units (e.g. glass, slice). Recipes for each food item in the FFQ are composed of one to seven food codes in the Finnish food composition database Fineli® (release 2) that is published in part on the Internet (National Public Health Institute, 2002). The nine frequency categories range from never or seldom to six or more times a day. The consumption of berries is recorded separately in winter and summer. The food consumption and nutrient intakes are calculated by multiplying the frequency of food consumption by fixed portion sizes to obtain the weight of each listed food item consumed as an average per day.

7.2.5 Assessment of circadian type

The Morningness-Eveningness Score (MEQ) is a self-report questionnaire that has been used for the assessment of preferred timing of behaviour (Horne and Östberg, 1975). The questionnaire includes 19 items, and the sum yields the Morningness-Eveningness Score (MES), which can range from 16 to 86. The highest scores indicate definite morningness, and the lowest ones definite eveningness. Morning types go to bed earlier and also rise earlier in the morning than evening types.

7.2.6 Assessment of other characteristics

The Finnish Twin Cohort Questionnaire (FTCQ) was used to study the sleep length and the subjective feeling of sleep debt (Study V) (Kaprio and Koskenvuo, 2002). Data were available from 1975, 1981 and 1990. The overall response rate was 89% in the 1975 survey, 84% in 1981, and 77% in 1990. The FTCQ also included two questions about sleep length ("How many hours do you usually sleep at night?", and "How many hours do you estimate you need to sleep, to feel refreshed next day?"). A new variable, sleep debt, was calculated from two questions by subtraction.

To study alcohol consumption and tobacco smoking (Study IV), data available from FTCQ in 1981 and 1990 were used. There were additional questions concerning the consumption of coffee and tea separately (cups per day). The questionnaire requested information on the frequency and quantity of alcohol used during an average week (or month), and the number of years smoked. For each type of beverage (spirits, wines, beer), consumption was converted into grams of absolute alcohol and summed to yield an estimate of total consumption in grams per day.

7.3 Statistical analyses

7.3.1 The ATBC Cancer Prevention Study

Cox's proportional hazards regression models were used to analyse of the relationships between the baseline dietary intakes of nutrients, and the first occurrence of self-reported depressed mood, first hospital admission period for either major depressive or bipolar disorder, and suicide (I, II). The intakes of nutrients were included in the models as quartile or tertile categories. Intakes of amino acids and omega-3 fatty acids were included in the models as tertile categories (II). The analyses (I, II, III) also compared the highest decile with the middle category. To limit the effect of confounding factors, the analyses were repeated after excluding subjects who had given a self-report of depressed mood already at study entry (I, II).

The dietary factors were adjusted for energy intake in the models (Willet, 1990). Possible risk factors for mood disorders entered into the models as covariates included age, body-mass index, energy intake, serum total cholesterol, serum HDL cholesterol, consumption of alcohol, education, marriage, self-reported depression, self-reported anxiety and smoking (I, II). The estimated relative risks and their 95% confidence intervals (CI) were calculated. Calculations were also done to test the association between consumption of fish and self-reported depressed mood.

7.3.2 Twin studies

To take into account the correlated nature of twin data, adjusted Pearson F-statistics and Wald tests for clustered data were used to compare bipolar with healthy twins (Stata Corporation, 2001) (V). This method accomodates the pairs in which both twins had bipolar disorder. Survey estimation prevalences were applied to assess the domain and sum variables of the data derived from the questionnaires (Colombo et al. 2000) (V). Wilcoxon signed ranks tests were computed for the analysis of differences in these scores within the discordant twin pairs, i.e. where one twin had bipolar disorder and the other did not. Intra-pair correlations were calculated for the GSS and GWS, and partial correlation coefficients to estimate the association between the MES and the GSS (V). Also, partial correlation were calculated to estimate the association between food items, nutrients and seasonal changes and circadian phenotype after controlling for sex, age, zygosity, and affection status (IV). Chi-square and Fisher's exact tests were used for the analysis of differences in categorical variables. Means and standard deviations of food consumption and nutrient intake were calculated. Nutrient intakes were adjusted for energy intake according to the residual method in the models (Willet, 1990.) Mann-Whitney, logistic regression, and linear regression tests were used for the analysis of continuous variables (IV, V). In the present studies the significance level of the test was $p < 0.05$.

8 RESULTS

8.1 Amino acids

The average intake of amino acids at baseline did not differ in subjects with self-reported depression, anxiety, insomnia, and hospital admission due to MDD, and suicide (Table 2, in I and Table 2, in III).

Significance associations

Two amino acids were associated with subsequent hospital admissions due to MDD, the relative risk (95% CI) being 1.40 (1.02-1.93) for lysine and 1.38 (1.00-1.90) for serine in the highest tertile, as compared with the lowest tertile (Study I). However, these associations disappeared after excluding those with self-reported 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, as compared with the lowest tertile.

No significance associations

There were no significant associations between the intake of any amino acids and the risk of self-reported depressed mood , the risk of hospital admission due to MDD or the risk of death from suicide during the follow-up (Table 2, in I). Tryptohan did not associate with depression. The highest decile and the lowest decile were also compared with the middle tertile of dietary intake of amino acids for each study end-point, but there were no significant differences (Table 3, in I). There was no significant association between the intake of amino acids and self-reported depressed mood, anxiety or insomnia (Table 2, in III). (Study III)

The main results of studies between amino acids and association of self-reported depressed mood, anxiety, insomnia, hospital admission due to MDD, or insomnia are seen in Table 6.

