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ANU RUUSUNEN

Diet and Depression

An Epidemiological Study

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ABSTRACT:

The association between diet and depression has previously mainly been studied in cross-sectional studies, and only few prospective studies have been published. The evidence suggests that folate and long-chain n-3 polyunsaturated fatty acids (PUFAs) may be connected to the decreased risk of depression. Furthermore, only few studies have concentrated on the association between general dietary patterns and depression.

The aim of this thesis was to investigate whether dietary intake of folate and vitamin B_{12}, serum concentrations of n-3 PUFAs, consumption of coffee and tea, or caffeine intake are associated with the risk of getting a discharge diagnosis of severe depression in population-based sample (the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study, *n*=2,077-2,313, works I, II and III) of middle-aged or older Eastern Finnish men during an average of 13-20 years of follow-up. In addition, the study focused on examining if dietary patterns are associated with the prevalence of depressive symptoms or the risk of depression requiring hospital treatment (the KIHD Study, *n*=1,003, work IV). Finally, the aim was to investigate how an intensive lifestyle intervention affects the depressive symptoms in an intervention study design (the Finnish Diabetes Prevention Study (DPS), *n*=140, work V).

It was observed that increased intake of folate and healthy dietary patterns (consumption of vegetables, fruits, berries, whole-grains, poultry, fish and low-fat cheese) were associated with a lower risk of depression. In addition, increased coffee consumption was non-linearly associated with a decreased risk of depression. Vitamin B_{12} intake, serum concentrations of n-3 PUFAs, serum ratio of n-6 to n-3 PUFAs, tea drinking and caffeine intake were not related to the risk of depression. Adherence to unhealthy dietary pattern (consumption of sausages, processed meats, sugar-containing desserts and snacks, sugary drinks, manufactured foods, French rolls and baked or processed potatoes) was associated with an increased prevalence of elevated depressive symptoms. In addition, participation in the three-year lifestyle intervention study improved depression scores with no specific group effect, although clinically non-significantly. Reduction of body weight was associated with a greater reduction in depressive symptoms.

The results of this thesis indicate that diet, especially a healthy diet rich in folate, and a dietary pattern rich in vegetables, fruits, berries, whole-grains, poultry, fish and low-fat cheese, may be protective against depression. N-3 PUFAs may not have a role in the prevention of depression, at least not in middle-aged or older men with generally low circulating concentrations of n-3 PUFAs.

National Library of Medicine Classification: QT 235, OU 188, WD 120, WM 171
Medical Subject Headings; Caffeine; Diet; Depression; Depressive Disorders; Depressive Symptoms; Food; Follow-Up Studies; Cohort Studies; Folic Acid; Fatty Acids; Risk Factors; Vitamin B12; Coffee; Tea; Male; Middle Aged; Vegetables

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TIIVISTELMÄ:

Ruokavalion yhteyttä masennukseen on selvitetty aikaisemmin lähinnä poikkileikkaustutkimuksissa, ja prospektiivisiä seurantatutkimuksia aiheesta on vähän. Etenkin folaatin ja n-3-sarjan pitkäketjuisten monityydyttymättömien rasvahappojen on esitetty vähentävän masennusriskiä. Ruokavalion kokonaisuuden merkityksestä masennuksessa on vasta vähän tutkimustietoa.

Tämän väitöskirjatyön tarkoituksena oli tutkia väestöaineistossa (Sepelvaltimotaudin vaaratekijätutkimus (SVVT), *n*=2077-2313, osatyöt I, II ja III), ovatko ravinnon folaatin ja B_{12}-vitamiinin saanti, seerumin rasvahappojen pitoisuus, sekä kahvin ja teen juominen ja kofeiinin saanti yhteydessä sairaalahoitoisen masennuksen riskiin keski-ikäisillä tai vanhemmilla itäsuomalaisilla miehillä 13-20 vuoden seurannan aikana. Lisäksi tutkittiin ruokavalion kokonaisuuden yhteyttä masennuksen esiintyvyyteen sekä masennusriskiin (*n*=1003, osatyö IV) ja selvitettiin kolmivuotisen elämäntapaintervention vaikutusta masennusoireisiin (Suomalainen Diabeteksen ehkäisytutkimus (DPS), *n*=140, osatyö V).

Tutkimuksessa havaittiin, että runsas folaatin saanti ja terveelliset ruokailutottumukset (kasvisten, hedelmien, marjojen, täysjyväviljan, kanan, kalan ja vähärasvaisen juuston syöminen) vähensivät masennusriskiä. Myös kahvin käyttö oli yhteydessä pienempään masennusriskiin, tosin yhteys ei ollut lineaarinen. Sen sijaan B_{12}-vitamiinin saannilla, n-3-rasvahappojen seerumipitoisuuksilla, teen juonnilla tai kofeiinin saannilla ei ollut yhteyttä masennusriskiin. Epäterveellinen ruokavalio (makkaroiden, lihavalmisteiden, sokeroitujen jälkiruokien, sokeripitoisten juomien, valmisruokien, vaalean vehnäleivän ja perunavalmisteiden syöminen) oli yhteydessä suurempaan masennuksen esiintyvyyteen. Lisäksi tutkimuksessa havaittiin, että kolmivuotisen elämäntapaintervention aikana tutkittavien masennuspisteet laskivat riippumatta siitä, oliko tutkittava intensiivisen intervention ryhmässä vai tavanomaisen, ns. mini-intervention, ryhmässä. Pistelasku ei kuitenkaan ollut kliinisesti merkittävä. Masennuspisteiden laskua interventiossa selitti painon lasku.

Väitöskirjatyön tulokset viittaavat siihen, että terveellisellä, runsaasti folaattia sisältävällä ravinnolla, ja ruokavaliolla, jossa on kasviksia, hedelmiä, marjoja, täysjyväviljaa, kanaa, kalaa ja vähärasvaista juustoa, saattaa olla merkitystä masennuksen ennaltaehkäisyssä. Sen sijaan seerumin rasvahappojen pitoisuuksilla ei havaittu yhteyttä masennusriskiin, ainakaan keski-ikäisillä tai ikääntyneillä miehillä, joilla n-3-rasvahappojen pitoisuudet olivat suhteellisen matalia.

Luokitus: QT 235, OU 188, WD 120, WM 171
Yleinen suomalainen asiasanasto: ravinto; ruoka; masennus; mieliala; mielenterveyshäiriöt; seurantatutkimus; kohorttitutkimus; folaatit; rasvahapot; riskitekijät; B12-vitamiini; kahvi; kofeiini; tee; terveysvaikutukset; ruokavaliot; miehet; keski-ikäiset; Itä-Suomi; kasvisravinto; ennaltaehkäisy

All will be well in the end. And if it is not, then trust me, it is not the end.

Paolo Coelho

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Kuopio, August 2013

Anu Ruusunen

List of the original publications

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

I Tolmunen T, Hintikka J, Ruusunen A, Voutilainen S, Tanskanen A, Valkonen V-P, Viinamäki H, Kaplan GA, Salonen JT. Dietary folate and the risk of depression in Finnish middle-aged men. A prospective follow-up study. *Psychother Psychosom* 2004; 73: 334-339.

II Ruusunen A, Virtanen J, Lehto SM, Tolmunen T, Kauhanen J, Voutilainen S. Serum polyunsaturated fatty acids are not associated with the risk of severe depression in middle-aged Finnish men: the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study. *Eur J Nutr* 2009; 50: 89-96.

III Ruusunen A, Lehto SM, Tolmunen T, Mursu J, Kaplan GA, Voutilainen S. Coffee consumption and the risk of severe depression in middle-aged Finnish men: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Public Health Nutr* 2010; 13: 1215-1220.

IV Ruusunen A, Lehto SM, Mursu J, Tolmunen T, Tuomainen T-P, Kauhanen J, Voutilainen S. Dietary patterns are associated with the prevalence of depressive symptoms and the risk of depression in middle-aged Finnish men. Submitted.

V Ruusunen A, Voutilainen S, Karhunen L, Lehto SM, Tolmunen T, Keinänen-Kiukaanniemi S, Eriksson J, Tuomilehto J, Uusitupa M, Lindström J. How does lifestyle intervention affect the depressive symptoms? Results from the Finnish Diabetes Prevention Study (DPS). *Diabet Med* 2012; 29: e126-e132.

Contents

TABLES

FIGURES

Abbreviations

AA	Arachidonic acid, C20:4n-6
AD	Antidepressant prescription
AHEI	Alternative Healthy Eating Index
ALA	Alpha-linolenic acid, C18:3n-3
ATBC	The Alpha-Tocopherol, Beta-Carotene
ANOVA	Analysis of variance
BDI	Beck Depression Inventory
BDNF	Brain-derived neurotrophic factor
BH_2	Quinonoid dihydrobiopterin
BMI	Body mass index
CARDIA	The Coronary Artery Risk Development in Young Adults Study
CES-D	Center for Epidemiological Studies Depression Scale
CI	Confidence interval
CNS	Central nervous system
CRP	C-reactive protein
CVD	Cardiovascular disease
DEPS	Finnish Depression Screening Tool
DHA	Docosahexaenoic acid, C22:6n-3
DHFR	Dihydrofolate reductase
DPA	Docosapentaenoic acid, C22:5n-3
DPP	Diabetes Prevention Program
DPS	The Finnish Diabetes Prevention Study
DR	Diet recall
DSM	Diagnostic and Statistical Manual of Mental Disorders
E-EPA	Ethyl-ester of eicosapentaenoic acid
EPA	Eicosapentaenoic acid, C20:5n-3
FFQ	Food frequency questionnaire
GCS	Greene Climacteric Scale
GDS	Geriatric Depression Scale
GHQ	General Health Questionnaire
GMSS	Geriatric Mental State Schedule
HADS	Hospital Anxiety and Depression Scale
HAM-D	Hamilton Depression Rating Scale
HEI	Healthy Eating Index
HPA	Hypothalamus-pituitary-adrenal gland
HPL	Human Population Laboratory
HR	Hazard ratio
ICD	International Classification of Diseases
IGT	Impaired glucose tolerance
KIHD	The Kuopio Ischaemic Heart Disease Risk Factor Study
LA	Linoleic acid, C18:2n-6
MDD	Major depressive disorder
MDS	Mediterranean Diet Score
MTHF	Methyltetrahydrofolate
MTHFR	Methylenetetrahydrofolate reductase
MUFA	Monounsaturated fatty acids
NADPH	Reduced form of nicotinamide adenine dinucleotide phosphate
NHANES	The National Health and Nutrition Examination Survey
NHS	The Nurses' Health Study
OR	Odds ratio
PUFA	Polyunsaturated fatty acids
r	Correlation coefficient
RCT	Randomized controlled trial
SAMe	S-adenosyl-methionine
SD	Standard deviation
SES	Socio-economic status
SFA	Saturated fatty acid
SPSS	Statistical Package for the Social Sciences
SRDS	Self-reported depressive symptoms
SSRI	Selective serotonin reuptake inhibitors
SUN	The Seguimiento Universidad de Navarra
SU.VI.MAX	The Supplémentation en Vitamines et Minéraux Antioxydants Study
T2D	Type 2 diabetes mellitus
U.S.	The United States of America
$X\text{-}CH_3$	Methyl group

1 Introduction

Major depressive disorder (MDD) is one of the leading health concerns in the world, with the average lifetime prevalence of 15-16% in high-income countries (1,2). In addition, MDD is predicted to hold the second position among diseases contributing to the global burden of diseases by 2030 (3), and there has been a 37% increase in disability-adjusted life years of depression from the year 1990 to 2010 (4). The effects of depression on public health and economics are extensive and on the increase.

Depression is a multifactorial disease with plenty of risk factors, including environmental, genetic and psychological factors, rendering the etiology of depression challenging to study. The importance of lifestyle habits, such as diet and physical exercise, is still poorly studied, even though the significance has been established in many other diseases, such as cardiovascular diseases (CVD) and cancer. Prevention strategies of depression have achieved much less publicity compared to treatment strategies (5).

Evidence slightly supports the notion that diet, certain foods or nutrients may have a role in the etiology and prevention of depression (6). However, there are relatively few prospective studies published, with inconsistent results. The inconsistency may be explained by methodological differences and by potential confounders and effect modifiers, like gender, age or smoking. In addition, the magnitude of total energy intake as a confounder has been shown to be remarkable, especially in cross-sectional studies. Diet measurements have mainly been valid, as long food frequency questionnaires (FFQs) or serum, plasma or red-cell concentrations have been the most common tools for assessment of food consumption or nutrient intakes.

Intake or circulating concentrations of folate have been suggested to have an inverse association with the risk of depression in some (7-9), but not in all prospective studies (10-12). In clinical trials, antidepressant augmentation with methylfolate or folic acid has improved recovery from depression (13,14).

High consumption of fish or high intakes of polyunsaturated fatty acids (PUFAs), mainly long-chain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been suggested to decrease the risk of depression (15-18). This association has been found especially in women (17,18). However, there are only few prospective studies conducted, and only one study to assess the association between circulating concentrations of n-3 PUFAs and depression (19). In addition, the ratio of n-6 to n-3 PUFAs has increased in Western countries during the last decades (20), but there is a lack of prospective studies on the relation between the ratio of n-6 to n-3 PUFAs and the risk of depression. The results from the clinical trials slightly support possible treatment effects of n-3 fatty acids (21).

The role of coffee consumption on mental health has been conflicting; in large amounts and in sensitive individuals, caffeine may increase depressive symptoms. On the other hand, caffeine relieves feeling of fatigue, and in short term, may be beneficial to mood (22). High coffee consumption has been associated with a decreased risk of many chronic diseases, such as type 2 diabetes mellitus (T2D) and Alzheimer's disease (23). Nevertheless, there is a lack of prospective studies published on the association between coffee, tea or caffeine intake and the risk of depression.

In addition to studying single food items or nutrients, the whole-diet approach is recommendable. Healthy dietary patterns have previously been connected to the decreased risk of depression in prospective studies conducted in the United Kingdom (24) and Australia (25), whereas unhealthy or Western dietary patterns have been associated with an elevated risk of depression in United Kingdom (24) and in France (26). However, this area of research is still quite new. Dietary patterns differ between study populations, and there

are no previous studies published on the association between Finnish dietary patterns and depression.

The effects of lifestyle interventions, with a combination of diet and physical exercise, on depressive symptoms in non-clinical populations are still largely unknown. In theory, intensive lifestyle intervention should decrease depressive symptoms as the quality of diet improves (24), and increased physical activity usually improves mood (27). However, only few lifestyle intervention studies focusing on the change in depressive symptoms have been conducted.

Taken together, a review of the literature clearly shows that there is a need of research on the association between diet and depression. Many of the previous studies are cross-sectional, which may reflect more the disease's effect on eating behavior and diet than the opposite. The aim of this thesis was to assess prospectively the associations between selected dietary factors (folate, vitamin B_{12}, n-3 and n-6 PUFAs, coffee, tea and caffeine) and depression in a population-based sample of Finnish men. In addition, we wanted to investigate if dietary patterns are associated with the prevalent depressive symptoms or the risk of depression in Finnish men. Finally, the aim was to investigate if an intensive lifestyle intervention reduces depressive symptoms in middle-aged overweight men and women with impaired glucose tolerance (IGT).

2 Depression

2.1 PUBLIC HEALTH RELEVANCY

The lifetime prevalence of MDD has been estimated to be 15-16%, with a 12-month prevalence 6-7% in high income countries (1,2). In Finland, the prevalence of MDD is comparable to that found in other Western countries. In 2000, the 12-month prevalence of MDD was estimated to be 9% and the age-adjusted prevalences for females and males 11% and 7%, respectively, in Finnish population (28). In 2005, the 12-month prevalence of MDD, based on the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), was 8% for females and 5% for males (6.5% for the whole population) in the Finnish Health 2000 Study (29). The earlier study included also younger age groups (15-30 years) (28), whereas the Health 2000 Study included only individuals over 30 years of age (29). It is also seen that female gender associates with the elevated prevalence of MDD (2,28,29).

MDD is a recurrent disease and relapses are very common; 50% of the patients with one MDD episode have a relapse, and the recurrence rate is 90% for those with three or more occurrences. Among those who suffered from MDD within the last 12 months, about 30% (27% of the females and 36% of the males) reported multiple episodes (29). Due to this recurrent nature, MDD is listed in the second position after HIV/AIDS among diseases predicted to contribute to the global burden of diseases by 2030 (3). Since the year 1990, there has been a 37% increase in disability-adjusted life-years of MDD (4).

MDD impairs working ability, increases the number of sick-leave days and predicts disability pensions (30). By the end of 2011, the number of disability pensions in Finland due to depression had almost doubled since the 1990s (31). Nevertheless, the previously increasing trend has started to decline; in 2010, 4,100 people retired due to depression, whereas in the top year 2007 there were 4,700 people who took early retirement due to depression. At the end of 2010, altogether 38,000 Finnish individuals were listed as retired due to depression (31).

Public health relevancy of MDD is characterized by the increased risk of comorbid diseases and suicides. Depression increases the risk of common diseases, such as T2D, CVD and dementia (32-34), and substance-related disorders, panic disorder, eating disorders and personality disorders frequently co-occur with MDD (35). Altogether 7% of men and 4% of women with unipolar affective disorder, of which MDD is the most common, committed suicide after first psychiatric contact in Denmark (36). In Finland, depression causes about 600 to 700 people to commit suicide each year (37). Suicides are the most common cause of death among young women, and the second most common cause of death among young men (38). Therefore, the relevance of depression to public health, economic burden and quality of life is extensive.

2.2 ASSESSMENT OF DEPRESSION STATUS AND DEPRESSIVE SYMPTOMS

The definition and assessment of depression and depressive symptoms has been a challenge throughout the history of psychiatric medicine. Distinguishing clinically significant depressive symptoms that need treatment is demanding, because depressive feelings are universally experienced by everyone at some point of life as a natural reaction to stressful life events. Nevertheless, in MDD, sadness and depressed mood do not remit when the external cause of these emotions has vanished (39). In addition, classic severe depression often has no external expedite cause (39).

MDD is characterized by depressed mood, change in sleeping patterns and weight, feelings of worthlessness or guilt, fatigue, a loss of interest in previously enjoyable activities and concentration and finally, ideation of death or suicide (40). Currently, diagnosis is based on the tenth version of the International Classification of Diseases (ICD) (41) and the new DSM-5 diagnostic classification, developed by the American Psychiatric Association (35). The ICD-10 criteria for clinical depression are presented in **Table 1**. Clinical depression is categorized into mild depression (F32.0), moderate depression (F32.1) and severe depression (F32.2 and F32.3) according to the number of symptoms present. The criteria can also be applied in recurrent depression (F33), in which a depressive episode has occurred at least once before. Mild depression involves subjective suffering but functioning usually remains good. Moderate depression, on the other hand, weakens the ability to function, while severe depression causes massive loss of functioning and need for everyday help (40).

According to the DSM-5 criteria, MDD diagnosis is based on the presence of at least five of the following nine symptom categories: depressed mood, loss of interest or pleasure, significant weight loss (when not dieting) or weight gain or change in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, cognitive abnormality, and recurrent thoughts of death or suicidal ideation (35). Symptoms should have been current for at least two weeks, most of the day, nearly every day, and represent a change compared to previous state. One of the symptoms should be depressed mood or the loss of pleasure or interest. In addition, symptoms should cause clinically significant distress or impairment in the areas of functioning, and the state should not be attributable to other medical conditions or substance abuse. Different subtypes of depression have also been defined. Atypical depression is characterized by mood reactivity, severe fatigue, and increase in appetite or sleepiness. In melancholic subtype of depression, loss of interest and decrease in appetite or sleepiness are commonly present (35).

In addition to diagnostic instruments, depressive symptoms can be assessed using rating scales, which provide an assessment of symptom severity on an ordinal scale. Depression rating scales, like the Beck Depression Inventory (BDI) scale (42) (21-item version in Finnish is presented and explained in more detail in **Appendix 1** and in chapter 9.2.4) and the Finnish Depression Screening tool (DEPS) (43) are valuable in the screening of depressive symptoms, estimating of symptom prevalence and in the follow-up of MDD patients. The Patient Health Questionnaire (PHQ-9) is a brief questionnaire based on the previous DSM-IV criteria of MDD (44), and has also been shown to have diagnostic validity (45). Many depression rating scales are validated by a clinical interview, and for example the BDI has been found to be a valid instrument for the diagnosis of depression in adults (46). Some of the rating scales are self-administrated (BDI, DEPS, PHQ-9), while others are filled in by the interviewer, for example Montgomery-Åsberg Depression Rating Scale (47) and Hamilton Depression Rating Scale (HAM-D) (48). In addition, there is a group of other inventories that assess the depressive symptoms and are used especially for study purposes, like the Center for Epidemiological Studies Depression Scale (CES-D) or the Human Population

Laboratory (HPL) depression scale (49). The HPL depression scale is presented and explained in more detail in **Appendix 2** and in chapter 9.1.5 of this thesis.

2.3 DEVELOPMENT AND COURSE

The first episode of MDD usually appears between puberty and 30 years of age**,** but it can appear at any age (35). However, although not common, a first episode is also possible in the elderly. Especially the first depression episode is usually triggered by negative life events. During the next six months after a negative life event, the risk of getting MDD is multiplied, and is often verified by acute or chronic psychosocial stress (50). The course of MDD is highly variable; some individuals stay in remission for years between the episodes, whereas others rarely or never achieve remission. Remission is usually defined as a period of two or more months without any symptoms or with only one or two mild symptoms.

Two out of five individuals with MDD usually recover within three months, and four out of five, within one year. The risk of having multiple episodes of MDD is elevated in younger individuals, those having multiple episodes behind, and those with a severe preceding episode (35)**.** It is possible that the risk factors and pathogenesis of acute depression are different from those of recurrent or chronic depression, although it is known that a single episode of depression increases the risk of developing a second or more episodes during the whole life-time (39). As the duration of remission increases, the possibility of recurrence of MDD decreases progressively (35). Life without any symptoms is an important goal, as even mild depressive symptoms during remission increase the risk of recurrence.

2.4 RISK FACTORS AND PATHOGENESIS

It is probable that a number of pathways lead to MDD and causation of depression is probabilistic, not deterministic (51). Since the 1950s, the risk factors and pathogenesis of depression have been studied from a neurochemical perspective. Both biological, psychological, sociological, genetic and environmental mechanisms are present in the pathogenesis of depression (39).

Low socio-economic status (SES), short education, low income, disability, unemployment and marital status (being divorced or widowed) are associated with an elevated prevalence of MDD (2,29). Lifestyle factors, such as smoking, may independently increase the risk of MDD (52). Growing evidence indicates that physical inactivity is an independent risk factor for depression, and physical exercise may be protective for mental health (27). Childhood maltreatment and trauma in early life are also independent predictors of MDD. However, the influence of these risk factors is modulated by numerous other factors, such as genetic background, temperament, received care, age and reconstructive factors in later life (53). Interestingly, traumas and early experiences of heightened stress may cause long-term neuroendocrinological changes, which may represent adaptations (54). These neurobiological changes tend to increase the risk of depression in later life, especially during stressful life events (54,55). In addition to these functional changes, differences in brain structure have also been reported (54).

Table 1. The ICD-10 criteria for diagnostic of clinical depression (F32). (41)

Criteria for depression	**Symptoms**		**State of depression**	**Number of symptoms**
A. Symptoms have lasted at least for two weeks	Key symptoms:	Persistent sadness or low mood	Severe depression	≥7, all 3 key symptoms
B. Symptoms include at least two key symptoms		Loss of interest or pleasure		
C. Altogether at least four symptoms (incl. key symptoms) is considered clinical depression		Fatigue or low energy	Moderate depression	5-6
	Other symptoms:	Disturbed sleep		
		Poor or increased appetite	Mild depression	4
		Low self-confidence		
		Poor concentration or indecisiveness	Not depressed	<4
		Agitation or slowing of movements		
		Guilt or self-blame		
		Suicidal thoughts or acts		

Abbreviations: ICD, International Classification of Diseases

Susceptibility to depression is at least partly heritable, but the magnitude of genetic factors is still unknown. Approximations of heritability in MDD vary from 31% to 42%, which is substantially lower than in bipolar disorder or schizophrenia (39,51). Heritability may play a greater role when depression is severe, recurrent or has begun in early age (56). Susceptibility to depression is explained by multiple genes (39,51). There is also a gene-environmental interaction in depression; for example, a polymorphism in the promoter region of the serotonin transporter gene moderates the influence of stressful life events on depression (57).

There are several theories of the pathogenesis of depression, and these theories are not separate, but highly connected (58). The most common biological candidates of interest have been monoamines, adenoreceptors, the dopaminergic system, the function of the hypothalamus-pituitary-adrenal gland (HPA) axis, corticosteroids, neurotrophins and atrophy or resynthesization of neuronal cells (58,59). The following sections present the hypotheses of monoamines, inflammation, stress and neurogenesis, which are the most promising candidates to explain the association between diet and depression.

2.4.1 Monoamine hypothesis

The monoamine hypothesis, an earlier major theory of depression, is based on the presumption that abnormalities in the metabolism of the neurotransmitters serotonin and noradrenaline may cause depression (39). The serotonergic and noradrenergic systems are capable of modulating the brain areas involved in behavior, sleep, eating, feelings and thoughts. Especially the role of serotonin has been supposed to be central in the pathogenesis of depression. According to this theory, depression could be defeated by returning the serotonin levels in the central nervous system (CNS) back to normal (39). However, the monoamine hypothesis has been argued to be an insufficient approach to the etiology of depression, since typical monoamine-based antidepressant treatments have not been efficient enough, and the advantages of antidepressants to mood are seen only after several weeks of administration, not immediately (60).

2.4.2 Inflammation hypothesis

The first findings of the role of inflammation and cell-mediated immune activation in depression were reported already in the 1990s (61). Today, low-grade inflammation is believed to play an important role in the development of depression (62,63). Cytokines, secreted by macrophages as a result of the activation of sympathetic nervous system in stress, are proteins with either pro-inflammatory or anti-inflammatory effects (64). Depressed patients have been observed to have high blood C-reactive protein (CRP) levels, as well as elevated levels of plasma pro-inflammatory cytokines, like interleukin 1, interleukin-6, interleukin-2 and tumor necrosis factor-α (58,62,63). It has also been suggested that the serotonergic disturbances in depression could be a consequence of cell-mediated immune activation (62), and pro-inflammatory cytokines reduce the functions of neurotransmitters in CNS (64). The inflammation theory supports the bi-directional relationships between depression and other non-communicable diseases, such as obesity, T2D and CVD (33,65).

2.4.3 Stress hypothesis

The stress hypothesis suggests that prolonged mental stress causes depression by hyperactivity of the HPA axis (66). Chronic mental stress disturbs the regulation of the HPA axis and causes chronic inflammation (67). Nevertheless, not all individuals who encounter acute or prolonged mental stress become depressed. Approximately half of the depressed patients have hyperactivity of the HPA axis (68) and elevated levels of cortisol are also common (39). It is possible that chronic mild elevations of cortisol levels have a pathogenic role in depression (39). In depressed patients, the ability of cortisol to restrict the activity of HPA axis is reduced, which further reinforces the hyperactivity of the HPA axis

(64). In addition, hypersecretion of corticotrophin-releasing hormone and impairment in responsiveness to glucocorticoids are typical in depression (58). Interestingly, the biological manifestations of mental stress are similar to depression at the biological level (69). Cytokine effects on behavior are believed to be related in part to their effects on neuropeptide and neurotransmitter functions, synaptic plasticity and neuroendocrine function (66). Specifically, cytokines accelerate the HPA axis and thus reinforce the secretion of cortisol (67,70).

2.4.4 Neurogenesis and neural network hypothesis

Depression has been linked to impaired neurogenesis and information-processing dysfunction within neural networks (71,72). Hypersecretion of cortisol elevates the activation of type II glucocorticoid receptors, which in turn increases the activity of the neurotransmitter glutamate in CNS and may lead to the loss of neurons in hippocampus, a center of mood and memory (64). The challenges in adaptation of neural networks to environmental conditions possibly predispose to MDD (71,72). Brain-derived neurotrophic factor (BDNF) is a critical mediator of activity-dependent neuronal plasticity in the cerebral cortex and deficit of neurotrophic factors have been suggested to cause mood disorders (71). Peripheral levels of BDNF have been found to be decreased in depressed patients (58,73). The network hypothesis suggests that it is not the level of neurotrophins including BDNF alone and directly, but together with environmental conditions that guides neuronal networks to adapt better to the environment (71). The network hypothesis is also related to other hypotheses of depression as low-grade inflammation status and endothelial dysfunction both prevent the expression of BDNF (74).

In summary, the pathogenesis of depression is multifactorial and only partly understood. There are plenty of biological changes involved in depression. Nevertheless, regardless of several candidates, there is no certain positive biomarker of depression (75). The magnitude of multiple factors in the prevention and the therapeutic potential of other pathways are under investigation.

2.5 TREATMENT OF DEPRESSION

The treatment strategies of depression in Finland are presented in **Table 2.** Depression is most often treated with antidepressant medication, but response to treatment is inconsistent, as approximately 50% to 60% of MDD patients do not receive adequate response (39,76). Ineffective antidepressant treatment usually leads to administration of a second drug, either simultaneously or separately. On average, patients with mild or moderate symptoms benefit from antidepressant treatment only slightly, whereas benefits increase with the severity of depression (77). In addition to neurotransmitter properties, antidepressant medication also induces changes in inflammatory factors, neuronal connectivity and improvements in neuronal plasticity (72,78,79).

Psychotherapeutic treatments, such as cognitive-behavioral psychotherapy, psychodynamic psychotherapy or interpersonal psychotherapy, are effective in the treatment of depression (40). Psychotherapies have also been shown to be connected to the greater plasticity of the neural network in a few studies (80). To optimize the benefits, antidepressant and psychotherapy treatments should be given in combination (78).

Table 2. Severity of depression and treatment strategies in acute phase.

Treatment	Mild	Moderate	Severe	Psychotic
Antidepressant treatment	+	+	+	+
Psychotherapy	+	+	(+)	-
Antipsychotic treatment	-	-	-	+
Electrotherapy	-	-	+	+

Modified from Finnish Current Care Guidelines 2010 (40).

2.6 DIET AND DEPRESSION

Diet influences the biological and neurochemical actions in the body that may affect the development and progression of depression. Diet has been found to be involved in monoamine synthesis and inflammation, as well as to affect the HPA axis, neurogenesis and neural network functioning, for example by the effects on BDNF levels (58). Two most commonly studied nutrients possibly related to depression are folate (6,8) and n-3 PUFAs, especially EPA and DHA (6,17). In addition, several other nutrients, such as other group B vitamins, like vitamin B_6 and B_{12} (10), vitamin D (81), and the amino acid trypthophan (82), and foods like fish (18), olive oil (6), fruits and vegetables (83), and healthy (26) and unhealthy (24) dietary patterns have been connected to the risk of depression.

The association between folate deficiency and increased depression was already demonstrated in the 1960s. Victor Herbert showed that his self-induced elimination of folate from diet caused depressive symptoms, which disappeared when folate was reintroduced to the diet and folic acid supplementation was administrated (84). Since then, prospective studies have found an inverse association between folate intake (9) or serum concentrations of folate (7,8) and the risk of depression. Folate and vitamin B_{12} are involved in monoamine synthesis, and the potential effects of these vitamins on depression are probably mainly based on the monoamines (85). Based on the evidence from previous studies and the involvement in monoamine synthesis, folate and vitamin B_{12} were chosen to be studied in this thesis.

Interest in the relationship between n-3 PUFAs and depression was sparked based on ecological studies. Strong cross-national correlations between fish consumption and annual prevalence of MDD was demonstrated in the 1990s (86). From an ecological point of view, it could be hypothesized that the increasing incidence of MDD in many Western countries could be connected to the decline in n-3 PUFA intake from fish consumption (86). The neurobiological background, inflammatory effects and reciprocal associations between n-3 PUFAs, depression and CVD have supported the hypothesis. However, the causation between the phenomena is impossible to verify based on ecological findings. Prospective studies on fish consumption or n-3 PUFA intake have been conducted since then, with partly inconsistent results (15,17-19,87-90). Especially the magnitude of gender has been argued, as n-3 PUFAs have been suggested to be protective especially in women (17,18). Therefore, as a part of this thesis, we decided to study the association between n-3 PUFAs and the risk of depression in male population.

The prospective associations between coffee or tea consumption and depression are practically unstudied, with only a few cross-sectional studies published (91-93). Coffee consumption and caffeine intake have previously been found to associate with a decreased risk of chronic diseases including various cancers, T2D, Parkinsonism, and Alzheimer's disease (23). Therefore, coffee, as well as tea and caffeine, and their associations with the risk of depression were chosen to be studied in this thesis.

The most recent area of research on the subject has focused on the association between general, extensive dietary patterns and depression, and both protective and predisposing factors have been proposed (24,26,94). The dietary pattern area of research is fairly new, as all the largest studies have been published during the last five years (24-26,94-96). However, no previous studies on dietary patterns in Finnish population have been published. The work on dietary patterns and depression complemented well the coherent whole of this thesis.

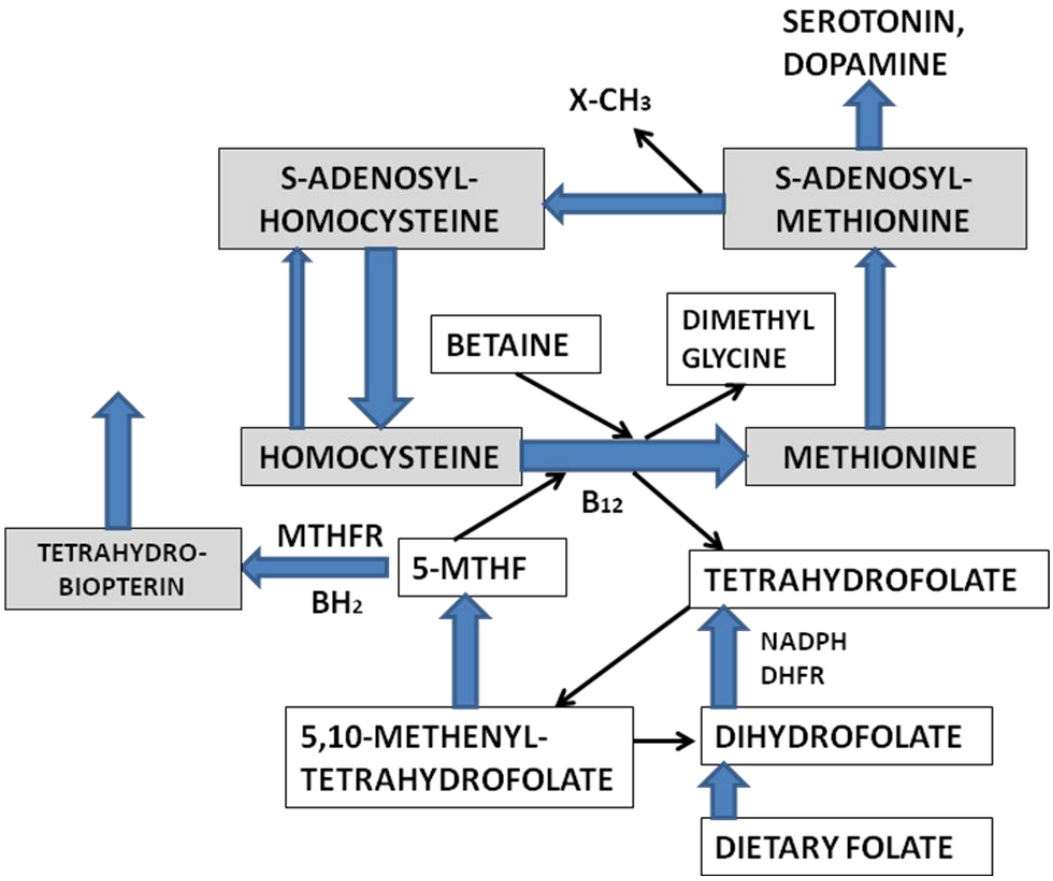
Finally, there is a lack of information of the effects of lifestyle-modified interventions on depressive symptoms. Therefore, we wanted to include a study on the effects of intensive three-year lifestyle intervention on the change in depressive symptoms in this thesis.

The following sections describe in more detail the selected dietary factors suggested to be associated with the risk of depression. Studies on MDD or depressive symptoms were included, whereas studies on prenatal, postpartum and bipolar depression were excluded. Moreover, intervention studies demonstrating the effects of lifestyle factors on depressive symptoms are introduced. In addition, the potential mechanisms that may explain the associations are presented.

3 Folate and vitamin B_{12}

3.1 FOLATE AND VITAMIN B_{12} METABOLISM

Folate and vitamin B_{12} (cobalamin) belong to the group B water-soluble vitamins. Folate presents in many forms, such as tetrahydrofolate and methylenetetrahydrofolate, or folic acid and folinic acid (the two synthesized forms of folate). Methyltetrahydrofolate (MTHF), also called L-methylfolate or levomefolic acid, is the bioavailable form of folate, and the only form that penetrates through the blood-brain barrier (13,97). Adequate intake of folate is important for the formation of the neural tube after conception of the fetus, development of the brain and nervous system, normal growth, nucleotide synthesis as well as programmed cell death (98,99). The metabolisms of folate and vitamin B_{12} are highly connected and both vitamins are essential in the remethylation processes of homocysteine (**Figure 1**).



Abbreviations: BH_2, quinonoid dihydrobiopterin; DHFR, dihydrofolate reductase; 5-MTHF, 5-methyltetrahydrofolate; MTHFR, methylenetetrahydrofolate reductase; NADPH, reduced form of nicotinamide adenine dinucleotide phosphate; $X\text{-}CH_3$, methyl group

Figure 1. Overview of the one-carbon metabolism, methylation cycles and monoamine metabolism. Modified from Reynolds et al. 2002 and Freeman et al. 2010 (100,101).

3.2 RECOMMENDATIONS AND DIETARY INTAKE

The recommendations for adequate daily folate intake suggest 300 μg for men and elderly women at population level (102). The recommendation for women of reproductive age is 400 μg daily. Energy-adjusted folate intake is recommended to be 45 μg/MJ of energy in all age groups. Folate can be found in dark green vegetables like spinach and broccoli, lentils, fruits, especially oranges, berries, beans, nuts, whole-grain products and liver. In Finnish general population, folate has mainly been derived from grain products (24%), fruits and berries (10%), meat (10%), milk (10%) and vegetables (9%) (103). It is noteworthy that folate is easily destroyed due to heating or oxygen, and folate compounds are also dissolved into boiling water during food preparation.

Folate is still one of the few vitamins Finnish people do not get enough of from their diet on population level (103). According to the National FINDIET 2007 survey, the mean daily folate intake in Finnish men and women was 270 μg and 226 μg, respectively. Also the elderly (65 to 74 years old) received less folate than recommended; men and women received 243 μg and 210 μg of folate daily, respectively. In addition, the energy-adjusted daily intakes of folate were lower than recommended in both men and women in all age groups, varying from 30 μg/MJ in working-aged men to 36 μg/MJ in elderly women (103).

The Finnish recommendation for daily vitamin B_{12} intake is 2.0 μg/day and 0.2 μg/MJ of energy (102). Vitamin B_{12} is mostly present in animal-based foods, and the most relevant sources of vitamin B_{12} in Finnish population are meat, fish, poultry, egg and dairy (103). The mean intake of vitamin B_{12} was 5.6/ μg/day and the energy-adjusted intake was 0.7 μg/MJ (103). On population level, vitamin B_{12} intake was sufficient in all age groups.

3.3 DEFICIENCY

Folate deficiency, which is one of the most common forms of vitamin deficiency in the world, is caused by low dietary intake, but also by improper absorption and decreased utilization (97). Certain gastro-intestinal diseases, alcohol consumption, smoking and several drugs, such as oral contraceptives, may predispose to deficiency (104). The symptoms of folate deficiency include nausea, irritability, insomnia, loss of appetite, diarrhea and muscular weakness. Macrocytic or megaloblastic anemia is caused by significant deficiency of folate for at least three months.

Genetic polymorphisms, like polymorphism in methylenetetrahydrofolate reductase (*MTHFR*) gene, affect the ability to metabolize folate and cause the lack of functional form of folate, MTHF (97). Approximately 10% of the population carries the *MTHFR* C677T TT genotype (105) and *MTHFR* C677T TT genotype, and to a lesser extent the C677T CT genotype, associated with an increase in the circulating serum concentrations of homocysteine and a decrease in serum concentrations of folate (106). This may lead to a potential reduction in monoamine neurotransmitter function as there is a similar reduction in MTHF in the CNS (106).

The reference range for serum concentrations of folate is 10.4-42.4 nmoles/L and for red-cell folate 1187-2854 nmol/L (107). Circulating concentrations of folate in serum or plasma reflect dietary intake during several weeks, and for example at the onset of a folate-deficient diet, it is seen that serum concentrations fall below normal in three to six weeks (108). However, red-cell concentrations reflect the intake and tissue stores of longer periods, at least months (109). In order to define folate deficiency, red-cell folate concentrations should be measured.

Deficiency of vitamin B_{12} is present in approximately 3-6% of population in Western countries and the prevalence of deficiency increases substantially in the elderly (110). Approximately 20% of older adults have marginal depletion of vitamin B_{12} in the United States of America (U.S.) and in United Kingdom (110). The vitamin B_{12} deficiency is usually

caused by the loss of an intrinsic factor, synthesized by the gastric cells. This state, called pernicious anemia, is most often driven by autoimmune atrophic gastritis (111). Reference range for plasma vitamin B_{12} concentrations is 140-490 picomoles/L, and serum active vitamin B_{12} concentrations should be >35 picomoles/L (107). In vitamin B_{12} deficiency, serum folate concentrations are usually normal or increased, whereas red-cell folate concentrations are low.

3.4 FOLATE, VITAMIN B_{12} AND DEPRESSION

In psychiatric patients, deficiency of folate affects as many as one-third of the individuals (112), which may be explained by disturbed appetite, lowered intake, altered absorption or increased requirement (5,97). Two thirds of individuals with megaloblastic anemia have been documented to have neuropsychiatric problems, and depression is the most common neuropsychiatric manifestation of folate deficiency (100). Depressed individuals have been observed to have lower circulating concentrations of folate (113-115) and lower intake or concentrations of vitamin B_{12} (116,117) compared to non-depressed individuals. However, even though low folate status and depression are connected, there is limited evidence concerning the direction of the association. The following sections present the cross-sectional studies and prospective studies clarifying the association. The most relevant studies for the assessment of the causality, intervention studies and clinical trials, are also presented.

3.4.1 Cross-sectional studies

The cross-sectional studies on the association between folate and depression are presented in **Table 3**. Most of the studies demonstrate an inverse association between folate intake or blood concentrations of folate and depression, and the majority of all studies were carried out in populations with elderly participants. However, energy intake may be a potential confounder of the association.

Dietary intake of folate and vitamin B_{12}

An inverse association between intake of folate and the prevalence of depression was observed in some (118-120), but not in all studies (121,122). The details of the study populations are presented in more detail in **Table 3**. Depressive symptoms may affect appetite and cause decreased intake of folate as a natural cause of disease. Nevertheless, only in two studies with no association (121,122) total energy intake was regarded as a potential confounder in the statistical models, which may explain the inconsistent results. One of the two studies with no association (90), was the largest of these studies with more than 27,000 smoking Finnish men. In the second largest of the studies, a study from the Mediterranean area, folate intake was inversely associated with the prevalence of depression, but only in smoking men. In addition, as regards vitamin B_{12}, high intake was related to lowered prevalence of depression in that study (123). However, in another Finnish study, a previous study based on the cohort studied in this thesis, an inverse association was shown even after adjustment for appetite, which is related to total energy intake (119). In that study, participants with elevated depressive symptoms had lower energy intake and poor appetite was more common compared to other participants. It has also been hypothesized that the association may differ according to the subtype of depression. Yet another study in Finnish adults showed that low dietary intake of folate associated with higher prevalence of melancholic depression, but no association with non-melancholic, atypical depression was observed (124). This cross-sectional association may be a natural result from decreased appetite related especially to melancholic symptoms of depression. In this study, however, neither total energy intake nor appetite was taken into account as a potential confounder.

Circulating concentrations of folate and vitamin B_{12}

The majority of the cross-sectional studies on the association between blood concentrations of folate and prevalence of depression demonstrated an inverse association (8,114,125-129). However, there are also few studies with no association detected (116,130-132). There were no observed differences in the age of the participants between the studies with an inverse association or no association. None of these studies included total energy intake as a potential confounder. Circulating concentrations of folate were also inversely associated with severity of depression in clinical population (133). Depression may differ from other mental illnesses, as depressed patients have been reported to have lower blood concentrations of folate compared to other psychiatric illnesses, such as bipolar disorder or schizophrenia, and the concentrations were as low as in patients with alcoholism (133).

Moreover, several studies have reported an inverse association between blood concentrations of vitamin B_{12} and depression. Deficiency of vitamin B_{12} was associated with an elevated prevalence of depression in Dutch middle-aged or older men and women (132), in Chinese elderly (114) and in elderly North-American women (131). In contrast, another North-American study in younger participants from general population (127) and a Norwegian study in middle-aged or older adults (129) reported no association. However, it has been suggested that the risk of depression may be elevated especially in the elderly, and already at plasma vitamin B_{12} concentrations under 250 picomoles/L, which is in the reference range (>140 picomoles/L) (134). In addition, high serum concentrations of vitamin B_{12}, but not red-cell concentrations of folate, have also been found to associate with improved recovery from MDD in Finnish 21- to 69-year-old outpatients (135).

3.4.2 Prospective studies

Only few prospective studies with inconsistent results have been published on the association between folate and depression (**Table 4**). Studies have mainly investigated the circulating concentrations of folate, whereas to date, only two studies have been published on dietary folate and depression in general population (9,10). The relation between folate and depression has been suggested to be shown especially in aging populations (100), but recent prospective studies do not support the hypothesis. Heterogeneity between the studies is large, which complicates the interpretation of the results.

Dietary intake of folate and vitamin B_{12}

No association was detected between energy-adjusted intake of folate and the risk of depression in 3,503 North American elderly men and women (10). Dietary intake from long FFQs and total folate intake including supplementation were studied separately and summarized. Neither dietary intake nor total intake associated with the risk of depression. Separate analyses may be regarded as a strength of this study. However, total energy intake was not adjusted for in the statistical models. In the French Supplémentation en Vitamines et Minéraux Antioxydants Study (SU.VI.MAX) cohort with almost 2,000 middle-aged participants, an inverse association was found between the intake of folate and the risk of recurrent depression, but only in men (9). Furthermore, no associations were found for the risk of any depressive episode, or a single depressive episode. These results support the hypothesis that sufficient intake of folate would be beneficial especially in the prevention of recurrent depression episodes. Repeated measurements of food intake, six 24-hour diet records during the first two years of the study, were used to assess folate intake. Though the 24-hour diet record method as such is not valid for assessing individuals' habitual diet due to large within-person variation in food intake, it has been stated that if collected over a long period, as in this study, it is a proper measurement of usual intake (136).

Table 3. Cross-sectional studies on the association between folate and depression. Studies are mainly population studies.

Study by	Study population	Age (years)	Number of depressed	Folate measured	Results
				Diet	
Tolmunen et al. 2003 (119)	2443 men from Eastern-Finland	42-60	228	4-day food record	Low intake of energy-adjusted folate was associated with occurrence of elevated depressive symptoms.
Hakkarainen et al. 2004 (121)	27,111 smoking Finnish men	50-69	4316	276-item FFQ	Energy-adjusted folate intake was not associated with the self-reported depressed mood.
Murakami et al. 2008 (118)	517 Japanese workers (309 men, 208 women)	21-67	188	56-item FFQ	Higher energy-adjusted intake of folate was associated with a lower prevalence of depressive symptoms in men, but not in women.
Kamphuis et al. 2008 (122)	332 Dutch men	70-90	72	Long FFQ	No association between energy-adjusted intake of folate and prevalence of depressive symptoms.
Sanchez-Villegas et al. 2009 (120)	9670 Spanish university graduates (4211 men, 5459 women)	18-70	363	136-item FFQ	Intake of folate was inversely associated with the prevalence of depression only in smoking men and men with low anxiety levels.
Seppälä et al. 2012 (124)	2806 Finnish individuals (1328 men, 1478 women)	45-74	429	132-item FFQ	Low energy-adjusted folate intake was associated with melancholic depression, but not with non-melancholic depression.
				Blood	
Ebly et al. 1998 (125)	1771 Canadian men and women	≥65	199	Serum	Low serum folate was associated with depression.
Lindeman et al. 2000 (130)	1130 North-American men and women	≥65	n/a	Serum	Low serum folate was associated with impaired cognitive function, but not with depression.
Penninx et al. 2000 (131)	700 North-American disabled, non-demented women	>65	222	Serum	Serum folate or folate deficiency were not associated with depression.
Tiemeier et al. 2002 (132)	3884 Dutch men and women, among whom chosen 278 depressed subjects and 416 randomly selected controls	>55	278	Serum	No associations between serum folate and depression.
Sachdev et al. 2005 (126)	412 community-dwelling Australian men and women	60-64	58	Serum	Low serum folate was associated with increased depressive symptoms.

Table 3 to be continued

Table 3 continues

Study by	Study population	Age (years)		Folate measured	Results
				Blood	
Ng et al. 2009 (114)	669 community-living Chinese (255 men, 414 women)	65 (mean)	178	Serum	Low serum folate was associated with greater prevalence of depressive symptoms.
Robinson et al. 2011 (116)	244 healthy community-dwelling Irish elderly (109 men, 135 women)	78 (mean)	35	Serum	No association between serum folate and depressive symptoms.
Nanri et al. 2012 (8)	545 Japanese employees (319 men, 226 women)	21-67	159	Serum	Serum folate was inversely associated with the prevalence of depressive symptoms
Morris et al. 2003 (127)	2948 North-American men and women	15-39	301	Serum Red-cell	Low red-cell or serum folate was associated with life-time depression diagnoses.
Ramos et al. 2004 (128)	1510 mainly Latin-Americans (627 men, 883 women)	>60	378	Plasma	Low plasma folate was associated with depression in women but not in men.
Bjelland et al. 2003 (129)	5948 Norwegian men and women	46–49 or 70–74	243	Plasma	High folate concentrations decreased the likelihood of depression only in a sub-group of middle-aged women.

Abbreviations: FFQ, food frequency questionnaire

In addition, the use of total energy intake as a potential confounder in the statistical models may be regarded as a strength. Both studies had long duration of follow-up, seven and eight years, respectively. There were no large differences between the mean intake of folate between the study populations: the range of the second folate tertile was 263 to 397 μg/day in the North American study (10) and the mean in the second folate tertile was 336 μg/day in the French study (9).

The North American study described above was the only prospective work to demonstrate an association between vitamin B_{12} and the risk of depression; high total intake of vitamin B_{12} (summarized from both diet and supplements) was shown to be inversely associated with depressive symptoms, whereas pure dietary intake of vitamin B_{12} was not (10). More specifically, each additional 10 μg of vitamin B_{12} derived from foods and supplements associated with a 2% lower likelihood of developing depressive symptoms (10). The result was explained by the impaired bioavailability and absorption of vitamin B_{12} from dietary intake, as these are suggested to be diminished in the elderly.