8.2 Omega-3 fatty acids and fish

Significance associations

A small, marginally elevated risk of self-reported depression was suggested in the highest tertile of fish consumption compare to the lowest tertile the relative risk (95% CI) being 1.06 (1.00-1.12). A small, marginally elevated risk of self-reported depression was suggested in the highest tertile of fish consumption compared as to the lowest tertile.The trend test showed the statistical significance of high fish consumption for self-reported depressed mood ($Z=2.09$, $df=1$, $p=0.04$) (Study II).

No significance associations

There were no significant associations of fish consumption or omega-3 fatty acids intake with self-reported depression, hospital admission due to depression or suicide (Table 1, in II) (Study II). Also, there was no significant association of fish consumption or intake of omega-3 fatty acids with bipolar disorder (Study IV). In addition, women with bipolar disorder ingested 26% less omega-3 fatty acids than healthy women, but the difference was not statistically significant. There were no significant associations of fish consumption or intake of omega-3 fatty acids with self-reported depression, anxiety or insomnia (Table 2, in III).

There were variations in the intake of omega-3 and omega-6 fatty acids between study groups, although the differences were not statistically significant. In subjects with depressed mood, the mean intake of omega-6 fatty acids was 7% greater than in symptom-free subjects. In individuals with anxiety, the mean intake of omega-6 fatty acids was 7% greater and that of omega-3 fatty acids from vegetables 5% greater than in subjects with no symptoms.

When the symptoms reported during the first trial follow-up year were taken into the analysis, some variation has founded. Both in subjects with depressed mood and with anxiety, the mean intake of total omega-3 fatty acids was 9% greater and that of omega-3 fatty acids from vegetables 6% greater than in respective symptom-free subjects, whereas

the mean intake of omega-6 fatty acids was 6% greater in subjects with depressed mood and 9% greater in subjects with anxiety.

The main results of studies between omega-3 fatty acids and fish, and the risk of self-reported depressed mood, anxiety, insomnia, hospital admission due to MDD, or insomnia are seen in Table 6.

Table 6. Results of the present study by end-points: self-reported depression, self-reported anxiety, self-reported insomnia, hospital admission due to MDD, suicide, and bipolar disorder.

Amino Acids	**Significant differences**	**No significant differences**
Tryptophan		No association with any of study end-points.
Serine	Associated with hospital admission due to MDD.	Associations disappeared after excluding those with the self-report of depressed mood at study entry
Lysine	Associated with hospital admission due to MDD.	Associations disappeared after excluding those with the self-report of depressed mood at study entry
Omega- 3 fatty acids		No association between any of study end-points.
Fish	Highest tertile of fish consumption associated with the risk of self-reported depression. Trend test showed significance of fish consumption for self-reported depressed mood.	No association between other end-points.

8.3 Vitamins

Significance associations

In linear regression analysis, after adjustment for sex and age, the intake of vitamin B_{12} was significantly associated with bipolar disorder ($t=2.1$, $p < 0.05$) (Study IV). The mean intake of vitamin B_{12} was 48% (7.9 μg) greater in the bipolar twins than in healthy individuals, but the difference was not statistically significant. The difference was stronger in women; the intake of vitamin B_{12} was 44% greater in women with bipolar disorder than in healthy women.

No significance associations

There were no significant associations between the intakes of any other vitamins and self-reported depression, anxiety, or insomnia (Table 2, in III). (Study III)

Table 7. Results of the present study by end-points: self-reported depression, self-reported anxiety, self-reported insomnia, hospital admission due to MDD, and mania, suicide, and bipolar disorder.

Vitamins	**Significant differences**	**No significant differences**
B_{12}, Cobalamin	Associated with vitamin B_{12} in the linear regression analyses.	No association between other end-points.
Folate		No association between any of study end-points.
B_1, Thiamine		No association between any of study end-points.
B_2, Riboflavin		No association between any of study end-points.
B_6, Pyridoxine		No association between any of study end-points.
Vitamin D		No association between any of study end-points.

Additional data on vitamins

Baseline characteristics of the study subjects with a hospital admission due to MDD and due to bipolar disorder are given in Table 7, and the intakes of dietary vitamins B and D in Table 8. The intakes on average were similar in all groups. There were no significant associations of intakes of vitamins or homocysteine with any of the study end-points (Table 9). Dietary intake of vitamin D was associated with baseline serum total and HDL cholesterol levels ($r=0.14$, $p=0.02$, and $r=0.12$, $p=0.05$, respectively).

Table.8 Baseline characteristics of subjects with hospital admission due to major depressive disorder and to manic episodes.*						
	Depression		Mania		Whole cohort	
	n=244		n=48		n= 28 844	
	Mean	s.d	Mean	s.d	Mean	s.d
Age (years)	56.9	5.02	56.1	4.13	57.7	5.08
Energy (kcal/day)	2845	837	2823	895	2814	786
Smoking (cig/day)	21.5	9.28	24.9	10.1	20.4	8.82
Alcohol (g/day)	16.8	19.8	18.5	30.7	18.0	21.6
Body mass index (kg/m^2)	26.3	4.06	27.3	4.48	26.3	3.81
Total serum cholesterol (mmol/l)	6.17	1.16	6.15	1.19	6.24	1.17
HDL serum cholesterol (mmol/l)	1.21	0.33	1.13	0.30	1.23	0.34
*There were no significant differences between groups and the whole cohort.						

Table 9. The intake of vitamins by hospital admission due to major depressive disorder and due to manic episode. *						
	Depression		Mania		Whole cohort	
	n=244		n=48		n= 28 844	
	Mean	s.d	Mean	s.d	Mean	s.d
B_{12}, Cobalamin (µg/day)	11.5	5.14	12.2	5.88	11.1	4.8
Folate (µg/day)	344	109	356	122	337	104
B_1, Thiamine (mg/day)	2.12	0.62	2.05	0.66	2.07	0.59
B_2, Riboflavin (mg/day)	3.03	1.02	3.08	1.10	2.93	0.98
B_6, Pyridoxine (mg/day)	2.59	0.73	2.56	0.82	2.51	0.71
Vitamin D (µg/day)	5.39	3.39	5.64	3.57	5.49	3.10
*There were no significant differences between groups and the whole cohort.						

Table 10. Relative risk (RR)[a] and 95% confidence intervals (CI) of hospital admission due to major depressive disorder and to manic episode by baseline intake of vitamins.

Intake of vitamins (in quartile)[b]		Depression		Mania	
B_{12}, Cobalamin (μg/day)	< 7.7	1.00		1.00	
	7.7-10.3	1.05	0.86-1.29	1.01	0.59-1.73
	10.3-13.5	1.06	0.94-1.18	0.88	0.62-1.26
	> 13.5	1.04	0.96-1.13	1.01	0.79-1.28
B_6, Pyridoxine (mg/day)	< 2.0	1.00		1.00	
	2.0-2.4	1.06	0.86-1.31	0.70	0.40-1.22
	2.4-2.9	1.06	0.94-1.20	0.73	0.47-1.14
	> 2.9	1.09	0.99-1.20	1.09	0.82-1.45
B_1, Thiamine (mg/day)	< 1.7	1.00		1.00	
	1.7-2.0	0.94	0.75-1.17	0.55	0.27-1.08
	2.0-2.4	1.11	0.97-1.27	0.89	0.57-1.37
	> 2.4	1.12	0.99-1.26	1.13	0.80-1.58
B_2, Riboflavin (mg/day)	< 2.2	1.00		1.00	
	2.2-2.8	0.87	0.70-1.08	1.08	0.62-1.88
	2.8-3.5	1.10	0.97-1.24	0.95	0.66-1.37
	> 3.5	1.09	0.99-1.20	1.09	0.82-1.45
Folate (μg/day)	< 265	1.00		1.00	
	265-325	1.04	0.85-1.28	0.54	0.28-1.06
	325-395	0.98	0.86-1.12	0.90	0.59-1.38
	> 395	1.06	0.95-1.18	1.15	0.85-1.55
Vitamin D (μg/day)	< 3.4	1.00		1.00	
	3.4-4.8	1.18	0.97-1.43	0.53	0.28-1.02
	4.8-6.9	0.97	0.87-1.09	0.96	0.96-1.38
	> 6.9	0.94	0.86-1.03	1.11	0.88-1.40

[a] The relative risk was adjusted for baseline age, body mass index, energy intake, education, marriage, self-reported depression, self-reported anxiety, and consumption of alcohol.
[b] The lowest intake quartile as reference.

8.4 Additional data on food consumption in those with symptoms of depressed mood, anxiety, and insomnia

At study entry, 4314 (16%) of men reported depressed mood in the past four months, 6498 (24%) feelings of anxiety, and 5550 (21%) insomnia. There were no statistical significant differences between study subjects, but there was some variation in the intake of energy, alcohol, coffee and milk between healthy subjects and subjects with self-reported depressed mood, anxiety, and insomnia.

The mean intake of energy was 1-3% greater and consumption of alcohol 30-33% greater in subjects with any such symptoms, compared with symptom-free individuals. Men reporting all three symptoms consumed as much as 47% more alcohol than those without any symptoms. Subjects with insomnia consumed 7% less coffee than symptom-free individuals, whereas those with depressed mood or anxiety consumed only about 2% less coffee.

On all four occasions when the symptoms were asked about during the first trial follow-up year, 782 men reported depressed mood, 1237 feelings of anxiety, 1234 insomnia, and 166 men all three symptoms. Their food consumption and nutrient intakes were similar to men without these symptoms at baseline (Table 2, in III). Some disparities from the symptom-free subjects were more obvious, although differences were not statistical significant. The mean intake of energy was 7.3% greater in subjects with all three co-existing symptoms compared with symptom-free individuals. Subjects with insomnia consumed 10.9% less coffee, but 10.2% more milk than those with no symptoms.

8.5 Additional data on food consumption and intakes of nutrients in subjects with bipolar disorder

There were no statistical significant differences in the consumption of food or intakes of nutrients between those with bipolar disorder and healthy individuals (Table 2, in V). Logistic regression models gave no significant results. However, there were some

variations in intakes of nutrients between bipolar disorder and healthy individuals. In addition, the intake of protein was associated with affective status in linear regression analysis (t= 2.70, p= 0.01).

Bipolar twins consumed more meat (31%), fruit and berries (64%), eggs (45%), and milk (39%) than healthy co-twins, as calculated in absolute rates between two groups. The mean intake of margarine was 34% greater in healthy individuals than in those with bipolar disorder. These differences did not remain significant after subjects with a high frequency were excluded. The mean consumption of alcohol was 9.9 g/day in the bipolar and 4.1 g/day in healthy individuals. There were no differences in the consumption of coffee or tea on average.

However, the intake of vitamin B_{12} was 44% greater in women with bipolar disorder than healthy women. In addition, women with bipolar disorder ingested 26% less omega-3 fatty acids, and drank less alcohol (p=0.002) than healthy women. Women with bipolar disorder also ingested 32% less sugar but 70% more fruits and berries, and gained more energy from protein (p=0.005) than healthy women.