Circulating concentrations of folate and vitamin B_{12}

An inverse association between serum concentrations of folate and the risk of depression was demonstrated in elderly Korean men and women (7) and in Japanese employees (8). In contrast, the largest of these studies, a study in young women in the United Kingdom measuring red-cell folate concentrations (11) and other in elderly European men and women measuring plasma folate concentrations (12) found no associations. In the Korean study with an inverse association (7), the mean serum concentration of folate was 24.2 nmol/L for the whole study population, which is high, whereas in the Japanese study with an inverse association, mean serum concentrations of folate were lower, 3.9 nmol/L in the lowest tertile and 9.7 nmol/L in the highest tertile of folate concentrations (8). In a multinational European study with no association, the mean plasma concentrations of folate varied between study centers from 12.0 nmol/L to 18.4 nmol/L (12). Unfortunately, there is no information available of the mean concentrations or the range of red-cell concentrations of folate in another study with no association (11). Red-cells reflect the intake over a longer period, even months of folate intake compared to plasma or serum concentrations, but the blood measurement, as well as other characteristics, such as age or gender, hardly explained the inconsistency in the results. In addition, energy intake was not taken into account as a potential confounder in these studies.

A meta-analysis based on observational studies (three case-control studies, seven population surveys and one cohort study) concluded that there is a statistically significant association between folate status and depression (85). However, this meta-analysis was published already in 2007, and the majority of the prospective studies have been published since then. Unfortunately, recent meta-analyses are lacking.

Table 4. Prospective population studies on the association between folate and the risk of depression.

Study by	**Study population**	**No of subjects (M/W)**	**Age (years)**	**Follow-up years**	**Depr. measured by**	**No of cases (%)**	**Folate measured by**	**Comparison**	**Results, adjusted *HRs/ORs (95% CI)***
Astorg et al. 2008 (9)	French SU.VI.MAX cohort	1864 (809/1055)	M 45-60, W 35-60	8	Number of AD	31 (4%) men had number of AD>1	Dietary intake (six 24-h food records)	3rd tertile mean 443 vs. 1st tertile mean 241 µg/day	Any depressive episode in M: 0.81 (0.39, 1.70) Any depressive episode in W: 0.91 (0.57, 1.45) Recurrent depression in M: 0.25 (0.06, 0.98)
Skarupski et al. 2010 (10)	U.S. elderly, Chicago Health and Aging Project	3503 (M 41%, W 59%)	≥65	7	CES-D	471 (14%)	Dietary intake (139-item FFQ) Total intake (diet + supplem.)	n/a >379 vs. <263 µg/day	0.76 (0.99, 1.00) 0.91 (0.99. 1.00)
Eussen et al. 2002 (12)	Elderly European men and women	586 (265/321)	70-75	5	GDS	54 (9%)	Plasma folate	Correlation between depression scores and folate status	No correlation; r=-0.068, P=0.116
Kendrick et al. 2008 (11)	Women from United Kingdom	W 2732	20-34	2	GHQ-12	307 (11%)	Red-cell folate	<550 vs. >1150 nmol/L	1.00 (0.97, 1.03)
Kim et al. 2008 (7)	Korean men and women	521 (234/287)	>65	2	GMSS	n/a	Serum folate	Lowest quintile vs. highest quintile Folate deficiency <11.4 vs. no-deficiency >11.4 nmol/L	1.31 (1.07, 1.61) 1.32 (0.49, 3.54)
Nanri et al. 2012 (8)	Japanese employees	272 (164/108)	21-67	3	CES-D	45 (17%)	Serum folate	9.7 vs. 3.9 ng/mL	0.36 (0.20, 0.63)

Abbreviations: AD, antidepressant prescriptions; CES-D, Center for Epidemiological Studies Depression Scale; CI, confidence interval; GDS, Geriatric Depression Scale; GHQ, General Health Questionnaire; GMSS, Geriatric Mental State Schedule; FFQ, food frequency questionnaire; HR, hazard ratio; M, men; n/a, not available; OR, odds ratio; SU.VI.MAX, The Supplémentation en Vitamines et Minéraux Antioxydants Study; U.S., The United States of America; W, women

3.4.3 Intervention studies

Prevention trials

To date, there are only three double-blind randomized controlled trials (RCTs) published to demonstrate the effects of group B vitamin supplementations, including folate and vitamin B_{12}, on the prevention of depression in non-depressed individuals. In a recent trial, daily supplementation with MTHF (560 μg), vitamin B_{12} (20 μg) and vitamin B_6 (3 mg) for almost five years showed no beneficial effect on depressive symptoms (adjusted odds ratio (*OR*): 0.91, 95% *CI*: 0.75 to 1.11) in 2,000 men and women who were CVD survivors (137). In a trial with 299 elderly men free from clinically significant depressive symptoms, daily supplementation of folic acid (2 mg), vitamin B_{12} (400 μg), and vitamin B_6 (25 mg) for two years did not show benefits in either reducing the severity of depressive symptoms or in reducing the incidence of depression compared to placebo (138). However, it was found that participants treated with vitamins were 24% more likely to remain free of depression during the trial, although the difference between the groups was not statistically significant (95% *CI*: 0.68 to 2.28). The third trial in 273 non-depressed men who were stroke survivors observed that daily supplementation of folic acid (2 mg), vitamin B_{12} (500 μg) and vitamin B_6 (25 mg) for approximately seven years decreased the risk of MDD with 52% (95% *CI*: 0.31 to 0.76) compared to placebo**,** which supports the evidence of the benefits (139). Such inconsistencies in the results could have occurred because of differences in dosage (in vitamin B_{12} the range was from 20 to 500 μg/daily between the trials), duration (two to seven years), or study population (high-risk individuals vs. others) between the trials.

There are also few short RCTs to demonstrate the effects of multivitamin and mineral supplementations, including folic acid and vitamin B_{12}, on depressive symptoms in healthy adults (140,141). Recently, a meta-analysis based on these RCTs and one unpublished trial (142), all conducted in male populations with supplementation durations of a maximum of eight weeks, showed no benefits on depressive symptoms (143). However, in addition to folic acid and vitamin B_{12}, which were delivered at doses above the recommended daily intakes, these supplementations included various other vitamins, as well as minerals, such as zinc, calcium and magnesium (141), herbal extracts and antioxidants (140) and DHA (142).

Treatment trials

Several trials (presented in **Table 5)** have demonstrated that antidepressant treatment augmentation with MTHF, folic acid or folinic acid (leucovorin) has improved the recovery from depression (13,14,144-148). However, one of these studies was not randomized (146). Based on the trials, MTHF is suggested to be the most effective form of folate supplementation compared to others, probably because it is able to pierce the blood-brain barrier. However, the study with the longest duration, two years, suggested no statistically significant benefit of supplementation with a combination of folic acid and vitamin B_{12} in participants with elevated psychological distress in non-clinical population, in which only one fifth of the participants used antidepressant medication (149). The duration of the other trials has been short, mainly weeks, apart from one study with a duration of six months (144). Remission in depression may occur gradually after weeks of treatment, which is why adequate duration of augmentation is necessary. It is also unknown whether the effectiveness of augmentation is antidepressant-specific, and; the benefits of folate augmentation on for example serotonin selective reuptake inhibitors (SSRIs) may therefore not necessarily be applicable to other types of antidepressants (13). Interestingly, MTHF or folic acid supplementation may benefit not only those who have low concentrations of folate, but also those whose concentrations of folate are at reference level (150).

A Cochrane analysis based on three RCTs (14,144,145) concluded that MTHF or folic acid supplementation as an augmentation treatment may be beneficial for depressed individuals

(151). Supplementation decreased depression scores on average by a further 2.65 points (95% CI: -0.38 to -4.93). In two of the trials (14,144) supplementation was added to antidepressant treatment, whereas in one (145) MTHF was delivered as an exclusive treatment and compared to trazodone. However, no evidence for efficacy as monotherapy was demonstrated (151). The meta-analysis was published already in 2003, which is why the most recent studies were not included.

In summary, the limited number of trials to study prevention of depression with supplementations including folate and vitamin B_{12}, have reported inconsistent results. In prevention trials, supplementation studies with long duration included altogether 2,572 participants, and short multivitamin and mineral supplementation RCTs only 303 participants. In treatment trials, evidence shows a slight benefit of augmentation of antidepressant treatment with MTHF or folic acid in depressed patients, but the limited number of studies constricts the precision of the results. Altogether 1,417 participants have been involved in treatment trials, 900 out of them taking part in trials concerning non-clinical population (149). Additional investigations are needed also to characterize those individuals who are the most responsive to augmentation.

3.4.4 Potential mechanisms

The potential protective effects of folate and vitamin B_{12} on depression are mainly based on the monoamine hypothesis. Deficiency of folate can cause irregularities in methylation and synthesis of monoamine neurotransmitters (152). Monoamine synthesis is presented in **Figure 1**. Folate forms share an interconversion potential and are present in the pathways of one-carbon cycles impacting the synthesis of norepinephrine, dopamine and serotonin (13,85,152). In detail, MTHF regulates the formation of tetrahydrobiopterin, which is a critical cofactor essential in the synthesis of neurotransmitters (13). MTHF indirectly regulates the levels of monoamines in CNS as deficiency of folate impairs the synthesis of tetrahydrobiopterin (114). However, these reactions in CNS are also dependent on the availability of B_{12} and homocysteine.

Folate in MTHF form is needed in the methylation reactions to reverse homocysteine, a sulphurated amino acid, back to methionine (**Figure 1**) (152)**.** Homocysteine is derived from dietary methionine, which is present in meat, fish, cheese, eggs and poultry (153). Elevated blood homocysteine is a functional marker of both folate and vitamin B_{12} deficiency (154). Homocysteine concentrations are usually higher among elderly people and in men compared to women (153). In addition to the influence on the monoamine metabolism, homocysteine is suggested to have neurotoxic effects (152). High blood concentrations of homocysteine have been associated with elevated prevalence of depression (129,154,155). Nevertheless, as low blood concentrations of folate, vitamin B_{12} and high blood concentrations of homocysteine are highly connected, it is difficult to distinguish which of them is more important in terms of depression (129).

MTHF is also required in the synthesis of S-adenosyl-methionine (SAMe), the vital methyl donor in several methylation reactions (**Figure 1**) (152,154). SAMe has been suggested to have independent antidepressant properties and to be more effective than placebo and equally effective with tricyclic antidepressants with fewer side effects in the treatment of depression (101,152,156,157). The dose-response rate and mechanisms behind SAMe's possible effects on depressive symptoms are still partly unrecognized, and hence SAMe is regarded with caution.

Table 5. Clinical trials on supplementation effects of folate or folic acid on depressive symptoms. Studies are mainly based on augmentation of antidepressant treatment with methyltetrahydrofolate or folic acid.

Study by	Study population	Participants (men/women)	Age (y)	Supplementation /day	Duration	Results
Godfrey et al. 1990 (144)	24 patients with MDD, who had low (<200 µg/L) concentrations of red-cell folate	11/13	20-70	MTHF 15 mg	6 months	Augmentation improved treatment effect statistically significantly compared to placebo.
Passeri et al. 1993 (145)	96 severely depressed patients with dementia, normal concentrations of red-cell folate	n/a	>65	MTHF 50 mg or trazodone medication 100 mg/day	8 weeks	Methylfolate was as effective as trazodone.
Guaraldi et al. 1993 (146)	16 elderly depressed patients, no other psychotropic medication. Not a randomized controlled trial.	n/a	Elderly	MTHF 50 mg	4 weeks	Supplementation improved depressive symptoms statistically significantly, 81% of considered responders.
Coppen and Bailey 2000 (14)	109 subjects with MDD, fluoxetine medication	40/69	>18	Folic acid 500 µg	10 weeks	Augmentation improved mood more compared to fluoxetine only in females.
Alpert et al. 2002 (147)	22 subjects with partial or no response to SSRI, no folate deficient patients	9/13	26-68	Folinic acid (leucovorin) 15-30 mg	8 weeks	Augmentation improved mood statistically significantly, 31% of subjects achieved a response, 19% remission. No placebo group.

Table 5 to be continued

Table 5 continues

Study	Study population	Participants (men/women)	Age (y)	Supplementation /day	Duration	Results
Resler et al. 2008 (148)	27 depressed patients with fluoxetine medication and 15 healthy subjects	4/23	21-58	Folic acid 10 mg	6 weeks	Depression scores decreased statistically significantly more in supplementation group.
Christensen et al. 2011 (149)	900 participants with elevated psychological distress, 23% reported antidepressant use	358/542	60-74	Folic acid 400 µg + vitamin B_{12} 100 µg	2 years	No statistically significant differences between the groups.
Papagostas et al. 2012 (13)	Trial one: 148 SSRI-resistant out-patients	45/103	18-65	7.5 mg of MTHF for 30 days followed by 15 mg for 30 days or placebo for 30 days followed by MTHF 7.5 mg for 30 days or pure placebo.	60 days	No statistically significant differences between the groups.
	Trial two: 75 SSRI-resistant out-patients	22/53	18-65	Identical to trial one except that dosage was 15 mg of MTHF during both 30-day periods.	60 days	Augmentation with 15 mg of MTHF showed statistically significantly greater efficacy.

Abbreviations: MDD, major depressive disorder; MTHF, methyltetrahydrofolate; n/a, not available; SSRI, serotonin selective reuptake inhibitors; y, year

3.4.5 Dietary therapy with folate or vitamin B_{12} in depression

Based on treatment RCTs, evidence suggests potential benefits of antidepressant augmentation with MTHF or folic acid, and several treatment strategies have been suggested (104,134,154,158). These strategies may be utilized, as more than half of the depressed patients treated with antidepressant monotherapy will fail to experience remission (39), and dietary supplementation is considered safe and well-tolerated.

The first screening and treatment strategy is to measure the blood concentrations of folate and vitamin B_{12} of all depressed patients with treatment resistance (158). Augmentation is given to those whose concentrations are below the reference values or close to the reference border (158). However, in populations with normal concentrations of folate, routine screening of folate concentrations is hardly to be indicated (109). The second approach is to measure blood folate and vitamin B_{12} concentrations of all depressed individuals, and supplementation is recommended for those whose concentrations of vitamins are decreased or close to the borderline (134). It is also recommended for psychiatric patients to assess vitamin status every three to five years because changes in diet or drug treatments may lead to deficiencies. The third strategy is to examine concentrations of folate in patients with severe or chronic depression, patients with treatment resistance, as well as in the individuals at elevated risk for folate deficiency (104). The fourth treatment approach is to give supplementation (folic acid 800 μg/day and vitamin B_{12} 1 mg/day) to all depressed patients as an adjunctive treatment, as in part of the augmentation studies treatment effect has increased regardless of the vitamin levels (154). It has been observed that especially those who have recently recovered from depression may have a deficiency of folate (127), and folate intake has been inversely associated especially with the risk of recurrent depression (9). Consequently, folic acid supplementation has been recommended for as long as a year following a depressive episode (127).

There are no general recommendations of the dosage of supplementation presented. However, it is assumed that smaller doses of folic acid from 800 μg up to two milligrams are preferable to bigger doses, as the blood-brain barrier limits the entry of folate to the CNS and large doses would go to waste (104,154). Large doses may also lead to neurological problems, such as hyperactivity and insomnia among individuals who are predisposed. In addition, large doses may conceal a potential deficiency of vitamin B_{12} (104).

In summary of the association between folate and depression: there are several cross-sectional, but only few prospective studies published. The majority of the cross-sectional studies were conducted in the elderly, and the magnitude of energy intake as a confounder was shown to be significant. Two out of six prospective studies showed an inverse association between folate and the risk of depression, three studies showed no association, and one study showed an inverse association only with recurrent depression only in men. Only two of the previous prospective studies investigated the association between dietary folate and the risk of depression, one of them with models adjusted for energy intake. Results from the prevention trials suggest no benefits, but treatment trials indicate that MTHF or folic acid augmentation of antidepressant medication may benefit depressed patients. However, the number of the studies is limited.

4 N-3 polyunsaturated fatty acids

4.1 N-3 POLYUNSATURATED FATTY ACID METABOLISM

PUFAs are typically classified into n-3 (or omega-3) and n-6 (or omega-6) fatty acids. N-3 PUFAs are a family of PUFAs, named due to the positioning of the first double carbon bond on the third atom from the methyl end of the acyl chain (159). The role of the n-3 PUFAs is important in the development of the nervous system, blood vessels and skin (160). Moreover, n-3 PUFAs are present in the synthesis of eicosanoids and needed in the aggregation of thrombocytes, regulation of blood pressure and inflammation, and defense reactions of the body (159,160). In addition, long-chain PUFAs are needed in the cell membranes of CNS and retina of the eyes (160).

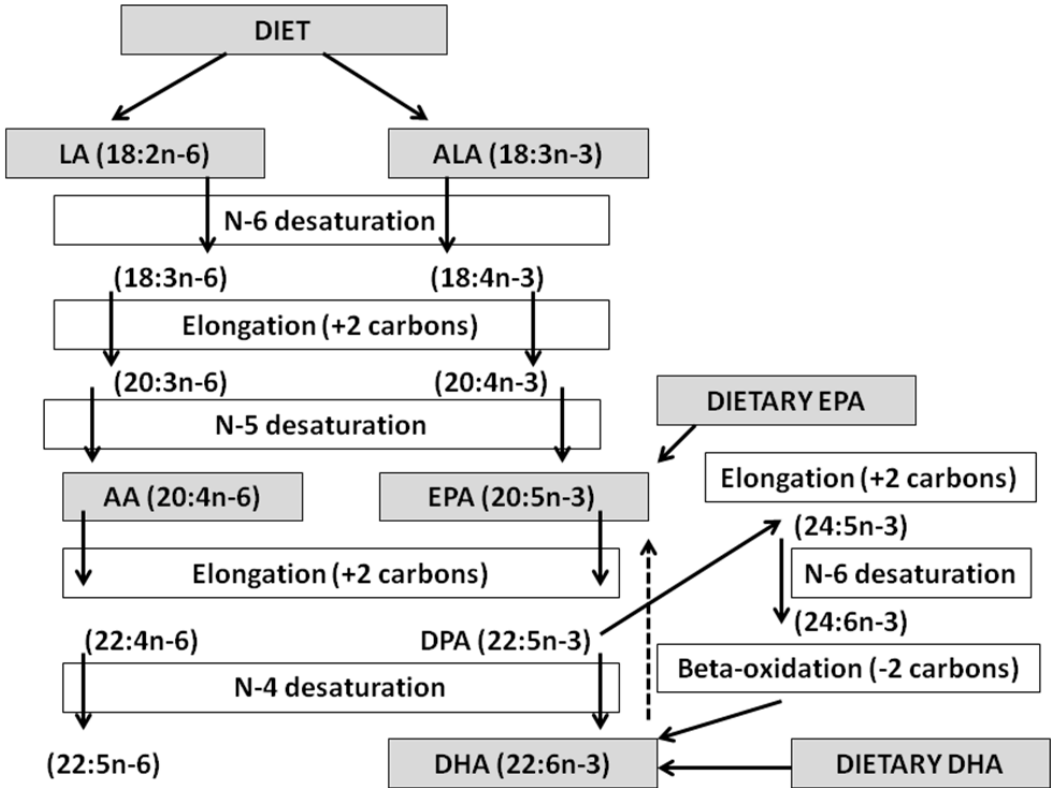
The long-chain n-3 PUFAs, EPA and DHA, are the major bioactive components of n-3 PUFAs, but also docosapentaenoic acid (DPA), which is in a minor role, is included in the long-chain n-3 PUFAs (161). The conversion of the long-chain PUFAs is presented in **Figure 2**. Alpha-linolenic acid (ALA) can be endogenously converted to 20-carbon EPA and further to 22-carbon DHA. However, current evidence suggests that this synthesis is not that effective and the rate of conversion in human is very low. Conversion of ALA to EPA is considered to be more effective compared to conversion of ALA to DHA, and it is estimated that approximately 4% to 15% of ALA from plant sources is converted to EPA or DHA (162-164). This conversion is suggested to be more efficient in women compared to men and in younger compared to elderly people (165,166). In addition, the intake of n-6 fatty acid arachidonic acid (AA) affects the production of EPA and DHA, as it competes for the same metabolizing enzymes (161).

4.2 RECOMMENDATIONS AND DIETARY INTAKE

The Finnish dietary recommendations suggest that at least one percent of total energy intake should be accounted for by n-3 PUFAs at population level (102). According to the National FINDIET 2007 survey Finnish people in general reach the recommended level of intake; the mean daily intake of n-3 PUFAs was 1.2% of energy for both women and men (103). Among the elderly, n-3 PUFA intake was even higher, 1.3% of total energy intake. However, the greatest proportion of the mean n-3 PUFA intake was from ALA intake (1.0% of total energy intake) (103).

Dietary sources of EPA and DHA include fatty fish like salmon, mackerel, herring, Baltic herring or vendace and other seafood, and certain eggs and animal products depending on the animals' diet (159). Fish oil supplements are also a good source of long-chain n-3 PUFAs. Plant-based n-3 PUFAs, especially in flaxseed, hempseed, walnuts and rapeseed oil, are usually in the form of ALA. ALA and linoleic acid (LA), which is an n-6 fatty acid, and mainly derived from plant and vegetable seeds and oils, are termed essential fatty acids, because human cells are unable to synthesize them.

The biomarkers of fatty fish consumption and intake of n-3 PUFAs include serum, plasma, red-cell or adipose tissue fatty acid concentrations. Fatty acid concentrations in triglycerides and free fatty acids are the most rapid to reflect the intake, showing concentration changes just hours after fatty acid intake (136). Plasma or serum cholesterol-esters reflect quite recent intake of fatty acids, usually one to two weeks of intake, while phospholipids reflect few weeks' longer intake before blood sampling. Fatty acid biomarkers from red-cell membranes reflect the intake over the past months while adipose tissue reflects longer-term intakes, even over years (19,136).



Abbreviations: AA, arachidonic acid; ALA, alpha-linolenic acid; EPA, eicosapentaenoic acid; LA, linoleic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid

Figure 2. Desaturation, elongation and retroconversion of polyunsaturated fatty acids. Modified from Holub et al. 2002 (162).

4.3 N-3 FATTY ACIDS AND DEPRESSION

Increasing evidence suggests that depletion of n-3 PUFAs may play an etiological role in several inflammatory and neuropsychiatric disorders including depression (167). Depressed individuals have been shown to have lower intake or concentrations of n-3 PUFAs compared to non-depressed individuals in some (168-171), but not in all studies (89,121). To clarify if n-3 PUFAs are potential protective nutrients against depression, following sections review the studies of the association between fish consumption or n-3 PUFAs and depression, concentrating on the long-chain n-3 PUFAs, EPA and DHA.

4.3.1 Cross-sectional studies

Consumption of fish and dietary intake of n-3 PUFAs

Fish consumption has been associated with lower prevalence of depression or psychological distress in several (16,172-176), but not in all studies (177,178). In most of these studies, fish consumption has been assessed by validated, long FFQs. In cross-sectional studies, however, the presence of depressive symptoms may affect appetite and food consumption, and hence, cause lower intake of n-3 PUFAs, which may in turn cause reverse causality. Therefore, cross-sectional studies alone are not good enough for assessing the risk. The greatest difference between the studies with observed association and studies with no association was that total energy intake was not taken into account as a potential confounder in the studies with observed association, except for a small study in 332 Dutch elderly men (174). In contrast, in both of the studies with no association (177,178) energy intake was adjusted for in the statistical models.

The largest of these studies with more than 10,000 middle-aged men from Northern Ireland and France showed that depressed mood was associated with a lower fish intake, but as fish intake increased, the incremental decrease in depressed mood was reduced (16). Studies in Finnish adults showed that regular (at least once a week) fish consumption associated with lower prevalence of depressive symptoms especially (172) or only (173) in women. The number of study participants was almost 3,000 and over 6,000, respectively. However, there is great heterogeneity in the frequency or amount of fish consumption in which the benefits have been observed. Consumption of ≥20 grams of fish daily was associated with a 37% lower likelihood of depressive symptoms compared to no fish consumption in Dutch elderly men (174), whereas in over 4,600 adults from New Zealand (175), fish consumption was examined as a dichotomous variable (yes/no), and an inverse association was found. One portion increase in fish consumption per week associated with 42% lower likelihood of having clinically relevant depressive symptoms in 1,200 elderly men and women from the Mediterranean area (176). In contrast, the large North American National Health and Nutrition Examination Survey (NHANES) with more than 10,000 participants demonstrated that all fish and non-breaded fish consumption, measured by 30-day FFQs, was not associated with symptom severity, while consumption of breaded fish showed an elevated risk of symptom severity (177). Similarly, a Finnish study with 5,840 men and women from general population and 308 high-fish-consumers demonstrated no associations between fish consumption and psychological distress (178). However, as previously stated, total energy was taken into account as a potential confounder in both of these studies with no associations.

Cross-sectional studies have also shown an association between a low intake of n-3 PUFAs and increased prevalence of depression in over 10,000 participants from the NHANES population (177), in almost 3,000 participants from the SU.VI.MAX cohort (87), and in 332 Dutch elderly men (174). However, in the NHANES study, intake of long-chain n-3 PUFAs was assessed by only two 24-h diet recalls (DR), which may not represent a valid method for the assessment of usual fatty acid intake. In contrast, a population study in almost 10,000 individuals from the Mediterranean area showed no association between n-3 PUFA intake and the likelihood of depression in men, although a protective trend was observed in women (179). The differences between these studies include that energy intake was taken into account as a potential confounder in three (174,177,179), but not in one study (87). However, there were no large differences in the intake level of n-3 PUFAs between the study populations that would explain the inconsistency. Nevertheless, in the SU.VI.MAX cohort, the intakes of n-3 PUFAs were relatively high (mean in the lowest quartile 0.9 g/day vs. mean in the highest quartile 1.8 g/day), and in the study from the Mediterranean area, the variation between n-3 PUFA intake was large (mean in the lowest quintile 0.4 g/day vs. mean in the highest quintile 1.9 g/day) (179).