Seasonal association with food items

In the present study sample, there were three significant associations between dietary intakes and the seasonal changes in mood and behaviour. First, the consumption of coffee was related to seasonal change in appetite (r=0.55, p=0.04). Second, there was a significant correlation between intake of energy and the seasonal change in sleep length (r=0.53, $p < 0.05$). Third, the intake of fruit and berries was linked to the seasonal change in levels of energy (r=0.63, p=0.02).

Finnish Twin Cohort Questionnaire

There were additional results from the Finnish Twin Cohort Questionnaire from 1981 and 1990. The mean consumption of alcohol differed significantly between the bipolar and healthy twins (6.5 versus 11.2 g/day, p=0.04) in 1981. The mean difference in alcohol consumption increase from 1981 to 1990 in twins with bipolar disorder was 2.0 g per day

(SD=7.1; 95% CI: -1.9 to 5.9) and in healthy twins 0.0 g per day (SD =7.0; 95% CI: -5.5 to 5.4). Twins with bipolar disorder drank on average 2.0 g more alcohol in 1990 and 0.3 g more alcohol in 2002, whereas healthy co-twins drank 5.0 g per day less alcohol in 2002 as compared with their daily consumption in 1981.

There was no significant difference in smoking between the bipolar and healthy twins. In 1990, the mean years smoked was 18.8 years in twins with bipolar disorder and 26.1 years in healthy co-twins. The mean difference in smoking from 1981 to 1990 in the twins with bipolar disorder was 6.8 years (SD= 4.0; 95% CI: 3.5 to 10.2) and in healthy twins 10.8 years (SD=2.3; 95% CI: 5.0 to 16.6).

There were no significant differences in the consumption of coffee or tea between the bipolar and healthy twins in the Finnish Twin Cohort Questionnaire data. Bipolar twins consumed 5.6 cups of coffee (SD=3.3; 95% CI: 3.9 to 7.2) and 2.2 cups of tea per day (SD=1.9; 95% CI: 1.0 to 3.3), whereas healthy twins consumed 5.1 cups of coffee (SD=2.7; 95% CI: 3.5 to 6.7) and 2.3 cups of tea per day (SD=2.9; 95% CI: 0.2 to 4.7).

8.6 Seasonal changes in subjects with bipolar disorder

At group level, there were significant differences in the extent of seasonal changes in mood (p=0.02), weight (p=0.02), appetite (p=0.04), and levels of energy (p=0.02), as well as in the GSS (p=0.004) between the bipolar and healthy twins. The changes were greater in the bipolar twins.

Twins with bipolar disorder had most (31%) of their hospital admissions during autumn, but there were no statistically significant differences between the season (Table 2, in IV). The distribution of depressive and manic episodes did not differ significantly by season (p=0.06), although the depressive episodes were tended most common in autumn and winter, and manic episodes in autumn and summer. Also taken into account was the most frequent season of admission for each individual with recurrent episodes (n=33). Most of the admissions (52%) occurred in autumn, admission due to depressive episodes being most frequent during autumn and winter (82%). Seasonal distribution of hospital

admissions was compared with self-reports of feeling the worst, (p=0.13). Similarly, the self-reported length of sleep was analysed. The period of sleeping most (longest length of sleep) did coincide with the admissions, but this association did not reach statistical significance. The period of sleeping least (shortest length of sleep) was not associated with admissions (p=0.48).

There was a significant difference in the effect of dry days on feelings of wellbeing (p=0.04) between the bipolar and healthy twins. Dry days induced a more positive effect on wellbeing in the bipolar twins. Interestingly, short days had only a negative effect on wellbeing in the monozygotic twins, whereas the response was diverse among the dizygotic twins (p=0.02).

Within twin pairs there were greater seasonal changes in sleep length (p=0.01), and mood (p=0.01), and the GSS (p=0.03) was higher in the bipolar twins compared with their healthy co-twins. In addition, sunny days (p=0.03) had a greater positive effect on wellbeing in the bipolar than healthy co-twins. The mean difference (95% CI) between the bipolar and healthy twins in the GSS was 3.40 (0.65 to 6.15), in sleep length 1.00 (0.36 to 1.64), in social activity 0.80 (0.01 to1.59), in mood 0.93 (0.29 to 1.58), and in sunny days 1.00 (0.15 to 1.85).

The intrapair correlation of the GSS was 0.16 for seven monozygotic twin pairs, and 0.21 for 20 dizygotic twins. The intrapair correlation of the GWS was -0.16 for the monozygotic twins, and 0.04 for the dizygotic twins.

8.7 Sleep length and debt in subjects with bipolar disorder

The bipolar twins slept longer nights, as self-reported with the FTCQ in 1990, compared with healthy twins (p=0.01, Table 3, in IV). At follow-up in 1999, as assessed in the interview, the mean sleep length was 8.21 hours in the morning types (morning larks) and 7.66 hours in the evening types (night owls), as calculated from the SPAQ. When data on sleep length derived from the SPAQ were compared with those from the FTCQ, healthy morning and evening types slept less in 1999 than 1981 (Table 4, in IV). The morning

types with bipolar disorder slept more in 1999 than 1981. The evening types with bipolar disorder slept the same time or less than before. When groups of morning types and evening types were analysed the longest length of sleep was 8.59 hours among the morning types (in winter), and the shortest was 6.70 hours among the evening types (in summer).

8.8 Circadian type in subjects with bipolar disorder

Among the twin cohort studied the stability of circadian preference remained good from 1981 to 1986 ($p < 0.0001$). The morning type tended to become slightly more prevalent with age in the whole cohort, as well as in this study sample (Figure 1, in IV). There were no significant differences in the MES, or in the circadian type preferences between the bipolar and healthy twins (Table 3, in IV). Whether the MES or GSS differed between monozygotic and dizygotic twins, or between men and women, was also checked. There were no differences.

The eveningness preference was associated with a higher GSS (partial correlation, $r = -0.045$, $p < 0.01$) after controlling for sex, age, zygosity, and affection status. This association was seen only for the total score, and there were no significant associations between the circadian type and seasonal changes in length of sleep, weight or appetite. In the present study, weight and appetite usually increased in winter and decreased in summer, but there were no statistical significant differences. In 51% of the individuals the most common change in weight was 2-3.5 kg during the year, and the 32% of individuals' food preferences changed by season.

9 DISCUSSION

9.1 Strengths and limitations of the study

9.1.1 Study subjects

The ATBC Cancer Prevention Study (I, II, II) was an exceptionally large population-based study sample. There were 29 133 men followed-up for six to eight years. The limitations of studies I, II, and III are that the participants were men only, of a restricted age cohort, and all were smokers at study entry. Strict exclusion criteria limit the generalizability of these study findings to the general population, but the study still provides valid and reliable data on a community-based, very homogenous sample of older men.

In the twin studies (IV, V) the sample size was small, but derived from an extensive population-based sample using the National Population Register and the Finnish Twin Cohort. The participation rate (88%, 67 out of 76 in total) was high. However, there were only 39 study subjects left in the final study analyses (67% of those invited). This participation rate could limit the generalizability of these findings. The reason for the low participation rate is most probably related to the personal tedium of long-lasting studies and to the general problems of participation. Using the Finnish twin cohort the estimated incidence of bipolar disorder I in the population during the follow up period of 1970 to 1991, the annual incidence in the 1954-1959 birth cohort was 5.8 to 100 000 (95% CI: 5.4 to 6.3; Kieseppä et al. 2004). The Health 2000 project reports a lifetime prevalence of bipolar I disorder of 0.24% in Finland (Perälä et al. 2007). The small number of study subjects limits the generalizability of the findings, but this study still provides valid and reliable data on bipolar twins. Because of the small study sample in Study IV differences in the dietary intake between bipolar disorder subjects and healthy subjects may not appear. Also, this was a study of twins, which as such can limit the generalizability of these results to the general population. The study sample was collected from Finland, a far northern country, which can limit the generalizablity of the findings on seasonal changes (Studies IV, V) for countries at less extreme latitudes.

9.1.2 Study design

The ATBC Cancer prevention study was a prospective study with a follow-up period of 6 to 8 years. Studies I and II applied a prospective study design. Study III was a partly cross-section study, which cannot prove causal connection between diet and symptoms of depression, anxiety, or insomnia.

Studies IV and V were cross-section studies, which again limits the findings, because causal connection between bipolar disorder and dietary intake of nutrients cannot be proved. However, there were data available on sleeping habits, alcohol and tobacco consumption for reference from the Finnish Twin Cohort Questionnaires from 1981 and 1990.

9.1.3 Psychiatric diagnoses

In the ATBC Cancer Prevention Study the data on hospital admissions were derived from the National Hospital Discharge Register, which covers in-patient admissions to all medical and psychiatric hospital beds in Finland. The accuracy of the register compared with medical records is excellent, with data being identical in about 95% of the primary diagnoses (Keskimäki and Aro, 1991). Versatile data on depression, which increases the validity and reliability of the assessment, were collected.

In the twin studies (IV, V) all the probands and co-twins were interviewed to confirm the diagnosis of the probands and to assess any mental disorders of the co-twins by one of the investigators (T.K) using the Structured Clinical Interview for DSM-IV (SCID) (Spitzer et al. 1997).

9.1.4 Questionnaires

Food Use Questionnaire and Food Frequency Questionnaire

Dietary intake and alcohol consumption were assessed with a self-report but validated food use questionnaire to measure the habitual dietary intake over the previous year as completely as possible. Both the food use and food frequency questionnaire have been validated against food records data (Pietinen et al 1988; Paalanen et al. 2006). In the food use and frequency questionnaires the information relies on the subject's memory, and because of the defined food list, some information about the foods actually eaten may be missed. Paalanen et al (2006) reported overestimation with the FFQ compared to food records. The most overestimated nutrients were polyunsaturated fatty acids, long chain n-3 fatty acids, carotenoids, vitamin E, and vitamin C in both women and men. However, since there is underreporting in food records, overestimation in the FFQ could be expected. Also, the correlations for nutrients between the FFQ and food records were higher in women than in men, but in the same range as earlier studies.

In the validation process of FFQ the food records data were not optimal, because the food record covered only three days. This may be a limitation of the validation study (Paalanen et al. 2006). Also, Pietinen et al (1988) reported that there was overestimation for potatoes, fruits and juices, while the consumption of fats, fish and coffee, alcohol, and sugar was slightly underreported.

In the ATBC Cancer Prevention Study the reproducibility of this method is 0.6-0.7 and the validity 0.6-0.7 for most nutrients (Pietinen et al. 1988). In the twin studies the Pearson correlation coefficients ranged from 0.14 for retinol to 0.70 for alcohol. The correlation coefficient for long-chain omega-3 fatty acids was 0.35 in men and 0.20 in women (Paalanen et al. 2006). These studies concluded that the self-administered food use questionnaires are useful for measuring individual or group intakes for a variety of nutrients. In the present study, only two healthy men filled in the FFQ in Study IV.