Circulating and adipose tissue concentrations of n-3 PUFAs
Depressed individuals have been reported to have lower circulating concentrations of n-3 PUFAs (169,180-184) and reduced adipose tissue levels of DHA (185) compared to non-depressed individuals. Lower n-3 PUFA concentrations resulted from significantly lower DHA concentrations (169,180,181,185), from lower EPA concentrations (183,184) or from both EPA and DHA concentrations (182). In the Finnish Fishermen Study with over 1,200 high fish consumers, higher serum DHA concentrations associated with higher scores of psychological distress (178). However, no associations between phospholipid or adipose tissue concentrations of n-3 PUFAs and depressive symptoms were observed in almost 400 Cretan adults (186). Some studies have also reported an inverse relationship between circulating concentrations of n-3 PUFAs and severity of depression (170,183,187). Severity of depression has been inversely associated with the concentrations of EPA, DHA, ALA and total n-3 PUFAs in two studies (183,187) and only with the circulating concentration of EPA in one study (170).

Ratio of n-6 to n-3 PUFAs
The potential association between depression and n-3 fatty acids might be explained by an unfavorable ratio of n-6 to n-3 PUFAs (161,187). During the last centuries in Western populations, n-3 fatty acids from fish, wild game and plants have been replaced by saturated fatty acids (SFAs) from domestic animals (20). In addition, intake of n-6 fatty acids, especially LA, has increased significantly because of increased consumption of vegetable oils. By a rough estimate, the ratio of n-6 to n-3 fatty acids has increased from 1:1 to even more than 10:1 in Western countries (162). This change may have caused an increase of an n-6 fatty acid, AA, a pro-inflammatory n-6 PUFA, in cell membranes replacing EPA, which may in turn have increased the proportion of inflammatory eicosainoids (188). Overlapping, the prevalence rates of depression have been rising, which has given reason to assume that the ratio of n-6 to n-3 PUFAs could play a role in the pathophysiology of depression (86). Nevertheless, recent evidence does not support this theory. Blood ratio of n-6 to n-3 PUFAs or concentrations of AA have been higher in depressed individuals compared to controls in some (169,180,181,187,189), but not in all studies (184,190). In addition, a study in the SU.VI.MAX cohort demonstrated that the ratio of n-6 to n-3 PUFAs was not associated with depressive symptoms after adjustments for several potential confounders, including total energy intake (87). Moreover, concentrations of AA are under close homeostatic regulation and changes in dietary LA intake do not appreciably affect the concentrations of AA (163). Further, not only n-3 PUFAs, but also n-6 PUFAs, especially LA, are involved in inhibition of the production of inflammatory factors (191). It is possible that the intake of n-6 PUFAs even in large amounts does not accelerate inflammation, as no elevations in plasma CRP or interleukin-6 were found in a RCT comparing 4% to 10% of energy intake from LA (192).

4.3.2 Prospective studies
Only few large prospective studies have been published on the relationship between n-3 PUFAs and depression, and the results are partly contradictory (**Table 6**). The studies were conducted in all age groups and almost all studies investigated either fish consumption or dietary intake of n-3 PUFAs; only one study with nested case-control design investigated circulating fatty acid concentrations (19). The analyses were mainly adjusted for total energy intake, except for two studies (17,89) and stratified analyses revealed that smoking and gender may be modifying the association.

Consumption of fish and dietary intake of n-3 PUFAs

An inverse association between fish consumption or intake of total or long-chain n-3 PUFAs and the risk of depression was reported in some prospective studies (15,17,18), whereas others have reported no association (87,88,90). The North American Nurses' Health Study (NHS) with more than 50,000 female participants demonstrated no association between EPA+DHA from fish and the risk of depression after ten years of follow-up (the adjusted hazard ratio (*HR*) for 0.3-g/d increment: 0.99; 95% *CI*: 0.88 to 1.10) (88). In that study, depression cases were defined as presence of both self-reported physician-diagnosed depression and antidepressant use, which increases the specificity. The cumulating average of four dietary assessments was used to measure long-term dietary exposure of fish consumption. The comparisons were made between women who ate fish <once a month, 1-3 times/month, once a week, 2-4 times/week or ≥5 times a week, which is quite a large range, and might be suitable for detecting differences. However, no differences in the risk of depression were found. In addition, separate analyses according to the fattiness of fish revealed that neither lean nor fatty fish consumption associated with the risk of depression, while intake of ALA had an inverse association (*HR* for 0.5 g/d increment: 0.82, 95% *CI:* 0.71 to 0.94), especially in women whose intake of LA was low, indicating that long-term dietary ALA intake may play an independent physiological role in depression.

The second largest of the prospective studies, a previous Finnish study with almost 30,000 smoking men followed up for nine years, demonstrated no association between fish consumption or total n-3 PUFA intake and severe depression (highest total n-3 PUFA intake tertile vs. lowest tertile *HR*: 0.96; 95% *CI:* 0.70 to 1.30) (90). However, men in the highest tertile of fish consumption had a marginally elevated risk of self-reported depressed mood compared to men in the lowest tertile (*HR*: 1.06; 95% *CI:* 1.00 to 1.12). The mean intake of total n-3 PUFAs at baseline was quite high, 2.2 g/day, for individuals who received depression during the follow-up, and 2.1 g/day for the rest of the population.

In a Spanish study with almost 8,000 men and women, a non-linear, inverse association was found, as moderate consumption of n-3 PUFAs (the median consumption of fish in this group was 112 g/day) associated with a 35% decreased *HR* reduction of depression (95% *CI:* 0.45 to 0.90) compared to the lowest consumption of n-3 PUFAs (the mean consumption of fish 36 g/day) (18). Separate analyses showed that the association was statistically significant in women only. Similarly, in over 3,000 young adults from the U.S., EPA+DHA intake (≥0.08% of energy) was inversely associated with the risk of depressive symptoms (highest quintile vs. lowest *HR*: 0.71; 95% *CI:* 0.52 to 0.95), after three years of follow-up, but only in women (17). However, depression scores were measured approximately 13 years after diet assessment, without taking the baseline depression scores into consideration, which is a limitation of the study.

In almost 2,000 middle-aged subjects from the French SU.VI.MAX cohort with eight years of follow-up, intake of long-chain n-3 PUFAs (higher than 0.1% of energy) was associated with 47% lower risk of having recurrent depression (*P* for trend=0.09), in men only (15). Nevertheless, in that study, there were no associations with long-chain PUFA intake and single episode of depression. In addition, high fatty fish consumption was associated with a decreased risk of recurrent depression in current non-smokers, whereas in smokers, fatty fish consumption associated with an elevated risk of recurrent depression (15). However, later in the sub-sample of the SU.VI.MAX cohort after 13 years of follow-up, prospective analyses showed no associations between n-3 PUFA intake and incidence of depressive symptoms (87). In addition, that was the only prospective study on the association between the ratio of n-6 to n-3 PUFAs and the risk of depression, reporting no association in either non-adjusted or adjusted (total energy intake included) models.

Circulating concentrations of n-3 PUFAs

To date, there is only one prospective study on the association between serum concentrations of n-3 PUFAs and depression published. A nested case-control study based on the French SU.VI.MAX cohort reported no associations between serum phospholipid concentrations of any n-3 PUFAs and the risk of depression (19). Surprisingly, as described above, in the same cohort, dietary long-chain n-3 PUFA intake had previously been associated with the risk of recurrent depression (15). The inconsistency in the results may be explained by the finding that dietary intakes of fatty acids were correlated with plasma fatty acid concentrations only weakly (r<0.3), regardless of the precision in the food intake assessment (six repeated 24-h diet records per year) (19). Plasma phospholipids reflect mainly recent, a couple of weeks' intake of fatty acids (136). However, it was suggested that especially the long-chain n-3 PUFA status at a determined time could predict the risk of depression even more precisely than the biomarkers of the long-term intake (19).

A recent systematic review based on the six cohort studies of n-3 PUFAs suggested potential benefits of intakes of total n-3 PUFAs and consumption of fish, but firm conclusions cannot be drawn based on the current evidence (6). Results from the observational studies may be biased, mainly by weaknesses in the assessment of exposure and outcomes, as well as by selection and publication bias.

4.3.3 Intervention studies

Prevention trials

To date, only two RCTs have investigated the effects of n-3 PUFA supplementation on mental health in non-depressed individuals. In the other trial with over 2,500 men and women who were CVD survivors, daily supplementation of EPA and DHA, 600 mg at a 2:1 ratio, showed no effect on depressive symptoms (adjusted *OR*: 1.16; 95% *CI:* 0.95 to 1.41) (137). However, in gender-specific analyses, a positive association was found in men (adjusted *OR*: 1.28; 95% *CI*: 1.03 to 1.61), but not in women (adjusted *OR*: 0.78; 95% *CI:* 0.51 to 1.20). This trial had a long duration, almost five years, and the participants were 45 to 80 years old. In the other study, daily supplementation of either 1.8 g of EPA+DHA or 0.4 g of EPA+DHA for 26 weeks did not statistically significantly improve mental well-being compared to placebo in independently living 302 elderly men and women from general population (193). After 26 weeks, mean changes in CES-D scores in the high-dose fish oil, low-dose fish oil and placebo groups were -0.2, 0.2, and -0.4; P=0.87, respectively (193).

Table 6. Prospective studies on the association between consumption of fish and intake or concentrations of n-3 PUFAs and the risk of depression.

Study by	Study population	Participants men/ women	Age (years)	Follow -up (years)	Exposure measu-red by	Depr. measu-red by	No of cases	Results
Hakkarainen et al. 2004 (90)	ATBC Cancer Prevention Study, Finland, smokers	29133/-	50-69	9	276-item FFQ	Register data, SRDS	246 8612	Fish consumption and n-3 PUFA intake: no associations found with the risk of depression. Higher fish consumption was associated with marginally elevated risk of SRDS
Jacka et al. 2004 (89)	Geelong Osteoporosis Study, Australia	-/755	23-97	6	74-item FFQ	SRDS	97	N-3 PUFAs: no statistically significant associations with depression risk.
Sanchez-Villegas et al. 2007 (18)	SUN cohort, Spain. University graduates	7903 (men and women)	18-70	2	136-item FFQ	SRDS or AD	173	Fish consumption and n-3 PUFAs: inverse association with depression, non-linear; statistically significantly reduced only at intermediate intakes of n-3 PUFAs in women only.
Astorg et al. 2008 (15)	SU.VI.MAX cohort, France	809/1055	Men 45-60/ women 36-60	8	Six 24-h records	AD	304	Fish consumption and intake of >0.1% of energy as long-chain n-3 PUFAs associated with a lower risk of recurrent depression, in men only. In smoking women, the risk increased with elevating fish consumption.
Colangelo et al. 2009 (17)	CARDIA Study, U.S., Caucasian and African-Americans	1481/1836	18-30	3	Long FFQ	CES-D	744	EPA, DHA and EPA+DHA intake: strong inverse association with depression in women.
Lucas et al. 2011 (88)	The NHS, U.S.	-/54632	50-77	10	116-item FFQ	AD and physician diagnosis	2823	N-3 PUFAs from fish: no statistically significant associations. ALA intake: inversely associated with depression risk, especially in women with lower LA intake.
Kesse-Guyot et al. 2012 (87)	SU.VI.MAX cohort, France	1231 (men and women)	Men 52/ women 47 (mean)	13	Six 24-h records	CES-D or AD	140	N-3 PUFA intake: no statistically significant associations. In cross-sectional analyses, low intake of n-3 PUFAs was associated with elevated depressive symptoms.
Astorg et al. 2009 (19)	SU.VI.MAX cohort, France (a nested case-control study within a cohort)	454 (~80% women)	Men 45-60/ women 36-60	8	Serum phospho-lipids	≥2 AD	222	Concentrations of n-3 PUFAs: no association with the risk of depression.

Abbreviations: AD, antidepressant prescription or use; ALA, alphalinolenic acid; ATBC, Alpha-Tocopherol, Beta-Carotene; CARDIA, Coronary Artery Risk Development in Young Adults Study; CES-D, Centre of Epidemiological Studies Depression Scale; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FFQ, food frequency questionnaire; LA, linoleic acid; NHS, The Nurses' Health Study; PUFA, polyunsaturated fatty acid; SRDS, self-reported depressive symptoms; SUN, Seguimiento Universidad de Navarra; SU.VI.MAX, The Supplémentation en Vitamines et Minéraux Antioxydants Study; U.S., United States of America

Treatment trials

The effects of the n-3 PUFAs on the treatment of depression have been more extensively studied compared to prevention (**Table 7**). Several studies have demonstrated the beneficial effect of supplementation with n-3 PUFAs on depressive symptoms (194-201), but not all (202-208). The most effective n-3 PUFA supplementation, as well as the optimal dosage of supplementation, has been argued. EPA may be more beneficial than DHA in the alleviation of depressive symptoms (21,209,210). However, the number of trials with pure DHA or mainly DHA supplementation is low (197,206,210) and patients might have had too minor depressive symptoms (202,204). As regards the dosage of supplementation, in a trial with patients with treatment resistance, 1 g/day, but not 2 or 4 g/day of ethyl-EPA (E-EPA) improved symptoms more likely than placebo (200). In addition, in almost all RCTs, participants were on antidepressant treatment, but in two trials with no benefits (202,203), n-3 PUFA supplementation was used as a monotherapy. Similarly, in a trial with the largest study population (201), 40% of the 432 participants were having antidepressant treatment at baseline, and the beneficial effect was on the borderline of statistical significance (*P* for the difference=0.053), and statistically significant only when patients with comorbid anxiety disorders were excluded. In addition, there were two trials in which the antidepressant treatment started simultaneously with the -3 PUFA administration (196,205). In the one, EPA and fluoxetine medication were reported to have similar efficacy, but the combination was superior to either of these alone (196). In the other, augmentation of sertraline treatment with EPA and DHA provided no extra benefits (205).

Meta-analyses propose that n-3 PUFA supplementation is more effective than placebo in the treatment of depression (21,210-212). The latest meta-analysis with 16 RCTs in adult MDD patients only, showed the greatest treatment effect for the supplementation of EPA being dominant (≥60%) compared to DHA (standardized mean difference: 0.62; 95% *CI*: 0.33 to 0.91). Similarly, a recent meta-analysis of EPA only showed that supplementation with EPA≥60% benefitted most vs. supplements with EPA<60% (effect size: 0.53; 95% *CI*: 0.28 to 0.73) (213).

In summary of the trials, only two prevention trials have been conducted with altogether 2,803 participants, with results that do not support the beneficial effects of n-3 PUFA supplementation. In treatment trials, individuals with more severe depressive symptoms have achieved the greatest benefit from n-3 PUFA, especially EPA, administration (21,210,212), but there is not enough evidence of the benefits for individuals without a diagnosis of MDD (21,212). During the trials, the participants' fish consumption was not taken into account, only the supplementation with n-3 PUFAs was, which is a limitation. It is still difficult to summarize the effects due to considerable heterogeneity between the trials (212). However, the RCTs published by now have included altogether 1,452 participants, which is a relatively low number of participants to form valid conclusions.

Table 7. Clinical trials on long-chain n-3 PUFAs in the treatment of depression.

Study by	Study population	Gender (M/W)	Duration (weeks)	Supplement (g/day)	Results
Nemets et al. 2002 (194)	20 patients with MDD	3/17	4	E-EPA 2.0	Augmentation with E-EPA was more effective compared to placebo. The effect increased when follow-up continued.
Peet and Horrobin 2002 (200)	70 depressed patients with symptoms of depression in spite of antidepressant treatment	11/59	12	E-EPA 1, 2 or 4	One gram of E-EPA a day as adjunctive to antidepressant medication relieved depressive symptoms more effectively than placebo. In those who took two or four grams a day the effect did not differ from the placebo.
Su et al. 2003 (195)	22 depressed out-patients	4/18	8	EPA 4,4 + DHA 2,2	Augmentation of antidepressants with EPA and DHA resulted in better recovery compared to placebo.
Marangel et al. 2003 (203)	35 patients with MDD	7/28	6	DHA 2.0	With DHA better response than with placebo, but no statistically significant differences. No antidepressant treatment.
Silvers et al. 2005 (204)	77 patients with MDD	36/41	12	8 g fish oil	No statistically significant differences between fish oil and placebo (olive oil) effect.
Grenyer et al. 2007 (206)	83 patients with MDD	32/51	16	EPA 0.6 + DHA 2.2	No statistically significant differences between the groups.
Rogers et al. 2008 (202)	218 patients with mild to moderate depression	50/168	12	EPA 0.63 + DHA 0.85	No statistically significant differences between the groups. No antidepressant treatment.
Jazayeri et al. 2008 (196)	48 patients with MDD	15/33	8	E-EPA 1.0	EPA with fluoxetine was more effective than fluoxetine or EPA alone.
Mischoulon et al. 2009 (207)	25 patients with MDD	9/16	8	E-EPA 1.0	EPA was more effective, but not statistically significantly more effective than placebo.
Carney et al. 2009 (205)	122 patients with MDD and coronary heart disease	81/41	10	EPA 0.93 + DHA 0.75 + sertraline	No statistically significant differences between the groups.
Rondanelli et al. 2010 (199)	46 elderly depressed females	-/46	8	EPA 1.67 +0.83 DHA	Depression scores decreased statistically significantly more compared to placebo. No antidepressant treatment.

Table 7 to be continued

Table 7 continues

Study by	Study population	Gender (M/W)	Duration (weeks)	Supplement (g/day)	Results
Bot et al. 2010 (214)	24 MDD patients with diabetes	11/13	12	E-EPA 1.0	No statistically significant differences between the groups.
Sinn et al. 2012 (197)	50 elderly patients with mild cognitive impairment and depressive symptoms	37/13	6 months	EPA 1.7 + DHA 0.2, or DHA 1.6 + EPA 0.4	Depression scores decreased statistically significantly more in both groups compared to placebo. Improved depression scores correlated with increased DHA plus EPA.
Lesperance et al. 2011 (201)	432 patients with MDD	136/296	8	EPA 1.05 + DHA 0.15	There was only a trend towards superiority of supplementation over placebo, but among patients with MDD without comorbid anxiety disorders, a clear benefit of EPA+DHA was observed.
Gertsik et al. 2012 (198)	42 patients with MDD	n/a	9	EPA 0.9 + DHA 0.2 + other n-3 PUFAs 0.1	Supplementation decreased depression scores statistically significantly more compared to placebo.

Abbreviations: DHA, docosahexaenoic acid; (E-)EPA, (ethyl-)eicosapentaenoic acid; M, men; MDD, Major depressive disorder; n/a, not available; PUFA, polyunsaturated fatty acid; W, women

4.3.4 Potential mechanisms

The physiological functions of n-3 PUFAs in the brain include regulation of cell membrane fluidity, membrane-bound enzymes, dopaminergic and serotoninergic transmission, and cellular signal transduction; n-3 PUFAs also participate in brain eicosanoid synthesis, which is connected to depression (161,167). High concentrations of n-3 PUFAs in neuronal membranes are hypothesized to play a role in synaptic neurotransmission including metabolism, release, uptake, and receptor functioning of neurotransmitters (209,215). N-3 PUFAs are involved in, or modulate, the mechanism by which brain neurons communicate (209). DHA is the predominant fatty acid in the brain (approximately 15% of fatty acids), whereas EPA exists in the brain to a lesser extent (approximately 0.2% of fatty acids) (216,217). Therefore, DHA concentration especially affects the permeability of membrane cells in CNS (218) and deficiency of DHA has been found to relate to dysfunctions and impaired transmission of serotonin, norepinephrine and dopamine (217). Phospholipids of neural cell membrane consist especially of PUFAs (200). Long-term supplementation with EPA may raise the stimulated release of AA from membrane phospholipids, whereas DHA has no such effect (219). Interestingly, the traditional view of the effects of n-3 PUFAs as antagonists of AA might become more complicated, since n-3 PUFAs have also been suggested to increase the abundance of AA in membrane phospholipids (220). In animal models, it was shown that a diet containing 0.01% or 0.1% of EPA increased the concentrations of EPA, DHA and also AA, but with higher intakes, a diet containing 1% of EPA increased EPA and DHA, but decreased AA concentrations (220). A similar phenomenon was also observed in humans: after receiving one gram or two grams of EPA daily, AA concentrations in red-cells increased, whereas with four grams daily AA concentrations decreased (200). This supports the hypothesis that there is a significant endogenous regulation of the metabolism of these fatty acids.

N-3 PUFAs and fish consumption have been connected to the inflammation theory (17,221). Traditionally, a high ratio of n-6 to n-3 has been thought to enhance pro-inflammatory cytokine production, whereas n-3 PUFAs as such have anti-inflammatory properties (221). Fish intake >150 grams/week has been linked to decreased levels of pro-inflammatory markers, such as CRP and cytokines, like interleukin-6 (176,222), which supports the hypothesis that eating more fish could lead to altered depressive symptoms through the modification of inflammation process (176). This theory has also been reinforced in the current Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study population, as serum n-3 PUFA and especially long-chain n-3 PUFA concentrations were found to be inversely associated with CRP levels (223).

Different PUFAs may have different effects on eicosanoid production (161). The details of this process have been presented in more detail elsewhere (224). In summary, AA, an n-6 fatty acid, can be metabolized to proinflammatory eicosanoids, whereas ALA, an n-3 fatty acid, can be converted to EPA, which can be further converted to anti-inflammatory eicosanoids (17). Higher dietary intake of ALA has been found to associate with lower plasma levels of inflammatory biomarkers (225). EPA and DHA reduce inflammation by decreasing the effect on the synthesis of eicosanoids by competing with AA (185).

N-3 PUFAs may also affect the HPA axis. In MDD patients, serum cortisol levels decreased with both EPA administration (one gram daily) alone and EPA (one gram daily) in combination with fluoxetine treatment (20 mg/day) groups in an eight-week trial (226). However, serum levels of cytokines, interleukin-1 and interleukin-6, did not change statistically significantly in the intervention.

N-3 PUFAs may also play a role in the neuroprogression, as n-3 PUFA supplementation (EPA 0.15 g/day and DHA 1.5 g/day) increased the concentrations of serum BDNF in an open-label trial for 12 weeks (227). However, the effects of n-3 PUFAs on BDNF levels may not be evident, as in a RCT in diabetic patients with MDD, E-EPA supplementation (one gram daily) for 12 weeks did not seem to increase the levels of BDNF (208). The differences may be explained by the varying dosage and fatty acids used in the supplementation.

However, it should also be taken into account that an increase in the consumption of one food group usually leads to a decrease in another. Increasing fish consumption, and thus increasing long-chain n-3 PUFA intake, is prone to decrease the consumption of other food groups that may have an independent connection to depression. Previously, fish consumption was shown to have a negative association with the consumption of unhealthy-considered foods like meat and sausages, and a positive linear association with other healthy-considered foods like vegetables, fruit and berries (228). Therefore, these potential confounders need to be considered.

4.3.5 Dietary therapy with n-3 PUFAs in depression

In 2006, the American Psychiatric Association's Omega-3 Fatty Acid Subcommittee published clinical recommendations for the n-3 PUFA intake and supplementation to prevent and treat depression (229). Firstly, all adults were recommended to eat fish according to present dietary recommendations, at least twice a week. Patients with mood disorders were recommended to take a supplementation of one to nine grams of EPA and DHA daily. Supplementation of more than three grams should, however, be monitored by a physician. Evidence did not support supplementation with essential fatty acids, ALA or LA. It is noteworthy, however, that increased fish consumption above at least two times a week was not recommended, only supplementation was recommended. In Finland, we have no recommendations for treatment augmentation for depression with fish consumption or n-3 PUFA supplementations.

In summary of the association between n-3 PUFAs and depression: there are several cross-sectional, but only few prospective studies published, and the results are partly inconsistent. Five out of eight prospective studies showed no association. One study showed an inverse association, one study a non-linear association, whereas one study showed an inverse association with recurrent depression in men**.** Only one of the previous prospective works examined the association between serum n-3 PUFAs and the risk of depression. However, the validity of the findings is limited by several methodological issues and gender may be a confounding factor. There is a lack of prevention trials concerning n-3 PUFAs and depression. However, treatment trials suggest that augmentation of antidepressant treatment with EPA and DHA may have a slight benefit in clinically depressed individuals, but the results are still partly inconsistent.

5 Coffee, tea and caffeine

5.1 COFFEE AND TEA CONSUMPTION

Coffee is one of the most popular beverages in the world. Finnish people rank first in coffee consumption (230). In 2011, Finnish people consumed coffee approximately 12.2 kg/person/year. According to the National FINDIET 2007 survey, 88% of Finnish working-aged men and 87% of women drank coffee daily (103). The mean daily coffee consumption for men and women was 553 mL and 429 mL, respectively. Among the elderly, coffee drinking was even more common: 93% of men and 92% of women aged 65 to 75 years drank coffee (103). Today, people in Finland usually drink filtered coffee while consumption of boiled, unfiltered coffee has decreased dramatically since the 1970s. Drinking instant coffee has never been popular in Finland and was practically non-existent still in the 1990s. Nevertheless, interest in special coffee types, such as espresso, cappuccino, café latte and café mocha, has probably increased during the latest decade. However, there are no statistics available of the consumption of these special types of coffees.

Coffee drinking is a life-style habit, usually enforced for hedonistic or psychosimulant purposes, sometimes also to complement meals, but not as nourishment (231). There are two species of coffee trees that are in commercial use, *Caffea arabica* and *Caffea robusta*. Globally, 80% of coffee consists of *arabica* with a more desirable flavor. *Robusta*, instead, contains more caffeine as well as polyphenols, including chlorogenic acid, and fewer lipids (232). The coffee consumed in Finland is usually *Caffea arabica.* Coffee contains thousands of different chemical compounds, many formed during the roasting process (23,233). However, it is suggested that there are only three groups of compounds that may be physiologically relevant with a sufficient concentration in coffee drink: caffeine, diterpene alcohols cafestol and kahweol, and polyphenols including chlorogenic acid (234).

Tea drinking is popular especially in Asian countries and in a few countries in North Africa and the Middle East, where green tea is commonly used. In Nordic countries, tea drinking is less popular, and the type of tea consumed is different; in Western countries black tea accounts for approximately 78% of tea consumption (235). However, the popularity of green tea is increasing also in Western populations (236). According to the National FINDIET 2007 survey, altogether 28% of Finnish working-aged men and 44% of women drank tea daily, the mean daily consumption being 94 mL for men and 154 mL for women (103). Tea contains plenty of bioactive substances, such as polyphenols, especially flavonoids (236). Especially green tea has been suggested to possess clinically significant health-promoting effects (237).

5.2 CAFFEINE METABOLISM

Caffeine, 1,3,7-trimethyl xanthine, is the most well-known and pharmacologically studied substance in coffee. Coffee and tea are the most important sources of caffeine consumed. Coffee consumption accounts for approximately 71% of the intake of caffeine in the U.S. (238). A cup of coffee (~110 mL) contains about 100 mg of caffeine, although caffeine content varies greatly depending on the composition of the blend, the method of brewing and the strength of the brew, and variation is large even when the same machines and processes are repeatedly used (239). Tea is also a source of caffeine even though the amounts are much smaller than in coffee; tea contains about half as much caffeine as coffee. Caffeine containing energy drinks have become popular since the 1990s especially among adolescents, and caffeine is also available, in addition to supplement form, in smaller

amounts in cola drinks, cocoa, hot chocolate and chocolate (240). Caffeine doses up to 450 mg/day for adults, 300 mg/day for pregnant women and 45 mg/day for children are regarded as safe (241). However, the Finnish recommendations for beverage consumption suggest caffeine intake of maximum of 2.5 mg/kg for children (242).

Caffeine is metabolized in the liver by an enzyme known as cytochrome P450 1A2. Caffeine typically increases mental alertness, speeds up information processing, promotes wakefulness, reduces fatigue, causes restlessness and delays the need for sleep (243). Thus, caffeine intake is suggested to lead to better cognitive performance (22). At daily levels above 500 mg of caffeine, dependency and withdrawal symptoms become evident (244).

5.3 COFFEE CONSUMPTION, CAFFEINE INTAKE AND DEPRESSION

The short-term effects of caffeine on mood are fairly well known, but the long-term effects are still mostly unknown. In theory, caffeine may contribute to many psychiatric disorders, such as depression, anxiety and psychosis (244). The psychiatric symptoms caused by caffeine consumption have been demonstrated to lead to a state called "caffeinism", which is usually related to daily intakes of 1000 to 1500 mg of caffeine (22). Similarly, a review of the caffeine effects reported that high single doses of caffeine (300 mg or higher), usually rarely ingested by the majority of people, may increase mental symptoms (22). In contrast, at lower doses, mood-state remains quite stable or even reduces self-rated depression or anxiety. Approximately 10% of regular caffeine consumers suffer from increased depressive symptoms when caffeine is withdrawn (245). Therefore, regular caffeine consumption is likely to substantially benefit drinkers, but mainly due to the "withdrawal relief" (246). However, this theory of the alleviation of caffeine withdrawal responsible for improved mood has been argued, as behavioral effects of withdrawal have also been observed in animals and caffeine non-consumers (247,248).

The following sections clarify the association between coffee or caffeine consumption and depression, based on cross-sectional and prospective studies. Studies demonstrating the association are presented in **Table 8.** Almost all of the previous studies assessed coffee consumption or caffeine intake with semi-quantitative FFQs, except for one with no quantitative analyses (249). In only one of these studies (250), total energy intake was taken into account as a potential confounder.

5.3.1 Cross-sectional studies

In general population, life-time caffeine intake was associated with a higher prevalence of many psychiatric disorders, including MDD, especially in heavy-consumers (≥625 mg of caffeine daily) (91). However, opposite findings have also been presented, as coffee and caffeine intake were inversely associated with depression in a British non-working sample (92) and in Japanese workers (251). A study with Eastern Finnish men and women from general population showed no association between daily coffee consumption and the prevalence of depressive symptoms (93). The review of the general effects of caffeine concluded that moderate caffeine intake (<six cups of coffee per day) was associated with less depressive symptoms compared to no caffeine consumption, due to caffeine's mood-elevating effect (252). Nevertheless, coffee drinking may be a common habit among depressed individuals and for example, partly replace eating meals. As these studies reviewed were cross-sectional, it is impossible to determine the causality, *i.e.*, whether coffee or caffeine consumption affects depression or vice versa.

5.3.2 Prospective studies

To date, there is only one prospective study published on the association between coffee consumption and the risk of depression. The large North American NHS, with over 50,000 female participants followed up for ten years, reported an inverse, dose-dependent relationship between caffeinated coffee consumption and the risk of depression (250). Consumption of three or more cups of coffee was associated with a 20% reduced risk of depression compared to those who consumed less than a cup of coffee daily (95% *CI*: 0.64 to 0.99). In addition, an inverse dose-response association was observed between total caffeine intake and the risk of depression, whereas decaffeinated coffee consumption showed no such association. Moreover, no association between caffeine from non-coffee sources and the risk of depression was found, which suggests that the combination of coffee and caffeine accounts for the association. The strengths of the study include that in order to reduce random measurement error, analyses were conducted using the cumulative average of caffeine consumption and a two-year latency period in exposure before depression. In addition, total energy intake and several other relevant potential confounders were taken into account. However, the NHS included women only.

Another prospective study examined the association between caffeine consumption and depression in more than 500 Australian middle-aged or older women and showed that baseline caffeine consumers had lower scores of mental well-being measured five years later, as compared to baseline non-caffeine consumers (249). However, caffeine consumption was not associated with mental well-being in cross-sectional analyses. The limitations include that there was a lack of quantitative information, as regular caffeine consumption was coded as a dichotomous variable (yes/no) and the amount of caffeine consumed was not assessed.

Depression is an important predictor of suicides (253). Supporting an inverse association, coffee consumption has been connected to a decreased risk of suicides in three cohort studies. In a Finnish study (254), a J-shaped association was found, whereas in an North American study (255), women who drank two or more cups of coffee per day had a 70% lower risk of suicide compared to never-drinkers. Another North American study reported a strong inverse association between coffee consumption and the risk of suicide, but also tea was found to decrease the risk of suicides (256).

There are no intervention studies or RCTs published on the effects of coffee consumption on depressive symptoms.

5.3.3 Potential mechanisms

The potential mechanisms of the effects of coffee or caffeine on depression are mainly based on monoamine metabolism and neurotransmission, but also on inflammation. In theory, caffeine could mediate the protective effect of coffee or tea for example by stimulating the CNS (257) and enhancing dopaminergic neurotransmission (258). Caffeine targets especially adenosine A1 and A2A receptors. Adenosine functions as a neuromodulator and caffeine assists the activity of dopamine, an important neurotransmitter (252).

Coffee contains plenty of substances with potential to affect both inflammation and oxidation. (23,259). Chlorogenic acid has anti-inflammatory effects *in vivo* (260) and therefore, it may slow down the process of inflammation. Oxidation may also play a role in depression (261), and the phenolic acids of coffee, especially chlorogenic acid and caffeic acid, have in some studies been found to have also antioxidant effects both *in vitro* (262) and *in vivo* (259). Antioxidants present in coffee may improve the overall antioxidant capacity and contribute to ameliorating oxidative stress (23). Previously, a positive association has been found between the potency of oxidative stress and severity of depression (263).

Table 8. Cross-sectional and prospective studies on the association between coffee, tea or caffeine intake and depression.

Study by	Study population	Study design (follow-up years)	No of sub-jects	Depression measured by	No of cases	Exposure measurement	Comparison	Results Adjusted *HR/OR (95% CI)*
Hintikka et al. 2005 (93)	Finnish general population	Cross-sectional	2011	BDI	210	Coffee consumption	Daily vs. no daily drinking	0.92 (0.64, 1.32)
						Tea consumption	Daily vs. no daily drinking	0.47 (0.27, 0.83)
Kendler et al. 2006 (91)	Virginia Twin Registry, U.S.	Cross-sectional	3706	Clinical interview	n/a	Life-time caffeine intake	Intake: yes vs. no	1.06 (1.04, 1.08)
						Life-time heavy caffeine intake	High intake (≥624 mg/day): yes vs. no	1.79 (1.47, 2.17)
Smith 2009 (92)	Non-working British population	Cross-sectional	3223	HADS	n/a	Caffeine intake	>260 mg/d vs. no intake	0.12 (0.10, 0.20)
Xu et al. 2010 (249)	Healthy Aging of Women Study, Australia	Prospective (5 years)	564	GCS	n/a	Caffeine intake	Correlation between caffeine intake (yes) and mental well-being scores	r=-0.496 (P=0.037)
Lucas et al. 2011 (250)	The NHS, U.S.	Prospective (10 years)	50739	AD + physician diagnosis	2607	Coffee consumption	2-3 vs. <1 cup/d	0.85 (0.75, 0.95)
							≥4 vs. <1 cup/d	0.80 (0.64, 0.99)
						Caffeine intake	≥550 vs. <100 mg/d	0.80 (0.68, 0.95)
Pham et al. 2013 (251)	Employees in Japan	Cross-sectional	537	CES-D	157	Coffee consumption	≥2 vs. <1 cup/d	0.61 (0.38, 0.98)
						Green tea consumption	≥4 vs. ≤1 cup/d	0.49 (0.27, 0.90)
Hozawa et al. 2009 (264) [1]	Ohsaki Cohort 2006 Study, Japan	Cross-sectional	42093	Kessler 6-psychologi-cal distress scale	2774	Green tea consumption	≥5 vs. <1 cup/d	0.80 (0.70, 0.91)
Niu et al. 2009 (265)	Community-dwelling elderly in Japan	Cross-sectional	1058	GDS	361	Green tea consumption	≥4 vs. ≤1 cup/d	0.56 (0.39, 0.81)
						Black or oolong tea	≥1 cup/day vs. almost never	0.71 (0.49, 1.02)
Chen et al. 2010 (266)	Breast cancer survivors, China	Prospective (18 months)	1399	CES-D	182	Green tea consumption	>100 g dried tea leaves/months vs. no consumption	0.39 (0.19, 0.84)

Abbreviations: AD, antidepressant use; BDI, Beck Depression Inventory depression scale; CES-D, Center for Epidemiologic Studies Depression Scale; *CI*, confidence interval; FFQ, food frequency questionnaire; GCS, Greene Climacteric Scale; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scale; *HR*, hazard ratio; NHS, Nurses' Health Study; *OR*, odds ratio; U.S., United States of America

[1]Study on psychological distress

5.4 TEA CONSUMPTION AND DEPRESSION

Studies demonstrating the association between tea consumption and depression are also presented in **Table 8**. Almost all of the studies are cross-sectional and no adjustment for energy intake was done. Moreover, almost all of the studies clarify the association between green tea consumption and depression, while information concerning black tea consumption is lacking.

5.4.1 Cross-sectional studies

A Japanese study in more than 40,000 participants reported an inverse relation between the frequency of green tea consumption and psychological distress (264). Those who consumed five or more cups of green tea daily had 20% lower risk of being depressed than those who drank less than one cup daily, after adjustments for a large number of confounders. Similarly, more frequent consumption of green tea was associated with a lower prevalence of depressive symptoms in more than 1,000 elderly Japanese (265). The prevalence of depressive symptoms was 44% lower for those who drank four or more cups of green tea daily compared to those who drank one cup or less daily. In addition, a weak but not statistically significant association was found between consumption of black tea and the prevalence of depressive symptoms (265). In a study of general population sample of Eastern Finnish men and women, it was observed that after adjustments for various confounders, those who drank tea daily had a 53% reduced risk of being depressed compared to tea non-drinkers (93). Tea drinking in that study, as generally in Finland, focused on black tea.

5.4.2 Prospective studies

There is only one prospective study published on tea consumption and the risk of depression with 18 months of follow-up (266). Participants with high green tea consumption (consumption of >100 g of dried tea leaves per month) had a 61% decreased risk of depression compared to those with no green tea consumption. However, that study was conducted in breast cancer survivors, and there are no prospective studies concerning men or general population. Therefore, further prospective studies should be conducted.
No intervention studies or RCTs have been published on the subject.

5.4.3 Potential mechanisms

The association between tea consumption and depression may be explained by the potential effects of caffeine on mood described earlier in this thesis. Moreover, tea contains catechin polyphenols, which have demonstrated anti-inflammatory and antioxidant properties in several studies (236). Tea extract has been shown antidepressive effects in animal studies, and antidepressant activity may be explained for example by the inhibition of monoamine oxidase enzymes (267). Green tea is rich in theanine, an amino acid, which has been shown to elevate brain concentrations of dopamine and serotonin in animal studies (268). In addition, green tea contains folate, but studies adjusting for folate concentrations have reported that the association between green tea and depression attenuated the shown association only slightly (251).

In summary, the evidence suggests that coffee and green tea consumption may be beneficial for mental health, though there is a lack of studies. Only one prospective study has been published on the association between coffee consumption and depression, showing an inverse association in female population**.** No prospective studies in the general population have been published on either green or black tea. In addition, there are no published RCTs focusing on the effects of coffee, tea or caffeine consumption on the prevention or treatment of depression.

6 Dietary patterns

6.1 RECOMMENDATIONS AND DIETARY INTAKE

The Finnish Dietary Recommendations have given recommendations for overall dietary patterns and food consumption (102). The recommendations suggest consumption of at least five portions of vegetables, fruits and berries daily, which is about 400 grams/day (102). It is also recommended to consume whole-grain products rich in fiber as part of all daily meals in order to achieve a total intake of 25 to 35 grams of fiber. Fish should be eaten at least twice a week. In addition, low-fat (≤7%) poultry, meat, meat products and sausages are recommended to replace high-fat products to avoid excess intake of SFAs. Low-fat (≤1%) milk and dairy is recommended to be consumed at least 500 mL/day, and two to three daily slices of low-fat and low-salt cheese is also recommended. Vegetable oils and margarines should be in every-day use. Furthermore, consumption of sucrose should be limited to 10% of energy intake and daily consumption of salt to seven grams in men and six grams in women. The daily alcohol consumption is suggested to be moderate, maximum of two alcohol units in men and one alcohol unit in women. In addition, regular frequency of meals is recommended.

The food consumption in Finnish general population mainly meets the recommended levels or is close to the borderline, but there are also intakes that do not meet the recommendations. According to the National FINDIET 2007 survey, the mean daily consumption of vegetables, fruits and berries in Finnish men and women was 339 g and 408 g, respectively (103). The mean consumption of fiber in men and women was 24 and 21 grams/day, respectively. The mean daily fish consumption was 28 g in men and 24 g in women, and the mean dairy consumption, including all milk and sour milk products, was 505 mL/day in men and 476 mL/day in women. The mean cheese consumption was 40 g/day in men and 34 grams/day in women. Finnish men ate meat (pork, poultry, beef, sausages and cold cuts summarized) approximately 167 grams/day and women 98 grams/day. In addition, the mean salt intake was approximately eight grams per day in men and six grams per day in women. The mean daily intake of sucrose was 9.7% of energy intake in men and 10.5% of energy intake in women. Finally, the mean daily alcohol consumption in men and women was 224 mL and 58 mL, respectively.

6.2 THE WHOLE-DIET APPROACH

The majority of the previous studies of the association between diet and diseases have focused on single food items or nutrients. Nevertheless, instead of isolated nutrients, people eat meals with mixed food groups, which are sources of several nutrients that may interact. Therefore, dietary patterns reflecting a combination of foods may be more useful in assessing the risk of diseases (269). The influence of overall diet can be studied using a whole-diet approach with dietary pattern analyses (270). Two main approaches, both data-driven methods, are factor analysis and cluster analysis. Factor analysis identifies the patterns of correlation between foods, while cluster analysis reduces data into patterns based upon individual differences in mean intakes (269). These analyses are not defined *a priori,* but *a posteriori,* and do not depend on the researcher's wish to define a healthy dietary pattern, for example by comparing the quality of the diet to dietary recommendations (269). However, researchers' decisions and definitions are prone to affect the interpretation of the patterns also in dietary pattern analysis conducted with factor analysis.

The third method for assessing diet quality involves using diet quality indices, which have been developed upon current knowledge of nutrition. Diet quality indices reflect the general quality of the diet and include variables thought to be healthy, and often determine the ideal diet for disease prevention based on recent evidence *a priori* (269). Higher diet quality scores usually indicate healthier dietary patterns. There is no certain golden standard regarding diet quality indices. The most well-known diet quality index instruments are the Healthy Eating Index (HEI), which is based on the U.S. Dietary Guidelines, and the latest modified version of the preceding, Alternative Healthy Eating Index (AHEI-10) (271). AHEI-10 delivers scores based on the number of portions for certain food items (*e.g.* fruit portions), but also for absolute intake (*e.g.* whole-grain products grams/day) and percentages of intakes (*e.g.* % of energy from trans-fatty acids out of total energy intake). AHEI-10 correlates well with the validated HEI, and both indices have been found to strongly predict the risk of chronic diseases (271). The commonly used Mediterranean Diet Score (MDS) was developed to assess the effect of Mediterranean diet on chronic diseases (272). High scores in MDS reflect high consumption of vegetables, fruits, nuts, cereal, legumes, fish, and also a high ratio of monounsaturated fatty acids (MUFAs) to SFAs. MDS has been found to assess adherence to the Mediterranean diet fairly well (273). In addition, there are diet quality indices developed in the Nordic countries, for example the Baltic Sea Diet Score, developed in Finland (274). The Baltic Sea Diet Score is based on the Nordic Dietary Recommendations and takes into account the consumption of foods regarded as traditional in the Baltic Sea area.

6.3 DIETARY PATTERNS, DIET QUALITY AND DEPRESSION

6.3.1 Dietary patterns in depressed individuals

Depressed individuals often have poor eating habits and unfavorable food choices, and the severity of depression predicts poorer overall diet quality (115,171,275). Depressed individuals have been reported to consume fewer servings of vegetables, fruits and grains both compared to controls and compared to the recommendations, both in the U.S. (171) and in Finland (276,277). In practice, it has been estimated that in order to meet the recommended standard, at least 45% of the patients with mood disorders should add two to three more servings of vegetables and fruits, and about 15% should add two extra daily servings of grains to their diet (171). In contrast, individuals suffering from mood disorders have been demonstrated to consume more unhealthy foods, such as processed meats and sugary, fatty and salty foods compared to others (171). In addition, depressed individuals have been documented to eat less foods containing protein, such as meat, fish, eggs and beans compared to others (115,278), although the consumption of processed meats has been higher among depressed individuals (171). Depressed individuals, especially those with atypical depression, have increased consumption of carbohydrates, mostly sucrose (278,279) and lower consumption of high-fiber grain products compared to non-depressed individuals (171).

Depressed individuals have more irregular frequency of meals, are more prone to eat an inadequate amount of meals, and the diversity of their meals is poorer compared to non-depressed controls (115). In addition, patients with mood disorders have been found to eat even two fifths of their meals outside the home, at least in Canada (171). Emotional eating is highly connected to both depressive symptoms and unhealthy food choices (276). However, emotional eating does not explain the association between depressive symptoms and food choices in general, but it may be one explaining factor behind the association between intake of particularly sweet foods and depressive symptoms (276).

6.3.2 Cross-sectional studies

Several studies have applied whole-diet approaches to examine the associations between dietary patterns and depression (**Table 9**). The majority of the studies were from Australia, Europe (France, United Kingdom, Spain, Norway) or Asia (Japan, China) and dietary pattern analyses were usually based on long FFQs. However, statistical models were adjusted for total energy intake only in about a half of the studies (24,25,95,280-285)**,** which is regarded as a limitation. In addition, gender may affect the observed association, as healthy dietary patterns or diet quality indices have been observed to be protective especially or only in women (25,95,283,285,286). Depression was usually measured by self-reported questionnaires, such as BDI or CES-D, whereas clinical interview was used to define depression in only one study (285). The following sections present in more detail the cross-sectional and prospective studies on healthy or unhealthy dietary patterns or diet quality indices and depression.

Healthy dietary patterns

Associations between dietary patterns and depression have been demonstrated by using *a posteriori* methods. Studies in adults in Australia (285), Norway (95), France (283) and Japan (281) as well as in adolescents in China (287) reported an inverse association between healthier dietary patterns and depression. However, the traditional Norwegian dietary pattern, which also included milk products and butter, was associated with a decreased prevalence of depressive symptoms only in men (95). In contrast, studies in Japanese community-dwelling adults (282) and in Australian adolescents (280) reported no associations between healthy dietary patterns and depressive symptoms. A healthy cluster characterized by high fish consumption in French men (283) and healthy dietary pattern in Norwegian men (95) showed no association, either. However, three out of four of the studies with no association (95,280,283) were energy-adjusted.

There are some differences between dietary patterns defined as "healthy", except for the presence of vegetables and fruits, which are usually included in the healthy patterns. In an Australian study (285), healthy diet was characterized by eating lots of vegetables, lean meat, fish and whole-grains, whereas in a Japanese study (281) it was characterized by high consumption of vegetables, fruits, mushrooms and soy products. A study conducted in China (287) demonstrated a traditional dietary pattern with gruel, oatmeal, whole-grains, vegetables, fruits and soya milk. In a Norwegian study, the healthy dietary pattern, protective in women, had high loadings for vegetables, fruits, rice, cereals and non-processed meat, whereas a traditional Norwegian dietary pattern, protective in men, was characterized by high consumption of fish, shellfish, potatoes, fruits, vegetables, butter, margarine and milk products (95). In a French study, a healthy cluster that associated with fewer depressive symptoms in women was characterized by high consumption of fruits and vegetables (283).

Unhealthy dietary patterns

Dietary patterns characterized by unhealthy Western-type food consumption were found to associate with prevalence of depression in Australian (280) and Chinese (287) adolescents. In Australian women, the positive association was diminished after adjustment for energy intake (285). In Australian adolescents, the unhealthy dietary pattern associated with elevated depression was characterized by high consumption of take-away foods, confectionery and red meat (280), whereas in Chinese adolescents, snack dietary pattern was rich in fruits, a sweet course, frozen confections, yoghurt, chocolate, candies and carbonated drinks (287). In Australian women, Western dietary pattern was based on processed or fried foods, refined grains, sugary products and beer (285). A dietary pattern based on animal foods was associated with higher likelihood of co-existing depression in Chinese adolescents (287). Nevertheless, in Norwegian adults (95), higher intake of processed and unhealthy foods and, in Japanese adults, Western, bread and confectionery,

or alcohol and accompanying patterns were not related to depression (282). The differences in the results may be explained by the age of the participants, as the association was shown especially studies in adolescents (280,287). However, adjustment for energy intake was done in almost all of these studies, except for the Japanese study with no association (282) and the Chinese study with a positive association (287).

Diet quality indices
Lower adherence to dietary guidelines has been demonstrated to have a cross-sectional association with elevated prevalence of depression in North American adults (288) and in Norwegian women, and after adjustments, also in men (95). Unhealthy diet quality scores associated with elevated mental health problems also in British (96) and in Australian (289) adolescents.

6.3.3 Prospective studies

Healthy dietary patterns
The protective relation between healthy dietary patterns and the risk of depression has been demonstrated in four large prospective studies in adults. The largest study showed that a healthy dietary pattern reflecting high consumption of vegetables, fruits and oils was protective in a study with over 12,000 middle-aged French working men and women (highest vs. lowest tertile, in men *OR*: 0.72; 95% *CI*: 0.63 to 0.83 and in women *OR*: 0.75; 95% *CI*: 0.61 to 0.93) (26). This was the first study on the subject to use repeated depression measurements (CES-D) over ten years. However, the dietary patterns were assessed by short FFQs and models were not adjusted for total energy intake. Adherence to a traditional Australian dietary pattern predicted lower scores in psychological distress scale (highest vs. lowest quartile *OR*: 0.61; 95% *CI:* 0.40 to 0.91) in a study with 8,660 participants and the longest follow-up on the subject, 12 years (94). The traditional Australian dietary pattern consisted of not only healthy-considered whole-grains, fruits, vegetables and margarine, but also sweet snacks and lack of olive oil (94). However, in that study, the Mediterranean dietary pattern was not associated with psychological distress (highest vs. lowest quartile *OR*: 0.94; 95% *CI*: 0.87 to 1.01). Nevertheless, the greatest limitation in that study was that psychological distress was not assessed at baseline, but only at the end of the study; thus it is possible that the dietary patterns were affected by the presence of symptoms. In contrast, in 7,588 Australian women, a strong protective association was demonstrated between adherence to Mediterranean dietary pattern and depression (*OR*: 0.84; 95% *CI*: 0.78 to 0.90) (25), also when energy intake was taken into account as a potential confounder. The pattern was characterized by high intake of garlic, peppers, mushrooms, salad greens, pasta and red wine. Nevertheless, in the same study, cooked vegetable pattern or fruit pattern did not show an association with depression risk, neither did high-fat and sugar or processed meat patterns. Similarly, in almost 3,500 middle-aged British men and women (24), adherence to a healthy dietary pattern, called whole-food pattern, characterized by high consumption of vegetables, fruits and fish, was associated with a 30% lower risk of depression in energy-adjusted model (second vs. lowest tertile *OR*: 0.70; 95% *CI*: 0.50 to 0.96).

Unhealthy dietary patterns
In the above-described British study, dietary pattern rich in processed foods, such as sweetened desserts, processed meats, fried foods, refined grains and high-fat dairy products associated with a 76% higher risk of depression (highest vs. lowest tertile *OR*: 1.76; 95% *CI*: 1.14 to 2.70) also in energy-adjusted models (24). Similarly, in the above-described French cohort, Western (*OR*: 1.36; 95% *CI*: 1.19 to 1.54), fat-sweet (*OR*: 1.49; 95% *CI*: 1.30 to 1.71) and snacking (*OR*: 1.50; 95% *CI*: 1.32 to 1.71) dietary patterns associated with an elevated risk of depression in men and snacking (*OR*: 1.43; 95% *CI*: 1.16 to 1.76) and low-fat patterns (*OR*: 1.39; 95% *CI*: 1.22 to 1.73) in women (comparisons were made for the highest

vs. lowest tertiles) (26). Nevertheless, in that study, energy intake was not taken into account as a potential confounder.