The eating habits of twins are rather similar, even in adulthood. The temporal pattern, energy intake, meal frequency, portion size, meal macronutrient intake, alcohol consumption, and water composition have strong heritabilities, whereas the shared familial environment has no major impact on the levels or patterns of eating in adulthood (de Castro, 1993). As study IV was a study of twins, this may limit the generalizability of these results.

Symptoms of depressed mood, anxiety and insomnia

Assessment of self-reported depression based only on a single item compromises the specificity. It has been reported that two to three questions only may be as effective as a more detailed screening instrument in detecting probable cases of major depression (Whooley et al. 1997; Arroll et al. 2005). One of these questions ("During the past month, have you often been bothered by feeling down, depressed, or hopeless?") is rather similar to the item that it was used for being indicative of depressed mood.

SPAQ

Magnusson et al (1997) found that six items of GSS correlated well in a population based study in Iceland and the scale had a high internal consistency. They concluded that GSS is well constructed and reliable in measuring seasonal changes. Young and co-workes (2003) also reported good internal consistency and two-month test-retest reliability. Magnusson (1996) also found excellent sensitivity and specificity (94% and 73%, respectively) for a "winter problem" group, which included subjects with seasonal affective disorder and subsyndromal seasonal affective disorder.

Both the seasonal variation in mood and behaviour and the changes in wellbeing attributed to local weather conditions were retrospectively assessed using a self-rating scale. Score on the SPAQ tend to vary by season, but not by day length (Lund and Hansen, 2001). However, this is not a true limitation in this study, because the SPAQ was administered via research interviews that were distributed evenly over the year. The linguistic accuracy of the Finnish version has been checked with back translation, but the psychometric properties are not published yet (personal communication, Timo Partonen).

MEQ

The MEQ has been validated by studying oral temperatures, typical bed and arising times, and sleep length of study subjects (Horne and Östberg, 1976). They reported that morning types had a significantly earlier peak time than evening types and tended to have a higher daytime temperature and lower post peak temperature. Morning types retired and arose significantly earlier than evening types. There was correlation between the peak time and MEQ (-0.51, $p < 0.01$). The linguistic accuracy has been checked with back translation, but the psychometric properties are not published yet (personal communication, Timo Partonen).

9.2 Associations between mood disorders and mood symptoms and dietary intakes of specific nutrients

9.2.1 Amino acids

The intakes of two amino acids, serine and lysine, were associated with the increased risk of hospital treatment due to MDD. Also, the intake of energy from protein was greater in subjects with bipolar disorder than healthy subjects. It has been reported that a high intake of protein seems to increase alertness (Rogers, 2001). Maybe patients prefer to eat foods with a high concentration of proteins because such meal may easily produce higher levels of activity.

Alternatively, the positive associations between serine and lysine intakes levels and the risk of MDD may have simple occurred by chance only due to multiple comparisons. There is evidence of differences in the plasma concentrations of serine in depressed subjects compared with healthy subjects (Fekkes et al. 1994; Maes et al. 1998, Sumiyoshi et al. 2004). These findings suggest that serine may participate in the regulation of mood. The role of lysine in brain function is still relatively unknown and evidently worth further study.

In the present study, there were no associations between intake of tryptophan and mood symptoms and disorders. Tryptophan is a precursorof serotonin, which is known to play a key role in many brain functions, such as mood regulation. A number of studies have shown that acute tryptophan depletion produces depressive symptoms and results in worsening of mood, mainly in subjects with depression or vulnerability to depression (Neumeister et al. 1998; Spillmann et al. 2001). For this reason, tryptophan supplementation has been applied for the treatment of depressed patients (Lam et al. 1997). However, a number of negative studies have been published recently, suggesting that the effects of tryptophan depletion on mood are less consistent (Bell et al. 2001; Van der Does, 2001), and the rationale for augmentation has now been challenged (Nelson, 2000). The present study results agree with these recent findings in that the effect of tryptophan on mood may be less robust than earlier assumed. Furthermore, there are no data showing whether serum serine or lysine concentrations can affect the brain tryptophan uptake by the brain. There are no data on the effects of smoking on amino acid metabolism.

9.2.2 Omega-3 fatty acids and fish

Neither dietary intake of omega-3 fatty acids, nor fish consumption showed any association with low mood and related outcomes. In the present study both the dietary intake of omega-3 fatty acids, and fish consumption , were linked to the three-level assessment of low mood: as a symptom (self-report) and as pathology (disorder or suicide) in a population. This finding conflicts with the some results of Finnish population based studies. Tanskanen et al. (2001a; 2001b) and Timonen et al. (2004) have reported that those who rarely eat fish have higher risk of depression, but this association was found only in women in two studies. Unfortunately, there were no women in the present study, but the study population was substantially bigger than other population based studies. Another strength of the present study was the MDD diagnoses from National Hospital Discharge Register. In other population based studies depressive diagnoses have been diagnosed by questionnaires. Even in same country (Finland) there are no consistent results for both sexes about the associations between fish consumption and mood disorders.

Moreover, there are conflicting findings from supplemental use of omega-3 fatty acids in mood disorders. Three placebo-controlled trial have found therapeutic effects of omega-3 fatty acids in depression (Nemets et al. 2002; Peet et al. 2002; Su et al. 2003), but other studies did not find beneficial effects (Marangell et al. 2003; Silvers et al. 2005). The primary study of Stoll et al. (1999) reported that supplemental use of omega-3 fatty acids may have therapeutic effects on patients with bipolar disorder. However, the latest study failed to confirm these findings (Keck et al. 2006).

The doses have been 1 g to 9.6 g per day in studies with supplemental use of omega-3 fatty acids. Usually the doses used in these studies have exceeded by several times the dietary intake levels (average intake of 2.2 g/day vs 0.47 g/day from fish). The average intake of omega-3 fatty acids tends to be rather similar across most Western countries. For example, the average intake of omega-3 fatty acids was 1.2 g/day in men in the USA (Suzuki et al. 2002). So the overall amount of omega-3 fatty acids in the diet of the present study population (2.2 g/day) is higher but still in line with that in other industrialized populations.

This study subjects reporting anxiety had higher intakes of omega-3 and omega-6 fatty acids. The one exception was that omega-3 fatty acids from fish were not linked to any of the symptoms. Margarine was revealed as the main source of omega-3 fatty acids from vegetables, and of omega-6 fatty acids. Subjects with depressed mood also had a higher intake of omega-6 fatty acids. Because 3,138 (73%) subjects with depressed mood also had feelings of anxiety, it may be that anxiety is the dominant symptom, and the greater intake of omega-3 and omega-6 fatty acids is primarily related to feelings of anxiety. There are no previous studies about associations between omega-6 fatty acids and mood. It has been reported that smokers have lower erythrocyte polyunsaturated fatty acids status (Hibbeln et al. 2003). In the present study there were no data on erythrocyte polyunsaturated fatty acids levels.

9.2.3 Vitamins

The main finding in the vitamin study was that there was no association between the intake of vitamins (folate, B_{12}, B_6, B_2, B_1, vitamin D), or of homocysteine, and the risk of

subsequent hospital treatment for affective disorder. The intakes of these vitamins exceeded the daily recommendations. It has been hypothesized that a combination of decreased appetite, decreased absorption, and increased utilization of folate results in folate depletion and eventually produces a central nervous system effect (Abou-Saleh and Coppen, 1986). The present study showed that there were no low intakes of folate or B_{12} vitamin.

In the bipolar twin study, too, the dietary intakes of vitamins exceeded the daily recommendations and showed no association with bipolar disorder, except for vitamin B_{12}. In this study sample, the intake of vitamin B_{12} was greater in twins with bipolar disorder than in healthy co-twins. The best sources of vitamin B_{12} are meat, liver, milk, and fish. There is no obvious explanation why the intake of vitamin B_{12} was greater in twins with bipolar disorder. The hypotheses which support an association of vitamin B_{12} and mood disorders need more study. Shortage of vitamin B_{12} has been linked to various neurological and psychiatric disorders, such as affective illness (Goggans, 1984; Hector and Burton, 1988; Lindenbaum et al. 1988; Healton et al. 1991). It has been reported that depressed subjects have low serum vitamin B_{12} levels (Pennincx et al. 2000; Tiemeier et al. 2002), but there are also contradictory findings (Fava et al.1997; de Jong et al. 2001; Bjelland et al. 2003).

Another explanation for the association of vitamin B_{12} with depression is the effect that vitamin B_{12} may have on the circadian system. Vitamin B_{12} seems to modulate melatonin secretion (Yamazaki et al. 1991), to increase core body temperature later in the day (Uchiyama et al. 1995), and to enhance response to light exposure (Hashimoto et al. 1996).

Smoking is known to be associated with an increased plasma homocysteine level and reduced levels of folate, vitamin B_{12} and vitamin B_6 (de Bree et al. 2001a; 2001b; O'Callaghan et al. 2002). In this study there were no data on serum levels of vitamins. However, smokers in this study clearly exceeded daily recommendations for the intakes of folate, vitamin B_{12} and vitamin B_6 clearly.

9.3 Dietary intakes of food consumption and nutrients in those with symptoms of depressed mood, anxiety, and insomnia

Subjects with any or all of the symptoms consumed more alcohol than the symptom-free subjects. Subjects with depressed mood, anxiety and insomnia consumed the most alcohol of all, and they received 6% of their total energy from alcohol, compared to 4.3% in subjects with no symptoms. Energy from alcohol did not, however, explain the differences in mean intake of energy between groups. Alcohol, in particular, is a notable source of extra energy, whose excessive consumption should be avoided when suffering mental health problems. Body-mass index was lower, despite a higher caloric intake, in subjects with symptoms compared to symptom-free subjects. It also found that subjects reporting depressed mood consumed more carbohydrates than subjects with no symptoms in the present study. This finding is consistent with the previous reports that some depressed subjects try to alleviate depressive symptoms by carbohydrate craving (Christensen and Pettijohn, 2001). Depressed subjects tend to consume more carbohydrates in their diets than non-depressed individuals (Christensen and Somers, 1996).

9.4 Dietary intake, drinking and smoking and bipolar disorder

There were no significant differences in the consumption of foods or the intakes of nutrients between twins with bipolar disorder and healthy co-twins. Logistic regression models gave no significant results. However, there were some variations in the dietary intakes of nutrients. The main findings of the this study are that the intake of energy from protein and the intake of vitamin B_{12} are greater in twins affected with bipolar disorder than in healthy co-twins. Bipolar twins also ingesteded more meat, fruits and berries, eggs, and milk, and drank more alcohol than healthy twins. Interestingly, women with bipolar disorder had a more healthy way of eating and drinking than healthy women. It was hypothesised in this study that women with bipolar disorder have less symptoms of bipolar disorder and less hospital admissions than men with bipolar disorder. However, there were no differences in the number of admissions between men and women with bipolar disorder.