Diet quality indices

Adherence to dietary guidelines has been related to the reduced risk of depression in prospective studies. In the Spanish Seguimiento Universidad de Navarra (SUN) cohort with more than 10,000 adults, higher MDS showed to predict decreased depression (*HR*: 0.58; 95% *CI*: 0.44 to 0.77) (284). In addition, an inverse dose-dependent association was found between consumption of fruits, nuts, ratio of MUFAs to SFAs and the risk of depression (284). Similarly, MDS had an inverse association with the risk of psychological distress in over 8,500 Australian adults (*OR*: 0.71; 95% *CI*: 0.54 to 0.95) (94) and MDS was also associated with a reduced number of newly occurring depressive symptoms in over 3,500 North American elderly (290). In over 4,000 British participants, AHEI scores were inversely and dose-dependently associated with recurrent depressive symptoms, but only in women (286). Women who maintained high AHEI scores had a 65% (95% *CI*: 0.19 to 0.64) and women who improved their scores a 68% (95% *CI*: 0.13 to 0.78) lower risk of recurrent depression compared to women who maintained lower AHEI scores during the ten years of follow-up. Among AHEI components, especially vegetables, fruits ant the ratio of PUFA to SFA were associated with the reduced risk of recurrent depression.

Prospective studies in adolescents have also shown that healthy diet quality scores were inversely associated with depression in almost 3,000 British (96) and in almost 3,000 Australian adolescents (289). Moreover, in Australian adolescents, higher unhealthy diet scores predicted higher depression scores at follow-up (289), whereas in British adolescents, unhealthy diet quality scores associated with elevated mental problems only before adjustments (96). However, no adjustments for energy intakes were done.

6.3.4 Intervention studies

There are no large-scale or long-lasting RCTs conducted on the effects of dietary patterns on depression. However, in a recent pilot RCT, healthy participants were assigned to eat fish three to four times a week and to avoid meat and poultry, to favor a vegetable-oriented diet and to avoid fish, meat and poultry, or to eat meat, fish and poultry (291). The study demonstrated that those in the vegetable group had greater improvements in mood compared to the fish or meat+fish group after two weeks of trial. However, there were only 39 participants in this short trial, but the results support the beneficial effects of a vegetable-oriented diet on mood.

6.3.5 Potential mechanisms

As presented earlier in this thesis, several nutrients, such as long-chain n-3 PUFAs, folate and vitamin B_{12} may be related to the risk of depression (10,21,132), but also foods or food groups, such as high consumption of vegetables and fruits (281,285) and fish (15,172,173) have been associated with a reduced risk of depression. Individuals' diets consist of mixed food groups instead of isolated nutrients, and different nutrients interact and modulate each other's effects. Thus, dietary patterns reflect more than just the effect of individual factors summarized.

Table 9. Cross-sectional and prospective studies on the association between dietary patterns, diet quality indices and depression.

Study by	Study design (follow-up years)	Study population	No of sub-jects	Gender (M/W)	Age (years)	No of cases	Method	Results
Dietary patterns								
Samieri et al. 2008 (283)	Cross-sectional	Three-City Study, elderly community dwellers, France	1724	711/1013	>65	n/a	Cluster analysis (long FFQ, 24h DR)	In women, healthy eating cluster was inversely associated with depressive symptoms. In men, pasta eating cluster associated with elevated depressive symptoms.
Oddy et al. 2009 (280)	Cross-sectional	The Western Australian Pregnancy Cohort, Australia	1598	818/779	14	n/a	Factor analysis (212-item FFQ)	Western dietary pattern (especially take-away foods, red meat and confectionery) associated with poorer mental health.
Jacka et al. 2010 (285)	Cross-sectional	Geelong Osteoporosis Study, Australia	1046	-/1046	20-93	121	Factor analysis Diet quality scores (74-item FFQ)	Traditional healthy dietary pattern and diet quality scores were inversely associated with lower odds for MDD. Unhealthy Western pattern associated with elevated MDD only before adjustment for energy intake.
Nanri et al. 2010 (281)	Cross-sectional	Employees, Japan	521	309/212	21-67	186	Factor analysis (65-item FFQ)	Healthy Japanese dietary pattern was inversely associated with fewer depressive symptoms.
Jacka et al. 2011 (95)	Cross-sectional	Hordaland Health Study, Norway	5731	2477/3254	46-49, 70-74	521	Factor analysis Diet quality score (169-item FFQ)	Healthy dietary pattern inversely associated with depression in women, whereas traditional Norwegian dietary pattern was inversely associated with depression only after adjustments in men. Diet quality score was inversely associated with depression in women and also in men after final adjustments.

Table 9 to be continued

Table 9
continues

Study by	Study design (follow-up years)	Study population	No of sub-jects	Gender (M/W)	Age (years)	No of cases	Method	Results
Weng et al. 2012 (287)	Cross-sectional	Adolescents, China	5003	2606/2397	11-16	560	Factor analysis (38-item FFQ)	Traditional dietary pattern was inversely associated with depressive symptoms. Snack dietary pattern and animal food dietary pattern associated with higher likelihood of depressive symptoms.
Sugawara et al. 2012 (282)	Cross-sectional	Community-dwelling individuals, Japan	791	303/488	22-86	97	Factor analysis (65-item FFQ)	No associations between dietary patterns and depressive symptoms found.
Akbaraly et al. 2009 (24)	Prospective (5 years)	Whitehall II cohort study, United Kingdom	3486	2572/914	35-55	455	Factor analysis (127-item FFQ)	Whole-food dietary pattern was inversely associated with depression (statistically non-significant after exclusions of depressed at baseline), while processed food pattern was positively associated with depression.
Le Port et al. 2012 (26)	Prospective (10 years)	Employees of national Gas and Electricity Company, France	12 404	9272/3132	35-50	n/a	Factor analysis (35-item FFQ)	Healthy pattern associated with lower likelihood of depressive symptoms. In women, snacking and low-fat patterns increased and traditional pattern decreased the risk of depression. In men, Western, fat-sweet and snacking dietary patterns increased the risk of depression.
Hodge et al. 2013 (94)	Prospective (12 years)	Melbourne Collaborative Cohort Study, Australia	8660	n/a	50-69	n/a	Factor analysis MDS (long FFQ)	The traditional Australian dietary pattern showed a weak inverse association with psychological distress. MDS was inversely associated with psychological distress.
Rienks et al. 2013 (25)	Cross-sectional, prospective (3 years)	The Longitudinal Study on Women's Health, Australia	7588	-/7588	50-55	660	Factor analysis (80-item FFQ)	Mediterranean dietary pattern was associated with reduced risk of depression in cross-sectional and longitudinal analyses.

Table 9 to be continued

Table 9
continues

Study by	Study design (follow-up years)	Study population	No of sub-jects	Gender (M/W)	Age (years)	No of cases	Method	Results
Diet quality indices								
Kuczmarski et al. 2010 (288)	Cross-sectional	Healthy Aging in Neighborhoods of Diversity across a Life Span –study, U.S.	1118	495/623	30-64	n/a	HEI scores (two 24h DRs)	Diet quality was inversely associated with reported symptoms of depression.
Jacka et al. 2011 (289)	Cross-sectional, prospective (2 years)	Adolescents, "It's Your move" -project, Australia	2915	1632/1283	11-18	n/a	Diet quality score (FFQ)	Healthy diet scores predicted better mental health status while unhealthy diet scores predicted lower mental health scores both cross-sectionally and prospectively.
Jacka et al. 2012 (96)	Cross-sectional, prospective (10 years)	Adolescents, United Kingdom	2790	1356/1433	11-14	463	Diet quality score (FFQ)	Cross-sectional association between unhealthy diet and mental health problems. Prospectively, healthy diet scores had an inverse and unhealthy diet scores a positive association with mental health problems, statistically non-significant after final adjustments.
Sanchez-Villegas et al. 2009 (284)	Prospective (4.4 years)	SUN cohort, Spain	10094	n/a	37 (mean)	480	MDS (136-item FFQ)	High adherence to Mediterranean diet was associated with a lower risk of depression.
Skarupski et al. 2013 (290)	Prospective (7 years)	(290)Chicago Health and Aging Project, U.S.	3502	n/a	>65	n/a	MDS (FFQ)	Higher MDS predicted reduced number of newly occurring depressive symptoms.
Akbaraly et al. 2013 (286)	Prospective (5 years)	Whitehall II cohort study, United Kingdom	4215	3155/1060	35-55	260	AHEI-scores (127-item FFQ)	AHEI scores were inversely associated with recurrent depressive symptoms in a dose-response fashion, but in women only.

Abbreviations: AHEI, Alternative Healthy Eating Index; DR, diet recall; FFQ, food frequency questionnaire; HEI, Healthy Eating Index; M, men; MDS, Mediterranean Diet Score; n/a, not available; SUN, Seguimiento Universidad de Navarra; U.S., United States of America; W, women

Among the indicators of diet quality, consumption of fruits and vegetables has especially been found to properly assess the quality of diet (292). Fruit and vegetable intakes have been the primary components of a healthy diet also in studies demonstrating the association between diet and depression (95,281,283-285). Interestingly, dietary antioxidants from fruits and vegetables were found to be protective against depression, whereas antioxidants from dietary supplements did not associate with depression (83), which indicates the benefits of elevated consumption of fruits and vegetables instead of supplementation. Recently, a short-term positive effect of fruit and vegetable consumption on mood was shown, as daily consumption of approximately seven to eight servings of fruits and vegetables predicted a greater positive affect the following day (293). Diet was assessed with 21-day food records and the association was stronger in men than women. However, positive affects, especially followed by the fruit and vegetable consumption only in days, may not be based on real physiological effects, but result from the perceived healthiness of fruits and vegetables. However, positive affects did not predict changes in next-day fruit and vegetable consumption.

In theory, a healthy, vegetable-oriented diet rich in vitamins, minerals, antioxidants, and n-3 PUFAs modulates several physiological systems, such as inflammatory and oxidative processes, brain plasticity, synthesis of monoaminergic neurotransmitters, brain cell membrane functions and the stress-response system (95,217,294). Hence, in theory, a healthy diet is likely to play a role in the genesis and course of depression (295). Adherence to a dietary pattern closer to the Mediterranean diet was shown to be associated with decreased levels of HPA axis disturbances (296). In addition, depressed patients who were assigned to the Mediterranean diet were found to have elevated plasma BDNF levels compared to patients assigned to a control diet (297).

Several mechanisms are suggested to explain the harmful effects of unhealthy dietary patterns. It is possible that not only do these unhealthy food items replace more nutritious foods causing a lack of protective nutrients, but an unhealthy diet may also contain potential harmful substances. Previously, a dietary pattern associated with lower mental health status was loaded with high refined sugar intake and red meat intake in adolescents (280). In theory, high consumption of sugar-containing products may affect for example inflammatory factors (298), and high intake of processed red meat may also be harmful to general health and increase the risk of non-communicable diseases (299). In addition, a high-fat, refined sugar diet decreased the levels of BDNF in hippocampus and decreased neuronal plasticity (300). Unhealthy dietary patterns may lead to chronic inflammation by elevating the levels of pro-inflammatory cytokines, which may in turn elevate the risk of MDD (301). It has also been suggested that rather than the proportion of unhealthy foods in the overall diet, it is the absolute amount of unhealthy foods consumed that is the most relevant for health (95).

In summary, several cross-sectional and prospective studies have shown an inverse association between healthy dietary patterns and depression in studies mainly from Australia, Europe or Asia. This association has been found especially in women. In some studies, unhealthy dietary patterns have been shown to predict elevated depressive symptoms, especially in studies conducted in adolescents, but most of the studies showed no associations. However, adjustment for total energy intake has not been done in about half of the studies, which may affect the results. A recent review reported that even if there is evidence of potential benefits for certain dietary patterns, due to large heterogeneity, a meta-analysis is still impossible to conduct (302). The review pointed out an urgent need for further studies. Moreover, there are no large-scale intervention studies published on the dietary modifications and the effects on depression status.

7 Lifestyle interventions

7.1 LIFESTYLE INTERVENTIONS IN NON-CLINICAL POPULATIONS

Lifestyle intervention studies are usually conducted to improve lifestyle habits, such as eating habits, to lose weight in overweight individuals, to increase physical activity, or to enhance sleep length or quality. In lifestyle interventions, these improvements are usually driven in combination, and social support is often given as a control treatment. **Table 10** presents the intervention studies aimed at improvements in lifestyle factors that have reported the effects on depressive symptoms in non-clinical individuals. Studies have mainly been conducted in high-risk populations for depression, such as stroke survivors, overweight and pregnant individuals or individuals with IGT or T2D.

In the Diabetes Prevention Program (DPP), participation in the intensive lifestyle modification group for three years was not associated with changes in depressive symptoms in over 3,000 overweight or obese subjects with IGT (303). The intervention group aimed at a mean loss of at least 7% of initial weight through a healthy low-fat diet and an increase of moderately intense physical activity to at least 150 minutes/week. Several individual and group sessions were included. There were also two control groups, a metformin and a placebo group (303). Similar results were achieved in elderly stroke survivors; improvements in mental health were seen in both groups, but the difference between intervention and control groups did not reach a statistically significant level (304). However, in that study the intervention group received 36 group sessions on lifestyle factors and 36 physical activity sessions while the control group received 36 exercise group sessions, so a "null-exposed" control group was lacking. In addition, an intervention study among nearly one hundred elderly stroke survivors compared the effects of a lifestyle course with physical activity intervention (intervention group) to a physical exercise alone group (control group) (304). Similarly, mental health improvements were seen in both groups, with no specific group effect. Additionally, an intervention among elderly individuals demonstrated that physical activity intervention showed no benefit over successful ageing counseling sessions as a control (305). In that study the intervention group received intensive exercise intervention including at least three 40- to 60-minute sessions per week, while a series of sessions on health topics were given to the control group. Finally, similar results were achieved in an intervention in obese pregnant women; an intensive, tailored dietary intervention based on Belgian National Dietary Recommendations had no difference in the effect on depressive symptoms compared to either brochure-delivered or normal care control groups (306). In overweight and obese women, dietary restrictions (~6000 kJ/day energy restricted high-protein meal plan) both alone and combined with physical exercise decreased depressive symptoms. The results suggest that exercise provided no additional benefit to the effect of diet alone (307). There was, however, no null-control group in that study.

In contrast, in over 4,000 participants from the 12-month Look AHEAD trial, aimed at weight reduction in overweight adults with T2D, BDI scores decreased more in the intensive lifestyle intervention group compared to diabetes support and education group as a control group (308). The intervention was aimed at reducing weight (≥7% of initial weight) and increasing moderately intense physical activity to at least 175 minutes per week. The weight control intervention was adapted from the DPP (303), in which participants had several group meetings as well as individual tailored counseling sessions. The control group received three one-hour group meetings that addressed diet, physical activity and social support. The mean reduction in weight was 8.8 kg in the intervention

and 0.9 kg in the control group, and weight change was regarded as a mediator on the effect of intervention on BDI reduction. Recently, also another study was published based on The Look AHEAD Trial (309) and this is the largest conducted trial on the subject with almost 5,000 participants. That study aimed at comparing the effects of intervention on incidence of symptoms of depression. The results showed that the incidence of potentially clinically significant symptoms of depression was statistically significantly lower in the intervention group compared to the control group (309).

An intervention among pregnant Latino women also demonstrated similar findings: women in IG had a statistically significant decrease in depression scores during the intervention compared to the control group (310). The intervention included a 14-session weekly curriculum and aimed at empowering women to develop knowledge and skills to promote healthy eating, regular exercise and social support. The intervention was rigorous and group meetings included healthy eating and exercise activities, such as healthy cooking, walking and dancing. The control group had only group meetings relating to general health in pregnancy and was given standard pregnancy education materials about eating and exercise (310).

Recently, the first trial comparing the effects of a combination of diet and physical exercise on the effects of diet and exercise separately was published (311). The results showed that although both diet and diet plus exercise improved mental health, the combination of diet and exercise showed greater improvements in mental health than diet alone. In addition, participation in the diet plus exercise group associated with a decrease in depression scores. There was also a statistically significant correlation between weight loss and reduced depressive symptoms. In that study, the participants were overweight or obese women without major medical conditions. The diet group received individualized counseling based on a reduced calorie weight loss intervention, which was a modification of the DPP lifestyle trial (303) and the Look AHEAD trial (309). The diet group was advised to restrict their total calorie intake to 1200-2000 kcal/day based on baseline weight, eat ≤30% of calories from fat, and achieve 10% weight loss within the intervention period. The exercise intervention was based on 45 minutes of moderate-to-vigorous intensity aerobic exercise daily five days per week including three supervised exercise sessions per week. The combined group received both diet and exercise intervention while controls were not given the intervention.

Table 10. Intervention studies on lifestyle factors and depressive symptoms.

Study by	Participants (age, years)	Duration	Specific intervention strategy/ advice to control group	Results
Rubin et al. 2005 (303)	3187 overweight/obese subjects with IGT in DPP trial (≥25 y)	3.2 years	IG: 1) A mean loss of at least 7% of initial weight through a healthy low-fat diet 2) to increase moderately intense physical activity to at least 150 min/week CG1: Metformin treatment CG2: Placebo treatment	DPP participation was not associated with changes in levels of depression. Weight loss associated with reduction of in the risk of elevated depression.
Williamson et al. 2009 (308)	4223 overweight/obese adults with T2D in Look AHEAD Trial (45-76 y)	12 months	IG: 1) A mean loss of at least 7% of initial weight, 2) to increase moderately intense physical activity to at least 175 min/week CG: Educational information, 3 group meetings	The BDI scores reduced in both IG (-0.83, $P<0.001$) and in CG (-0.23, $P<0.001$) (P for the difference <0.001)
Thomson et al. 2010 (307)	94 overweight/obese women with polycystic ovary syndrome (mean age 29 y)	20 weeks	IG1: Improving diet only IG2: Improving diet and aerobic exercise IG3: Improving both aerobic and resistance exercise	IG1 and IG2 had similar benefits in improving depression, no statistically significant differences between the groups.
Lund et al. 2011 (304)	86 stroke survivors (≥65 y)	9 months	IG: Improving physical activity + other lifestyle-relating factors CG: Improving physical activity	No statistically significant differences: mental reduction in depression scores: IG (-0.8; 95% *CI:* -1.7 to 0.2), CG (-1.1; *95% CI:* -2.0 to 0.2) (P for the difference=0.66)
Mathews et al. 2011 (305)	424 sedentary, non-institutionalized adults elderly individuals (70-89 y)	12 months	IG: Improving physical activity CG: Successful ageing: sessions in health topics	No statistically significant differences between the groups (P=0.85).
Imayama et al. 2011 (311)	439 overweight/obese postmenopausal women in the Nutrition and Exercise Trial (50-75 y)	12 months	IG1: Dietary weight loss of 10% IG2: Moderate-to-vigorous aerobic exercise (225 min/week) IG3: Combined diet and exercise CG: No intervention	IG1 and IG3 improved mental health statistically significantly more compared to CG (P=0.05 and P=0.01, respectively), IG2 had no effect (P=0.29). Effect of IG3 was greater than IG1 or IG2 alone (P=0.04).

Table 10 to be continued

Table 10
continues

Study by	Participants (age, years)	Duration	Specific intervention strategy/ advice to control group	Results
Faulconbridge et al. 2012 (309)	4802 overweight/obese adults with T2D in Look AHEAD Trial (45-76 y)	12 months	IG: 1) A mean weight loss of ≥7% of initial 2) increase physical activity ≥175 min/week CG: Educational information, three group meetings	The incidence of depression lower in IG compared to CG (6.3% and 9.6%, respectively; IG *HR*: 0.66; *P* for the difference <0.001). Mean reduction in the BDI scores: 1.4±4.7 in IG and 0.4±4.5 in CG (*P* for the difference <0.001).
Bogaerts et al. 2012 (306)	205 obese pregnant women	1-3 trimesters	IG: Dietary goals based on the National Dietary Recommendations + increasing exercise CG1: Brochure group CG2: Normal care	No differences in depressive symptoms were found between the groups (*P*=0.76).
Kieffer et al. 2013 (310)	249 pregnant Latino women in Healthy Moms Lifestyle intervention	2-3 trimesters	IG: Increasing healthy eating, exercise activities + social support: group meetings and home visits CG: General advice	IG had a statistically significantly greater decrease in depression scores from baseline to follow-up compared to CG. Mean difference between the groups: -1.83 points*; 95% CI* -3.59, -0.07; *P*=0.04.

Abbreviations: BDI, Beck Depression Inventory; CG, control group; *CI*, confidence interval; DPP, The Diabetes Prevention Program; *HR*, hazard ratio; IG, intervention group; T2D, type 2 diabetes mellitus

7.2 LIFESTYLE INTERVENTIONS IN DEPRESSED INDIVIDUALS

There is a lack of large-scale dietary or lifestyle interventions among depressed patients. Based on the information of the impaired quality of diet and decreased dietary intakes of essential nutrients, it is evident that depressed individuals would benefit from dietary improvements that are possible to achieve in dietary or lifestyle specific interventions (171). Positive effects have been shown in interventions (312), but the effects of improved lifestyle factors on depression course are still partly unclear.

The beneficial effect of physical exercise is suggested to be considerable in the treatment of depression. A recent Cochrane review concluded that exercise seems to improve depressive symptoms (27). The results indicated a moderate clinical effect in people with a diagnosis of depression when compared with no treatment or control intervention. Physical exercise is effective especially in the prevention of recurrent depression (101). However, 12 months of pure exercise intervention reported no statistically significant effect on depressive symptoms in elderly depressed individuals (305). In contrast, a psycho-educational group program aimed at healthier lifestyle in patients with depression showed benefits compared to usual care as a control (313).

A recent RCT clarified the effects of four lifestyle recommendations on the treatment of depression (314). The study consisted of 80 depressive out-patients on antidepressant treatment. The intervention aimed at four goals: improving sleep (detailed instructions, for example go to bed before 11 pm), walking at least one hour a day, being exposed to sunlight at least two hours per day and finally, eating a healthy and balanced diet and regular meals. Specific dietary aims were to eat fish at least three times per week, consume vegetables, fruits, cereals and nuts daily and avoid sugary drinks. The control group received only general advice, for example "try to eat a healthy and balanced diet". After six months of intervention, all scales indicated better recovery in the intervention group (mean decrease of the BDI scores in intervention and control group was 9.3 and 5.3, respectively). In addition, the number of psychopharmacological treatment prescriptions was reduced more in the intervention compared to the control group. The study suggested that lifestyle recommendations may be used as an effective antidepressant complementary treatment in clinical practice.

Recently, a study protocol was published for the "Supporting the Modification of Lifestyle In Lowered Emotional States" study, an RCT investigating the effects of dietary intervention for adults with MDD (315). This is the first diet-only based trial with 12 weeks of intervention focusing on advocating a healthy diet based on the Australian Dietary Guidelines and the Dietary Guidelines for Adults in Greece, started at the end of 2012. After completion of this trial, there will be more evidence of the effects of dietary intervention in depressed individuals.

It has been assumed that current depression may affect adherence to intervention instructions, achieving goals and the possibility of dropping out during the intervention. In the elderly, intervention participants with high depressive symptoms did not benefit from physical exercise intervention as much as healthy controls (305). However, in that study adherence rates to the exercise sessions did not differ between depressed individuals and others. In a recent Finnish study, a diagnosis of MDD, chronic depression or specific symptoms of depression did not predict quitting a weight loss intervention (316). It was observed that only anhedonia predicted drop-outs.

7.3 POTENTIAL MECHANISMS

Lifestyle factors are interrelated, and when one of these habits is modified it usually facilitates change in others (16). Therefore, the mechanism that may explain why these lifestyle habits can prevent or improve depression is probably complex (312). The possible effects of dietary factors on depression have been presented in detail earlier in this thesis. On biological level, it is likely that exercise improves the balance of serotonergic, dopaminergic and noradrenergic systems in contrast to stress, which impairs the systems (317). In addition, the magnitude of social support and regular meetings may affect depressive symptoms.

In summary, results from the lifestyle intervention studies aimed at improving diet and/or increasing physical activity in non-clinical high-risk populations, as well as in depressed individuals, are inconsistent. There is great heterogeneity between the studies. It seems that increasing physical exercise alone does not benefit participants as much as the combination of lifestyle factors. In addition, the effect of comprehensive lifestyle intervention aimed at healthy diet, increased physical activity and weight reduction has been less studied compared to intervention studies with only one aim, usually increasing the amount of exercise or losing weight.

In summary of the review of the literature section of this thesis, the evidence suggests that diet may have a role in the prevention and treatment of depression although heterogeneity between the studies is large. The inconsistency in the results may partly be explained by potential confounders, such as total energy intake, gender, age or smoking. Further prospective studies and intervention studies are especially needed.

8 Aims of the study

The general aim of this study was to examine the associations between diet and depression.

The specific aims for each sub-study were:

I To examine whether dietary folate and vitamin B_{12} are associated with the risk of depression in a prospective setting in middle-aged men (work I)

II To study if serum concentrations of total long-chain n-3 PUFAs (sum of EPA+DPA+DHA), individual PUFAs, or the ratio of n-6 to n-3 PUFAs are associated with the risk of depression in a prospective setting in middle-aged men (work II).

III To study if coffee or tea consumption or intake of caffeine are associated with the risk of depression in a prospective setting in middle-aged men (work III).

IV To examine if dietary patterns are associated with a prevalence of depressive symptoms or the risk of clinical depression in middle-aged men. Both cross-sectional and prospective settings where used to clarify the associations (work IV).

V To investigate how lifestyle intervention affects the depressive symptoms assessed by BDI score in middle-aged men and women, and to ascertain the determinants of this effect (work V).

9 Subjects and methods

The data used in this thesis were from two separate studies, the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study and the Finnish Diabetes Prevention Study (DPS) (**Table 11**).