9.5 Sleep habits and seasonal changes in subjects with bipolar disorder

It is known that sleep disturbances have an impact on the mood, and the present study aimed to include the investigation of sleep habits and circadian rhythms in subjects with bipolar disorder. The circadian system is responsible for regulating many physiological and behavioural rhythms in 24-hour cycles (Reppert and Weaver, 2002). Deletions of the circadian genes results not only in circadian abnormalities, but also in metabolic abnormalities of glucose and lipid homeostasis, a phenotype resembling the metabolic syndrome. Turek et al (2005) reported that rats with a mutation in the circadian clock gene had disturbances in the diurnal feeding rhythm which resulted in them becoming obese and developing metabolic syndrome. Rudic et al. (2004) have demonstrated that mutations in the clock gene affected to plasma glucose and triglyceride concentrations and influence the development of glucose intolerance and insulin resistance in response to a high-fat diet. Research is urgently needed to clarify these connections in detail.

9.5.1 Sleep habits

During 1981 to 1999 follow-up, the length of sleep shortened among the healthy twins. Shortage of sleep has been a common phenomenon in western societies. In contrast, the bipolar twins of sample slept even more in 1999. When subjects with a greater sleep debt and subjects with no sleep debt were compared, there was no difference in the intake of energy. It has been observed that those who sleep less than seven hours per night are more likely to be obese (Gangwisch et al. 2005; Patel et al. 2006). It has also been reported that that subjects with sleep debt have more obesity, and that sleep debt is a risk factor for metabolic syndrome (Wolk and Somers, 2007). The verification of this association needs further research.

9.5.2 Circadian type

There were no differences in circadian type between patients with bipolar disorder and healthy study subjects. Preference for evening activities has been associated with a greater need for sleep (Taillard et al. 1999). In this study, the evening types had greater sleep debt

than the morning types. This finding agrees with previous data showing that the evening types do experience a need for longer sleep (Taillard et al. 1999).

9.5.3 Seasonal changes

It was found that seasonal changes in sleep length and in mood were greater in twins with bipolar disorder compared with their co-twins with no mental disorder. This accords with previous finding of a circadian fluctuation in bipolar disorder (Shin et al. 2005).

There was a positive correlation between the intake of energy and the seasonal change in sleep length. Twins with bipolar disorder ingested more energy than healthy twins. Disturbances in circadian rhythms probably induce fatigue. It is possible that those who feel tired tend to eat more, for instance fruits and berries, and to drink more coffee in order to reduce sleepiness and stay alert.

It was found that autumn was generally the worst time for patients with depressive and manic episodes, especially those with recurrent episodes. This may also affect dietary intake.

9.6 Implications for future research

1. In this study there were no associations found between nutrition and mood disorders in men, although these results need to be confirmed with population based-studies which also include women. In particular, the possible beneficial effects of omega-3 fatty acids on mood need further research.

2. In this study the intake of nutrients exceeded the daily recommendations and there were no associations between in the dietary intakes of nutrients and mood disorders and symptoms. It remains to be elucidated whether there is a difference in the metabolism of nutrients between subjects with mood disorders and healthy controls. Such studies would require total serum levels of different nutrients in depressed people and healthy study subjects. It is important to find out whether there are individual differences in metabolism or bioavalability, because if so it may be possible to maybe prevent depression by increasing the daily intake of specific nutrients.

3. This present study did not clarify the value of supplemental use of omega-3fatty acids. However, the findings of earlier studies indicate that more research is needed to clarify the beneficial effects of supplemental use ofomega-3 fatty acids on mood disorder.

4. More studies of the circadian clock genes and their associations with mood disorders are needed. It is important to investigate how these genes affect the diurnal rhythms of feeding and sleeping and whether polymorphisms of these genes can to some extent explain the pathogenesis of bipolar disorder. This may pave the way to new options in the prevention and treatment of bipolar disorder. It will also be important to study how diet and lifestyle habits (exercise, sleep) affect regulation of these genes and whether mood disorders can be prevented by specific interventions of life habits, especially in those with high risk of mood disorders.

5. The present study found that autumn was the worst time for bipolar patients, as most of hospital admissions were in autumn. This should be taken into account in future studies, especially in the assessment of the dietary intake. It should also be noted in clinical work.

10 CONCLUSIONS

The present study focused on five specific questions as follows.

Is the intake of tryptophan related to depression? (Study I)
Finding: Tryptophan did not associate with self-reported depression, hospital admission due to MDD, or suicide.

Is the intake of omega-3 fatty acids related to depression? (Study II)
Finding: Omega-3 fatty acids did not associate with self-reported depression, hospital admission due to MDD, or suicide.

How does mood affect eating habits? (Study III)
Finding: There were no statistically significant differences between healthy subjects and subjects with depressed mood, anxiety symptoms, or insomnia. However, men reporting all three symptoms consumed as much as 47% more alcohol than those without any symptoms.

How does bipolar disorder affect eating habits? (Study IV)
Finding: After adjustment for sex and age, the intakes of vitamin B_{12} and of protein were significantly associated with bipolar disorder.

How does bipolar disorder affect seasonal changes in mood and behaviour? (Study V)
Finding: It was found that seasonal changes in sleep length and in mood were greater in twins with bipolar disorder compared with their co-twins with no psychiatric disorder.

In conclusion, no significant association between dietary intakes of nutrients and mood disorders in the present study. These results did not lend support to the view that dietary intakes have a major role in mental health. More studies are needed to clarify these connections in future.

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