9.1 THE KUOPIO ISCHAEMIC HEART DISEASE RISK FACTOR (KIHD) STUDY (I-IV)

9.1.1 Study population and participants

The KIHD study is an ongoing population-based cohort study designed to investigate the risk factors for CVD and other chronic diseases in middle-aged men in Eastern Finland (318). The study population consists of a stratified balanced one third random sample of men aged 42, 48, 54 or 60 years living in the city of Kuopio or one of the six neighboring rural communities. Baseline characteristics of the KIHD study population are presented in **Table 12**. Baseline examinations occurred between March 1984 and December 1989. The study population is based on two cohorts: the first cohort consisted of men aged 54 years enrolled in 1984 to 1986, while the second cohort included men aged 42, 48, 54 and 60 years enrolled in 1986 to 1989. Of 3,235 eligible men, a total of 2,682 (83%) participated in the study at baseline, 1,166 in the first and 1,516 in the second cohort. The subjects gave written informed consent.

Those men in the second KIHD cohort who had been studied between January 1987 and December 1989 and who had undergone ultrasound examination of the right and left carotid arteries at baseline, a total of 1,229 men eligible, were asked to participate in the four-year re-examination. Out of them, 52 could not participate because of death, severe illness or relocation, and 139 could not be contacted or refused to participate. Thus, 1,038 men (88% of those eligible) were examined between March 1991 and December 1993. Study participants were 46 to 65 years old at the four-year re-examinations.

Altogether 1,007 men from the four-year re-examinations were invited to participate in the 11-year examinations of the KIHD study. In addition, 1,714 women were invited to participate. Altogether 854 men and 921 women participated in the 11-year re-examinations between March 1998 and February 2000. The KIHD study protocol was approved by the Research Ethics Committee of the University of Kuopio.

Table 11. Summary of the study designs, data materials, and main outcomes of interest in works I-V.

Sub-work	Design	Study	Study subjects	Exposure of interest	Time	Outcome of interest	No of cases
Work I	Prospective	KIHD	2313 men[1]	Dietary intake of folate and vitamin B_{12}	13.6 years of follow-up	Hospital discharge diagnosis of depression	*n*=47
				Dietary intake of folate and vitamin B_{12}	18.8 years of follow-up	Hospital discharge diagnosis of depression	*n*=58
Work II	Prospective	KIHD	2077 men[1]	Serum concentrations of fatty acids	18.3 years of follow-up	Hospital discharge diagnosis of depression	*n*=46
Work III	Prospective	KIHD	2232 men[1]	Dietary coffee, tea and caffeine intake	17.5 years of follow-up	Hospital discharge diagnosis of depression	*n*=49
Work IV	Cross-sectional	KIHD	1003 men[1]	Dietary patterns	Four-year follow-up re-examination	Elevated depressive symptoms assessed by the HPL depression scale (HPL≥5)	*n*=72
	Prospective	KIHD	1003 men[1]	Dietary patterns	16.5 years of follow-up	Hospital discharge diagnosis of depression	*n*=28
Work V	Intervention	DPS	140; 59 men, 81 women[2]	Lifestyle intervention	Three years of intervention	Three-year change in the BDI scores	

Abbreviations: BDI, Beck Depression Inventory; DPS, Finnish Diabetes Prevention Study; HPL, Human Population Laboratory; KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study

[1]The number of KIHD study participants in the each work varied depending on the information available and potential exclusions. For example, in work IV, the food frequency questionnaires were available only at one time-point, the four-year follow-up examination, and filled only by a sub-group of the original KIHD cohort.

[2]The number of DPS study participants was altogether 140, as only two out of five study centers had BDI scores available

Table 12. The baseline characteristics of the KIHD study cohort, according to the works of this thesis.

Characteristics	**Work I, *n*=2313[1]**	**Work II, *n*=2077[1]**	**Work III, *n*=2232[1]**	**Work IV, *n*=1003[2]**
Age (years)	52.9 (5.2)	52.9 (5.2)	53.0 (5.2)	56.1 (6.6)
Education (years)	8.7 (3.4)	8.7 (3.4)	8.7 (3.5)	9.3 (3.6)
Marital status (living alone %)	13	12	12	11
Adulthood socio-economic status (points)	9.2 (4.6)	9.1 (4.6)	9.2 (4.6)	-
HPL depression score (points)	1.3 (1.3)	1.3 (1.3)	1.3 (1.3)	1.5 (2.0)
Maximal oxygen uptake (ml/kg/min)	30.9 (7.6)	31.1 (7.6)	30.9 (7.6)	-
BMI (kg/m^2)	26.8 (3.5)	26.9 (3.4)	26.8 (3.5)	27.6 (3.6)
Total energy intake (MJ/day)	9.9 (2.6)	9.9 (2.6)	9.9 (2.6)	-
Total PUFA intake (E%)	4.6 (1.3)	4.5 (1.4)	4.6 (1.4)	-
Fiber intake (g/day)	25.2 (7.3)	25.2 (8.7)	25.2 (7.2)	-
Alcohol intake (g/week)	72.1 (134)	71 .6 (126)	71.8 (134)	80 (125)
Smoking (%)	31	31	31	28

Abbreviations: BMI, body mass index; HPL, Human Population Laboratory; KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study; PUFA, polyunsaturated fatty acid
[1]Work is based on the baseline examinations of the KIHD cohort
[2]Work is based on the four-year re-examinations of the KIHD cohort

9.1.2 Assessment of diet

Food records

The dietary intake of foods and beverages was quantitatively assessed by a four-day food recording at the KIHD study baseline. The food records were instructed and delivered at study visits, and participants filled them in by household measures. Four days were supposed to be consecutive, three work days and one weekend day. Food records were returned and interview-checked at the next study visit. In the case of atypical day, food records were approved if they were otherwise properly filled; in the case of clear scarcity, the food records were rejected.

Nutrient intakes were calculated using the Finnish Nutrica® software, which is mainly compiled using Finnish values for the nutrient composition of foods. The calculations also take into account the loss of vitamins during food preparation. The software has been developed at the Research Center of the Social Insurance Institution of Finland. The nutrient compositions of foods in the Nutrica® software version 2.5 were mainly obtained from analyses carried out in the 1990s. Nutrica® software contained the latest data on the vitamin contents of fruits and vegetables. It includes a comprehensive database comprising over 1,300 food items and dishes and 30 nutrients.

Intake of dietary folate was obtained from the four-day food records (**work I**). Folate intake was adjusted for total energy intake using the regression residual method (136). Energy-adjustment is based on the assumption that a larger, more physically active person requires greater energy intake, which is also associated with a greater absolute intake of all nutrients. Energy-adjustment takes into account the differences in energy requirements among individuals. The residuals were standardized by the mean nutrient intake of a participant consuming 10 MJ/d, the approximate average total energy intake in the KIHD study population.

Information on coffee and tea consumption was obtained from the four-day food records (**work III**). In addition, we calculated the caffeine intake of the participants. As mentioned previously, caffeine content varies greatly depending on the composition of the blend, brewing method *etc.* (239) and for these calculations, we assumed that 100 mL of coffee and tea contain 100 mg and 40 mg of caffeine, respectively. The brewing method (boiling vs. filtering) was not taken into account, as the information on the usual method of brewing coffee at home was available only for a sub-sample of 1,002 men in the KIHD cohort. In the 1980s, it was very uncommon for middle-aged men to consume any other caffeine-containing drinks or foods, thus they were not added on total caffeine amount. In addition, in the KIHD cohort, there was no information on the use of decaffeinated coffee, since it was almost non-existent during the baseline analyses in the early 1980s. The food record data from the 11-year examinations was used in assessing the consistency of dietary intakes and food consumption during the follow-up period. The information on dietary covariants used in multi-adjusted models (**works I-III**); total energy intake, daily energy-adjusted intakes of vitamin C, folate, fiber, EPA and DHA, PUFAs, MUFAs, SFAs, total fat, and use of dairy products, were also obtained from four-day food records.

Food frequency questionnaire

At four-year examinations, the consumption of food items was assessed with an instructed unvalidated FFQ**,** developed especially for this cohort. Responders were asked about their frequency of consumption of 38 food and beverage items during the previous 12 months. There were six possible frequency categories: never or more seldom than once a month, once or twice a month, once a week, a couple of times a week, almost every day, once a day or more often. In addition, some items, such as coffee, tea and egg consumption were assessed quantitatively. Altogether 11 participants had missing information on food consumption. All the completed FFQs (n=1,003) were checked by a nutritionist and unclear

or missing responses were clarified. The information based on the FFQs was used to determine the dietary patterns in the KIHD study population (**work IV**).

9.1.3 Identification of dietary patterns

Dietary patterns were identified using *a posteriori* method, factor analysis. Principal components analysis with promax rotation was used, and 25 food and drink frequency groups with 38 food and beverage items (presented in **work IV**) were entered into the factor analysis. Eigenvalues greater than 1.5 were retained. The scree plot of eigenvalues indicated that there were three main dietary patterns. The three patterns were chosen and named based on the rationality in the co-operation with statistician. Factors were retained as variables in the data set, labeled on the basis of the behavioral concept and named as: "prudent", "Western" and "mixed" dietary pattern. The higher the pattern score for the subjects was, the more the diet reflected the particular dietary pattern. For each pattern, a label was proposed based on food groups displaying factor loading >0.20. These three dietary patterns accounted for 11.5%, 9.1% and 6.9%, respectively, of the variance in food consumption and explained altogether 27.5% of the variance distribution. The patterns are described in more detail in the Results section of **work IV**.

9.1.4 Ascertainment of follow-up events

In the prospective works, we used depression diagnosis set by a physician as the outcome (**works I-IV**). Data included participants who received a hospital discharge diagnosis of depressive disorder during the follow-up period. The information was obtained by computer linkage to the national hospital discharge register. Diagnoses were made according to the ICD criteria: ICD-8 for the years 1985-1986, ICD-9 for the years 1987-1995 and ICD-10 for the years 1996-2011. The category of depressive disorders included diagnoses of major depression (ICD-9: 2961-, ICD-10: F32.1-3, F33.1-3), a depressive, otherwise unspecified disorder (ICD-9: 2968A, ICD-10: F32.9, F33.9), chronic depression (ICD-8: 300.41, ICD-9: 3004A, ICD-10: F34.1) and adjustment disorder with depressive symptoms (ICD-9: 3090A). After an average 20.4 years of follow-up at the end of 2011, altogether 82 men had received a hospital discharge diagnosis of depressive disorder in the KIHD cohort.

9.1.5 Assessment of depressive symptoms

Depressive symptoms were assessed by the 18-item HPL depression scale at the baseline and at the four-year examinations (49). HPL depression score was used in assessing the depressive symptoms in **work IV**. The scale consists of items dealing with mood disturbance, negative self-concept, loss of energy, problems with eating and sleeping, trouble with concentration, and psychomotor retardation or agitation (**Appendix 2**). The HPL depression score is generated by defining one point for each true or false answer that is indicative of depression. For some items, the response "often" or "never", whichever is appropriate, was assigned one point. The range of the HPL scale is 0-18 points. Appetite was attained from the HPL depression score statement "I have a good appetite". The cut-off score of five or more has been used to define depression (49,119,319). The HPL depression scale was developed especially for screening general population samples (49) and it also conceptually resembles other brief symptom checklists such as CES-D (319,320). The HPL depression scale is highly correlated with the 21-item BDI (42,49). The Cronbach's alpha for the HPL depression scale was 0.60 at the baseline after exclusion of the participants with a previous psychiatric disorder, and 0.71 at the four-year examination.

9.1.6 Exclusion criteria

In the prospective **works I-III,** those whose HPL depression scores were five or more at baseline were considered to have elevated depressive symptoms. To prevent reverse

causation, these subjects were excluded, thus eliminating a group of men at higher risk of severe depression.

In the prospective work concerning the association between the dietary folate and vitamin B_{12} intake and the risk of receiving a hospital discharge diagnosis of depression (**work I**), the information of dietary intakes was missing in 82 participants. After exclusion of men having depressive symptoms at baseline (*n*=287), a total of 2,313 participants were included.

In the prospective work focusing on the association between serum concentrations of n-3 fatty acids and depression (**work II**), after exclusions of men with current depressive symptoms and previously diagnosed psychiatric disorder (*n*=409) and missing data on serum fatty acids (*n*=196), 2,077 participants were left to be analyzed.

In the prospective work of the association between coffee, tea and caffeine consumption and depression (**work III**), complete data were available for 2,232 men. Exclusions included previous psychiatric disorders (*n*=153) and current depressive symptoms (*n*=271). In addition, 26 participants were excluded due to missing data on coffee, tea or caffeine consumption.

In the cross-sectional and prospective work concerning dietary patterns and elevated depressive symptoms or depression (**work IV**), data from the KIHD study four-year re-examination was utilized. Altogether 1,038 men participated in the four-year examination, but 35 participants had missing data on food consumption frequency (*n*=11) or depressive symptoms (*n*=32). Thus, 1,003 men were included in the analyses.

9.1.7 Biochemical measurements

Serum esterified and non-esterified fatty acids (**work II**) were determined in one gas chromatographic run without pre-separation (321). Fatty acids (s-EPA, s-DHA, s-DPA, s-ALA, s-LA, s-AA) were chromatographed in an NB-351 capillary column (HNU-Nordion, Helsinki, Finland) by a Hewlett-Packard 5890 Series II gas chromatograph (Hewlett-Packard, Avondale, Pennsylvania, U.S.) with a flame ionization detector. The coefficient of variation for repeated measurements of major esterified fatty acids was about 5%. Because the relative degree of fatty acid saturation varies among the various types of esterified fatty acids (*i.e.,* cholesterol esters, phospholipids, and triglycerides), the concentration of esterified fatty acids was adjusted for serum low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations. The coefficient of variation for major non-esterified fatty acids was about 15%. For non-esterified fatty acids no adjustment was necessary. Based on serum fatty acid concentrations, we calculated the concentrations of total long-chain n-3 PUFAs (EPA+DPA+DHA), total n-6 PUFAs (LA+AA) and ratio of n-6 to n-3 PUFAs.

Serum folate was used as a potential confounder in **work IV**. Serum concentrations of folate were measured by radioimmunoassay (Quantaphase II, Bio-Rad, Hercules, California, U.S.). These measurements were carried out in 1998 from serum samples collected during 1991–1993 and kept frozen at −80°C.

9.1.8 Assessment of other variables

At the baseline and the four-year examinations, the KIHD participants completed questionnaires on their background, marital status (married or living as a couple, not married, separated or divorced, widowed), history of morbidity (hypertension, diabetes) and education (years of education, educational level) (321,322). A trained nurse checked and completed the questionnaires during an interview. Smoking habits were also reported, including ever-smoking, current smoking, cigarettes, cigars and pipefuls per day and duration of regular smoking. The number of years smoked was defined as the sum of smoking years, whether the smoking had occurred continuously or during several periods. The lifetime exposure to smoking (pack years) was estimated as a product of years smoked and the number of tobacco products smoked daily at the time of the examination, or for ex-

smokers, at the time when they had last smoked. The variable of adulthood SES was compiled from current income, current and previous occupations, the highest level of education, the perception of financial security, and housing tenure. In addition, an index of material living conditions was created by summing the number of material possessions (*e.g.*, dishwasher, car, summer cottage) from a list of 12 items. The variable "adulthood SES" was formed from these indicators (323).

Alcohol consumption (grams/week) was assessed with a structured quantity-frequency method using the Nordic Alcohol Consumption Inventory for drinking behavior over the previous 12 months (324). Physical activity was assessed using the 12-month Leisure-time Physical Activity Questionnaire (325). The questionnaire included the most common leisure-time physical activities of middle-aged Finnish men, selected based on a previous population study in Finland, and is described in more detail elsewhere (326). The participants were asked to record the frequency, average duration and intensity of each activity. The energy expenditure from physical activity was expressed as kcal per day. Description of the determination of maximal oxygen uptake has been published previously (321). The criteria for the history of CVD included a diagnosis of at least one coronary condition and have been presented earlier in more detail (327). The weight and height of the participants was measured by a study nurse, and the BMI was calculated as the ratio of weight in kilograms to the square of height in meters.

9.1.9 Statistical methods

In **works I-IV**, the heterogeneity of means of the baseline variables was tested by using the analysis of variance (*ANOVA*), Student's *t*-test, Mann-Whitney *U*-test, chi-squared test and Fisher's Exact test. The normal distributions were tested with the Kolmogorov-Smirnov (Lilliefors) test. The non-parametric Mann-Whitney *U*-test was utilized when the distribution of the values was skewed. Correlations were examined using Pearson's correlation coefficient or Spearman's correlation coefficient. Potential confounders in multivariate models were selected based on the literature and the characteristics of the study population. For entry, backward stepwise method was used, and those confounders with the strongest association with depression were chosen. Potential confounders were discarded from the models if they did not change the associations (*HR* change <5%).

In **work I**, the participants were classified into two categories according to the median energy-adjusted intake of folate: ≤248 μg/day and >248 μg/day. We also divided the study population into two groups according to the median daily intake of vitamin B_{12}: ≤7.09 μg/day and >7.09 μg/day. The *HR* for depression was examined using the Cox proportional hazard's model adjusted for age and examination year (Model 1) and further, for adulthood SES, baseline HPL depression score, energy-adjusted intake of vitamin C and fiber, and total fat intake (Model 2), and further, for total energy intake, marital status, education, current smoking habits and alcohol consumption.

In **work II**, to study the differences between serum fatty acid groups, we divided the study population into three groups according to the tertile values: n-3 PUFA (EPA+DPA+DHA: <3.85%, 3.85% to 4.92% and >4.92% of all serum fatty acids), EPA (<1.21%, 1.21% to 1.76% and >1.76%), DPA (<0.50%, 0.50% to 0.58% and >0.58%), DHA (<2.09%, 2.09% to 2.63% and >2.63%), LA (<24.6%, 24.6% to 28.3% and >28.3%), ALA (<0.62%, 0.62% to 0.80% and >0.80%), AA (<4.3%, 4.3% to 5.2% and >5.2%), ratio of n-6 to n-3 PUFAs (<5.3:1, 5.3:1 to 6.8:1, >6.8:1) and total n-6 PUFA (<29.6%, 29.6% to 33.6% and >33.6%). Because of the modest number of cases, in the stratified analyses dichotomous variables were used instead of tertiles; median values were used as the cut-off point: n-3 PUFAs (<4.36% and ≥4.36%) and n-6 PUFAs (<31.7% and ≥31.7%). Tests of linear trend were conducted by assessing the median values for each category of exposure variable and treating those as a single continuous variable. For the tests of non-linear trend, the linear trend variable was squared after centering it at median serum fatty acid value. The *HR* for depression was examined using the Cox proportional hazard's model adjusted for age and

examination year (Model 1) and further, for adulthood SES, maximal oxygen uptake, smoking (lifetime exposure), alcohol consumption and BMI (Model 2), and further, for total energy intake, appetite, energy-adjusted intake of folate, education, and baseline HPL depression score.

In **work III**, the participants were divided into four groups according to coffee drinking: non-drinkers, light drinkers (<375 mL/day), moderate drinkers (375 to 813 mL/day) and heavy drinkers (>813 mL/day). These coffee drinking categories have been used earlier in the KIHD cohort (328). Because of the low amount of tea consumed by the tea drinkers (mean intake 105 mL/day), subjects were categorized into tea drinkers and non-drinkers. The cohort was also divided into quartiles based on caffeine intake: <425 mg/day, 425 to 594 mg/day, 595 to 781 mg/day and >781 mg/day. The *HR* for depression was examined using the Cox proportional hazard's model adjusted for age and examination year (Model 1) and further, for adulthood SES, smoking (lifetime exposure), alcohol consumption, maximal oxygen uptake, BMI and daily intakes of folate and PUFAs (Model 2). Model 3 included Model 2 covariates plus baseline HPL depression score. In addition, total energy intake, the energy-adjusted intakes of EPA and DHA, use of dairy products, marital status, medical co-morbidity (hypertension, diabetes and CVD) and leisure-time physical activity, as well as substituting the intake of PUFAs with MUFAs and SFAs, were tested as potential confounders.

In **work IV**, the associations between dietary patterns and elevated depressive symptoms were examined using logistic regression models. Depressive symptoms (HPL$\geq$5) were treated as a binary dependent variable, and each dietary pattern score as a continuous variable. In cross-sectional analyses, the *OR*s were calculated in multivariate models, adjusted for age and examination year (Model 1), and further, for alcohol consumption, current smoking, marital status, education, leisure-time physical activity and history of CVD and mental illnesses (Model 2). The *HR* for getting a hospital discharge diagnosis of depression during the follow-up was examined using the Cox proportional hazard's model adjusted for age and examination year (Model 1), and further, for HPL depression score in four-year examination, history of mental illnesses and education (Model 2). Leisure-time physical activity, marital status, BMI, history of CVD, alcohol consumption and current smoking were tested for entry, but did not change the associations (*HR* change <5%) and were thus excluded from the models.

The 95% confidence intervals (CI) were estimated based on the assumption of asymptotic normality of estimates. *P*-value <0.05 was considered statistically significant. All statistical analyses were conducted using the Statistical Package for the Social Sciences software (*SPSS)* 14.0 for Windows or a newer version (*SPSS* Inc., Chicago, Illinois, U.S.).

9.2 THE FINNISH DIABETES PREVENTION STUDY (DPS) (V)

9.2.1 Study population

The DPS is a randomized, controlled, multicenter lifestyle intervention study conducted in Finland. The DPS included five study centers in Helsinki, Kuopio, Turku, Tampere, and Oulu. The main aim of the DPS was to assess the efficacy of lifestyle modification on preventing or delaying the onset of T2D in people with IGT. Study participants were recruited mainly by screening of high-risk individuals, such as first-degree relatives of T2D patients, who voluntarily responded to local advertisements, or were identified in earlier epidemiological surveys. The main inclusion criteria were BMI over 25 kg/m^2, age 40–64 years, and IGT on the basis of the mean values of two oral glucose tolerance tests. Randomization of the study participants started in November 1993, the recruitment period lasted until June 1998 and the intervention period lasted until the end of 2001. The data used in this work was based on the information of the study baseline and three-year

examinations. The study design and the methodology are described in more detail elsewhere (329-331).

The characteristics for the DPS population are presented in **Table 13**. Altogether 522 overweight individuals, 172 men and 350 women with IGT participated, and were randomly allocated to an intensive, individualized diet and exercise intervention or a control group. Randomization was done by the study physician, with the use of a randomization list, with stratification according to center, gender, and the mean plasma glucose concentration two hours after oral glucose challenge (331). Study design was single-blinded, as the staff members involved in the intervention had to be aware of the group assignment. Criteria for exclusion included the presence of chronic disease rendering survival for six years unlikely, and other characteristics (psychological or physical disabilities) deemed likely to interfere with participation in the study. The participants gave written informed consent. The study protocol was approved by the Ethics Committee of the National Public Health Institute in Helsinki, Finland.

9.2.2 Advice for the lifestyle intervention group

The main goals of the lifestyle intervention were based upon available evidence on risk factors of diabetes. The participants in the intervention group (n=265) were given detailed advice to achieve the goals: 1) weight reduction of ≥5%, 2) fat intake <30% of the total energy intake, 3) SFAs <10% of total energy intake, 4) dietary fiber intake to ≥15 g per 1000 kcal, and 5) moderate exercise for ≥30 minutes per day.

The intensive intervention consisted of seven face-to-face counseling sessions with the study nutritionist during the first year of the study, and one session every three months thereafter for three years. The first-year sessions were tailored based on the food records, focusing on specific individual problems. However, each session had a preplanned topic, for example regular meal patterns and substituting energy-dense foods containing SFAs, sugar, or alcohol with lower-energy items. Consumption of whole-grains instead of refined grains, abundant daily consumption of vegetables and fruits, consumption of low-fat milk and meat products, soft margarines and vegetable oils rich in unsaturated fatty acids were also recommended. The plate model was used to estimate portion sizes. Additionally, there were voluntary group sessions, expert lectures, low-fat cooking lessons, visits to local supermarkets, and possibility to have between-visit phone calls and discussions by letters. The goal was to equip the participants with the necessary knowledge and skills and to achieve gradual, permanent behavioral changes (330). Very-low-calorie diet was considered to be used for two to five weeks, if preferred by the subject, to boost weight loss.

The exercise intervention was individualized and aimed at increasing all physical activity. It was based on daily physical activities, endurance exercise (such as walking, jogging, swimming, aerobic ball games, or skiing) and muscle strengthening. Progressive, individually tailored, supervised circuit-type resistance training sessions to improve the functional capacity and strength of the large muscle groups of the upper and lower body were also offered. Training sessions began four to six months after randomization. The exercise intervention has been described in more detail elsewhere (330,331).

9.2.3 Advice for the control group

At baseline, the participants in the control group (n=257) were given general verbal and written information, a two-page leaflet, on diet and exercise. This was done either individually or in one group session. The principles of the message for the control group were the same as for the intervention group participants: to reduce weight, increase physical activity, and to make qualitative changes in diet. The advice the control group received concerning healthy lifestyle could be regarded “a mini-intervention”. The control group visited the research centers once a year for three years and all the measurements were similar in both groups.

Table 13. The baseline characteristics of the participants in the Finnish DPS.[1]

	DPS participants without BDI scores available *n*=382			BDI-scores available *n*=140		
	Intervention (*n*=196)	**Control (*n*=186)**	***P*-value[2]**	**Intervention (*n*=69)**	**Control (*n*=71)**	***P*-value[2]**
Men/women	63/133	50/136	0.260	28/41	31/40	0.422
Age (years)	54.7 (7.5)	53.9 (6.9)	0.333	57.7 (6.4)	57.4 (6.5)	0.786
Education: high school or upper (%)	37	33	0.236	22	31	0.566
Living without a spouse (%)	26	23	0.554	22	15	0.756
BDI scores (points)				6.8 (5.6)	6.7 (5.5)	0.945
BDI scores ≥11 (*n*/%)				14/20	16/23	0.453
Antidepressant medicine use (*n*)	5	4	0.533	1	2	0.511
Body mass index (kg/m^2)	31.8 (4.8)	31.0 (4.4)	0.111	30.2 (3.4)	31.2 (4.7)	0.166
Physical activity (min/week)	375 (319)	410 (378)	0.335	535 (353)	507 (390)	0.663
Total energy (kcal/day)	1780 (527)	1737 (532)	0.432	1744 (503)	1760 (515)	0.857
Fat (% of energy)	36.4 (6.9)	37.2 (6.2)	0.202	35.2 (6.3)	36.8 (7.2)	0.147
PUFAs (% of energy)	5.85 (1.73)	5.94 (2.26)	0.633	5.33 (1.66)	5.58 (1.32)	0.408
Fiber (g/day)	20.0 (7.3)	19.3 (7.7)	0.381	21.1(6.9)	20.4 (7.0)	0.805
Alcohol (g/day)	8.9 (17.8)	6.1 (12.9)	0.080	5.1 (16.4)	4.8 (9.4)	0.885
Smoking (ever smokers %)	41	45	0.272	44	55	0.118

Abbreviations: BDI, Beck Depression Inventory; DPS, Diabetes Prevention Study; PUFA, polyunsaturated fatty acid
[1]Data are expressed as the mean (*SD*) unless otherwise indicated.
[2]Significance of the difference between groups was assessed by Student's *t* test, Mann-Whitney *U*-test and $\chi 2$ test.

9.2.4 Assessment of depressive symptoms

Depressive symptoms were assessed with the Finnish version of the self-administered 21-item BDI, which is one of the most commonly used instruments for measuring the severity of depression (42). The BDI is a well-known and well-validated self-report measurement method of depressive symptoms (332). Also the Finnish version of the 21-BDI has been validated (333). The version used in the DPS, BDI Ia (**Appendix 1**), is a modestly modified version of the original version, as for example the alternative "a" and "b" statements have been removed to ease the use, and symptoms are asked for the preceding two weeks (334). However, the symptom evaluation scale is similar to the previous version. In clinical work, the BDI has been established as a common tool for assessing depressive symptoms and progress in the follow-up. Moreover, the mean BDI scores correlate well with the prevalence of depression determined by clinical interviews (335).

Patients choose from a group of sentences the one which best describes how they have been feeling during the past two weeks, resulting in total scores from 0 to 63. The cut-off point for elevated depressive symptoms was set at 11 points, 0 to 10 indicating normal mood and 11 or more indicating elevated depressive symptoms. The same cut-off point was used in an earlier intervention study (303). Participants reported the use of antidepressant medication at baseline and subsequently at each annual study visit. There were two study centers out of five that carried out the BDI, and therefore the BDI scores were available for 140 individuals (69 in the intervention group and 71 in the control group; 59 men and 81 women, respectively). **Table 13** presents the baseline characteristics for those participants who had BDI scores available, as well as for the rest of the study population. There were no statistically significant differences in any of the variables between intervention and control groups.

9.2.5 Assessment of diet and other variables

Diet was assessed using three-day food records four times a year. Intakes of nutrients were calculated using a dietary analysis program, the Finnish Food Composition Database (Fineli), developed by the National Public Health Institute (336). The program allows modification of database recipes, *e.g.*, the use of skimmed instead of whole milk can be coded (330). Participants completed a medical-history questionnaire and underwent a physical examination. Participants underwent a 75-g oral glucose tolerance test at baseline and at each annual visit, as described previously (329,331). Physical activity was assessed at baseline and at each annual visit with the validated the 12-month Leisure-time Physical Activity Questionnaire (325). Information on antidepressant prescriptions was obtained from a linkage to the medication reimbursement register of the Finnish Social Insurance Institution. The weight and height of the participants was measured by a study nurse, and the BMI was calculated as the ratio of weight in kilograms to the square of height in meters. Anthropometric measurements of height, weight, waist circumference and blood pressure measurements have been described in more detail previously (329). Weight was measured at every visit, and a weight chart was drawn.

9.2.6 Statistical methods

The data were expressed as means ± standard deviations (*SD*). The α–level was set at ≤ 0.05. The differences in baseline variables between intervention and control group were tested by using the *ANOVA*, Student's *t*-test, Mann-Whitney *U*-test and chi-squared test. Normal distributions were tested with the Kolmogorov-Smirnov (Lilliefors) test. The non-parametric Mann-Whitney *U*-test was utilized when the distribution of the values was skewed. Non-parametric two-related samples test (Wilcoxon) was used to evaluate the changes in BDI scores within the intervention and control groups during the intervention. Because the BDI scores had skewed distributions, unadjusted differences in mean BDI scores between groups were evaluated using Mann-Whitney *U*-tests both at baseline and at

three years. A forward stepwise linear multivariate regression analysis was used to find the strongest determinants of the change in BDI scores (*P* in 0.10, *P* out 0.20). All statistical tests were two-tailed. Data were analyzed using *SPSS* for Windows version 14.0 statistical software (*SPSS* Inc., Chicago, Illinois, U.S.).

10 Results

10.1 DIETARY FOLATE AND THE RISK OF DEPRESSION (I)

A total of 47 (2.0%) individuals were hospitalized due to depression during the average 13.6 years of follow-up and 58 (2.5 %) during the average 18.8 years of follow-up. The men who were hospitalized because of depression during the 13.6 years of follow-up period had higher intake of energy and higher HPL depression scores at baseline as compared to those who remained non-depressed. Participants having developed diagnosed depression during the 18.8 years of follow-up had, on the average, higher total energy intake, higher baseline HPL depression scores and they were slightly younger at baseline compared to other participants (data not shown).

At the baseline examinations, the mean daily intake of folate was 256 μg/day (*SD* 76). Altogether 24.6% of the participants reached the Finnish recommended daily folate intake of 300 μg/day (102). The correlation coefficient between folate intake at the baseline and at the 11-year follow-up examinations was 0.30 ($P<0.001$).

In multivariate analysis adjusted for adulthood SES, baseline HPL depression score, energy-adjusted daily intake of fiber and vitamin C, and total fat intake, when compared the lower folate intake median to the higher median, the risk of having a hospital discharge diagnosis of depression was two-and-a-half-fold higher (*HR*: 2.53; 95% *CI*: 1.17 to 5.48; $P=0.019$) in analyses of 13.6 years of follow-up and two-fold higher (*HR*: 2.07; 95% *CI:* 1.07 to 4.00; $P=0.032$) in analyses after 18.8 years of follow-up. Further adjustments for marital status, education, current smoking habits and alcohol consumption did not alter the associations either during the average 13.6 years of follow-up (*HR*: 2.51; 95% *CI:* 1.16 to 5.45; $P=0.020$) or during the average 18.8 years of follow-up (*HR*: 2.11; 95% *CI*: 1.08 to 4.11; $P=0.028$). Further adjustment for the total energy intake had little effect on the association between folate intake and the incidence of depression during 13.6 years of follow-up (*HR:* 3.01; 95% *CI:* 1.56 to 5.82; $P=0.001$) and after 18.8 years of follow-up (*HR*: 2.13; 95% *CI*: 1.10 to 4.12; $P=0.025$).

Table 14 presents the *HR*s of depression according to the energy-adjusted mean intake of folate at different time-points: from 10.3 to 20.7 years of follow-up (from year 2002 to 2011). Generally, participants in the lower (below median) folate intake group had higher risk of depression compared to men in the higher (above median) folate intake group. However, the risk of depression did not reach statistical significance in 10 to 12 follow-up years. In addition, the risk flagged with prolonged follow-up, after 19 years of follow-up.

The mean daily intake of vitamin B_{12} was 9.5 μg/day (*SD* 9.3) for the whole population at the baseline examinations. Intake of vitamin B_{12} was not associated with the risk of depression in either 13.6 years of follow-up: upper median of intake of B_{12} vitamin vs. lower median (*HR*: 0.40, 95% *CI*: 0.43 to 1.39, $P=0.401$) or in 20.1 years of follow-up (*HR*: 0.78; 95% *CI*: 0.47 to 1.31; $P=0.347$) with similar adjustments as in the analyses of folate (**Table 15**). Furthermore, dividing the mean vitamin B_{12} intake into tertiles or quartiles still revealed no association between cobalamin intake and risk of depression (data not shown).

Table 14. The hazard ratios of getting a hospital discharge diagnosis of depression according to the energy-adjusted mean dietary intake of folate with the number of follow-up years.

Mean follow-up time (years)	**Cases in lower half[1], *n* (%)**	**Cases in upper half, n (%)**	**Hazard ratio[2] (95% *CI*)**	***P* value**
10.3	24 (2.1)	10 (0.9)	2.08 (0.86, 5.07)	0.106
11.2	29 (2.5)	13 (1.1)	2.04 (0.93, 4.49)	0.076
12.0	29 (2.5)	13 (1.1)	2.04 (0.93, 4.49)	0.076
12.8	33 (2.8)	13 (1.1)	2.28 (1.06, 4.89)	0.036
13.6	35 (3.1)	13 (1.1)	2.53 (1.17, 5.48)	0.019
14.4	36 (3.1)	15 (1.3)	2.30 (1.12, 4.73)	0.024
15.2	37 (3.2)	15 (1.3)	2.42 (1.18, 4.96)	0.016
16.0	37 (3.2)	16 (1.4)	2.25 (1.11, 4.55)	0.024
16.7	38 (3.3)	17 (1.5)	2.20 (1.11, 4.37)	0.025
17.4	38 (3.3)	19 (1.6)	2.01 (1.03, 3.91)	0.040
18.1	39 (3.4)	19 (1.6)	2.07 (1.07, 4.01)	0.032
18.8	39 (3.4)	19 (1.6)	2.07 (1.07, 4.01)	0.032
19.5	40 (3.4)	20 (1.7)	1.91 (1.00, 3.66)	0.050
20.1	40 (3.5)	20 (1.7)	1.91 (1.00, 3.66)	0.050
20.7	41 (3.5)	22 (1.9)	1.74 (0.93, 3.25)	0.084

Abbreviations: *CI*, confidence interval; HPL, Human Population Laboratory
[1]According to the median
[2]Comparisons: lower median (≤248 µg/day) vs. upper median (>248 µg/day) of energy-adjusted folate intake. Models adjusted for age and examination year, current socio-economic status, baseline HPL depression score, energy-adjusted daily intake of fibre and vitamin C, and total fat intake

Table 15. The hazard ratios of getting a hospital discharge diagnosis of depression during the average 13.6 and 20.1 years of follow-up according to the energy-adjusted mean dietary intake of vitamin B_{12}.

Follow-up time (years)	**Cases in lower half[1] *n* (%)**	**Cases in upper half *n* (%)**	**Hazard ratio Model 1[2] (Model 2[3])**	**95% *CI* Model 1 (Model 2)**	***P*-value**
13.6	22 (2.0)	25 (2.2)	0.85	0.48, 1.51	0.590
			(0.40)	(0.43, 1.39)	(0.401)
20.1	28 (2.4)	32 (2.8)	0.84	0.51, 1.40	0.505
			(0.78)	(0.47, 1.31)	(0.347)

Abbreviations: CI, confidence interval, HPL, Human Population Laboratory
[1]According to the median
[2]Adjusted for age and examination year
[3]Adjusted for age and examination year, current socio-economic status, baseline HPL depression score, energy-adjusted daily intake of fibre and vitamin C, and total fat intake

10.2 SERUM POLYUNSATURATED FATTY ACIDS AND THE RISK OF DEPRESSION (II)

There were 46 participants who were given a hospital discharge diagnosis of depression during the average 18.3 years of follow-up. The mean baseline serum concentration of n-3 PUFAs was 4.7% (*SD* 1.6) for the whole population and 4.5% (*SD* 1.4) for those with diagnosis of depression. The men who were hospitalized due to depression during the follow-up had higher intake of energy and higher baseline HPL depression scores. The correlation coefficient between the serum n-3 PUFAs (EPA+DPA+DHA) at baseline and at 11-year follow-up was 0.42 ($P<0.001$) and for the serum n-6 PUFAs 0.47 ($P<0.001$).

Table 16 presents the *HR*s for the association between serum fatty acids and the risk of getting a hospital discharge diagnosis of depression during the follow-up. There were no statistically significant associations between the serum concentrations of total n-3 PUFAs, total n-6 PUFAs or any individual fatty acids (EPA, DHA, LA, ALA or AA) and the risk of depression. Further adjustments for total energy intake, energy-adjusted intake of folate, appetite, education, and baseline HPL depression score did not change the association markedly (*HR* change <5%). In addition, the ratio of n-6 to n-3 PUFAs was not associated with the risk of depression.

Evaluations of the interaction between total n-3 and total n-6 PUFAs by using stratified analyses (both divided at median) were also conducted. However, no evidence for effect modification by total n-6 PUFAs was found (*P* for interaction 0.72).

Table 16. The hazard ratios of getting a hospital discharge diagnosis of depression during the average follow-up of 18.3 years according to tertiles of serum fatty acid concentrations.

	Model 1[1]			**Model 2[2]**		
	HR	**95 % *CI***	***P* for trend**	***HR***	**95 % *CI***	***P* for trend**
N-3 (EPA+DHA+DPA)			0.29			0.33
1 (lowest)	1			1		
2	0.41	0.19, 0.91		0.41	0.19, 0.91	
3 (highest)	0.71	0.38, 1.38		0.71	0.38, 1.43	
N-6			0.76			0.55
1	1			1		
2	0.91	0.43, 1.91		0.96	0.45, 2.04	
3	1.10	0.55, 2.23		1.25	0.59, 2.65	
EPA			0.19			0.17
1	1			1		
2	0.57	0.28, 1.16		0.55	0.26, 1.12	
3	0.64	0.33, 1.32		0.62	0.31, 1.25	
DHA			0.79			0.98
1	1			1		
2	0.93	0.46, 1.87		0.96	0.47, 1.96	
3	0.91	0.45, 1.84		0.99	0.48, 2.04	
Linoleic acid			0.47			0.28
1	1			1		
2	0.62	0.28, 1.37		0.67	0.29, 1.51	
3	1.23	0.63, 2.39		1.43	0.70, 2.91	
Alpha-linolenic acid			0.35			0.22
1	1			1		
2	1.07	0.50, 2.28		1.16	0.54, 2.51	
3	1.41	0.67, 2.94		1.60	0.75, 3.43	
Arachidonic acid			0.21			0.20
1	1			1		
2	0.77	0.39, 1.53		0.77	0.39, 1.53	
3	0.64	0.31, 1.30		0.62	0.30, 1.29	
Ratio of n-6 to n-3			0.99			0.98
1	1			1		
2	0.79	0.38, 1.65		0.77	0.37, 1.62	
3	0.99	0.50, 1.96		0.97	0.49, 2.00	

Abbreviations: BMI, body mass index; *CI*, confidence interval; *HR* hazard ratio; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; SES, socio-economic status;
[1]*HR* derived from Cox proportional hazard's models. Model 1: adjusted for age and examination years.
[2]*HR* derived from Cox proportional hazard's models. Model 2: adjusted for age, examination year, BMI, adulthood SES, cigarette smoking, alcohol consumption and maximal oxygen uptake.

10.3 COFFEE, TEA AND CAFFEINE CONSUMPTION AND THE RISK OF DEPRESSION (III)

There were 49 men who were given a hospital discharge diagnosis of depression during the average 17.5 years of follow-up. The mean coffee consumption (*SD*) was 565 (293) mL/day, the mean tea consumption 105 (183) mL/day and mean caffeine intake 494 (221) mg/day for the whole cohort.

The coffee drinkers had a statistically significantly lower intake of folate, and they were more likely to be smokers than the non-drinkers at baseline (**work III**). In addition, coffee drinkers had higher energy intake and higher SES compared to non-drinkers. A total of 4.9% of the coffee non-drinkers, 1.3% of the light coffee drinkers, 2.6% of the moderate coffee drinkers and 1.5% of the heavy coffee drinkers received a hospital discharge diagnosis of depression during the follow-up. There was a statistically significant correlation between the reported coffee drinking at the baseline and at the 11-year follow-up (r=0.54, P<0.001).

Heavy coffee drinkers had a 72% (95% *CI:* 0.02 to 0.98) lower risk of hospitalization due to depression as compared to the non-drinkers (**Table 17, Model 1**). Further adjustments (Model 2 and Model 3) did not significantly attenuate the association, nor did further adjustment for total energy intake, energy-adjusted intakes of EPA and DHA, use of dairy products, marital status, medical co-morbidity (hypertension, diabetes and CVD) and leisure-time physical activity. Substituting the intake of PUFA with MUFA and SFA did not attenuate the results appreciably.

Tea drinking or caffeine intake was not associated with the risk of depression (**Table 17**). The results remained consistent regardless of whether caffeine intake groups were categorized as medians (*HR*: 1.31; 95% *CI:* 0.74 to 2.31; P=0.355) or tertiles (highest tertile v. lowest tertile; *HR*: 1.14; 95% *CI*: 0.53 to 2.44; P=0.744).

Table 17. The hazard ratios of getting a hospital discharge diagnosis of depression during the average follow-up of 17.5 years according to mean daily consumption of coffee, tea or caffeine.[1]

Coffee consumption category[2]	**None (*n*=82)**	**Light (*n*=517)**	**Moderate (*n*=1243)**	**Heavy (*n*=390)**	***P*-value[3]**
Mean coffee consumption mL/day	0	250	595	1007	
Number of events (%)	4 (4.9)	7 (1.3)	32 (2.6)	6 (1.5)	
Model 1[4]	1	0.27 (0.08, 0.93)	0.49 (0.17, 1.40)	0.28 (0.08, 0.98)	0.047
Model 2[5]	1	0.28 (0.08, 0.96)	0.45 (0.16, 1.29)	0.23 (0.06, 0.83)	0.025
Model 3[6]	1	0.29 (0.08, 0.98)	0.48 (0.17, 1.36)	0.25 (0.07, 0.91)	0.035
Tea consumption category	**Non-tea drinkers (*n*=1264)**	**Tea drinkers (*n*=968)**			***P*-value**
Mean tea consumption mL/day	0	242 (209)			
Number of events (%)	25 (1.9)	24 (2.5)			
Model 1[4]	1	1.19 (0.69, 2.08)			0.549
Model 2[5]	1	1.43 (0.80, 2.56)			0.222
Model 3[6]	1	1.40 (0.78, 2.51)			0.252
Quartiles of caffeine intake[7]	**1**	**2**	**3**	**4**	***P*-value**
Mg/day	<425	425-594	595-781	>781	
Number of events (%)	9 (1.6)	12 (2.1)	18 (3.3)	10 (1.8)	
Model 1[4]	1	1.22 (0.52, 2.91)	1.97 (0.89, 4.42)	0.99 (0.40, 2.45)	0.981
Model 2[5]	1	1.12 (0.47, 2.67)	1.83 (0.82, 4.11)	0.85 (0.34, 2.16)	0.739
Model[6]	1	1.07 (0.45, 2.56)	1.83 (0.82, 4.09)	0.85 (0.34, 2.15)	0.732

Abbreviations: BMI, body mass index; *CI*, confidence interval; HPL, Human Population Laboratory; *HR*, hazard ratio; PUFA, polyunsaturated fatty acid; SES, socio-economic status

[1]All values are *HR* (95% *CI*)

[2]Light <375 mL/day; moderate 375-813 mL/day; and heavy >813 mL/day.

[3] *P*-value for the difference between heavy-drinkers and non-drinkers

[4]*HR*: hazard ratio derived from Cox proportional hazard's models. Model 1: adjusted for age and examination years.

[5]Model 2: adjusted for Model 1 and adulthood SES, smoking, alcohol consumption, BMI, daily intake of folate and PUFAs.

[6]Model 3: adjusted for Model 2 and baseline HPL depression scale score.

[7]*P*-value for the difference between the lowest and the highest caffeine intake group

10.4 DIETARY PATTERNS AND DEPRESSION (IV)

Altogether 72 subjects (7.2% of the population) had elevated depressive symptoms at the four-year examination. The mean age (*SD*) of the study subjects was 56.2 (6.7) years (range 46 to 65 years). The baseline characteristics of the study participants with current depressive symptoms and the rest of the cohort showed that depressed participants had lower leisure-time energy expenditure compared to non-depressed subjects. In addition, depressed subjects had more often a history of CVD and mental illnesses.

The factor-loading matrix for the three dietary patterns, prudent, Western and mixed, is shown in **Table 18.** Higher factor scores indicated greater consumption of these types of foods and lower score indicated lower consumption. Prudent dietary pattern was rich in fresh vegetables, cooked vegetables, fruits, berries, whole-grain bread, poultry, fish and low-fat cheese. Western dietary pattern was characterized by higher consumption of sausages, processed meat, sweet snacks like ice-cream, candies and chocolate, sweet soft drinks and juices, baked potatoes and French fries, French rolls, manufactured foods, cheese and eggs. Mixed dietary pattern was rich in sweet coffee breads, fresh and frozen berries, porridge, sweet snacks, sweet soft drinks and juices and low in alcohol consumption.

Those participants with higher scores of prudent dietary pattern were more likely to have better education and they were more likely to be married and non-smokers and have higher leisure-time physical activity, compared to those with lower scores (divided according to median scores). Those with higher scores in Western dietary pattern had higher alcohol consumption and they were more likely to be younger and smokers than those with lower scores in this factor. Participants with high loading in the mixed pattern had shorter education, lower alcohol consumption, lower BMI and they were younger compared to those with lower scores in this pattern.

Results from the analyses are presented in **Table 19**. In cross-sectional analyses, after adjusting for potential confounders (age, examination year, BMI, alcohol consumption, smoking, marital status, education, leisure-time physical activity, history of mental illnesses and history of CVD) the prudent, healthy dietary pattern was associated with a decreased prevalence of depressive symptoms (*OR:* 0.75; 95% *CI:* 0.57 to 0.99; *P*=0.036), the Western dietary pattern was associated with an increased prevalence of depressive symptoms (*OR:* 1.41; 95% *CI:* 1.08 to 1.84; *P*=0.011) while the mixed dietary pattern showed no association (*OR:* 1.10; 95% *CI:* 0.83 to 1.47; *P*=0.492). To explore whether the association between the prudent dietary pattern and depression is explained by folate status, we additionally adjusted for serum concentrations of folate. This did not attenuate the found inverse association between the prudent dietary pattern and depressive symptoms (*OR*: 0.75; 95% *CI:* 0.57 to 0.99; *P*=0.044).

In the prospective analyses with the average follow-up time of 16.5 years and 28 cases of depression requiring hospital treatment, the prudent dietary pattern was inversely associated with the risk of depression (*HR*: 0.66; 95% *CI*: 0.47 to 0.93; *P*=0.018) after adjustment for age, year of examination, four-year HPL depression score, education and history of mental illnesses. The Western or mixed dietary patterns were not associated with depression risk in prospective analyses.

Table 18. Factor loading matrix for the three dietary patterns identified in the KIHD study cohort by principal component analysis.[1,2]

	Correlation coefficients (*n*=1003)		
Foods or food groups	**"Prudent"**	**"Western"**	**"Mixed"**
Fresh vegetables, roots, salads	0.72	**-**	**-**
Cooked vegetable foods	0.65	**-**	**-**
Fresh fruits	0.48	**-**	**-**
Fresh or frozen berries	0.35	-0.33	0.54
Boiled potatoes	**-**	**-**	0.33
Baked potatoes or French fries	**-**	0.52	**-**
Fish and fish foods	0.32	**-**	**-**
Poultry	0.54	**-**	**-**
Sausage, processed meat	-	0.62	**-**
Egg	-	0.35	**-**
Fatty cheese	0.36	0.38	**-**
Low fat cheese	0.50	-	**-**
Milk	-	-	**-**
Coffee	-0.22	0.25	**-**
Tea	0.25	-	**-**
Alcohol	0.26	0.27	-0.43
Sweet soft drinks and juices	-	0.53	0.45
Candies, chocolate and ice cream	-	0.64	0.43
Sweet coffee bread	-	-	0.62
Manufactured foods	-	0.38	-
Yeast, graham and whole-grain bread	0.42	-	-
French roll	0.26	0.45	-
Rye bread, crispbread	-	-	0.23
Porridge	-	-0.24	0.54
Breakfast cereal, corn flakes	-	-	-

Abbreviations: KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study
[1]A positive loading indicates that food group is positively associated with the factor, a negative loading denotes an inverse association
[2]To simplify data presentation, loadings with absolute value less than 0.20 are not shown.

Table 19. Prevalence of depressive symptoms and risk of getting a hospital discharge diagnosis of depression during the average 16.5 years of follow-up according to the dietary patterns.

Type of analysis and factor	**Depressive symptoms, HPL≥5 (*n*=72)[1]**		**Hospitalization due to depression (*n*=28)[2]**	
Dietary pattern	Odds ratio (95% *CI*)	*P*-value	Hazard ratio (95% *CI*)	*P*-value
Model 1[3]				
Prudent	0.76 (0.60, 0.97)	0.025	0.65 (0.46, 0.91)	0.013
Western	1.46 (1.15, 1.86)	0.002	0.98 (0.67, 1.42)	0.892
Mixed	1.05 (0.83, 1.34)	0.672	1.08 (0.74, 1.57)	0.707
Model 2[4]			Model 2[5]	
Prudent	0.75 (0.57, 0.99)	0.036	0.66 (0.47, 0.93)	0.018
Western	1.41 (1.08, 1.84)	0.011	0.91 (0.63, 1.32)	0.615
Mixed	1.10 (0.83, 1.47)	0.492	0.97 (0.66, 1.41)	0.858

Abbreviations: *CI*, confidence interval; HPL, Human Population Laboratory
[1]Cross-sectional analyses conducted with logistic regression based on four-year examination
[2]Prospective analyses conducted with Cox proportional hazard's model
[3]Model 1 is adjusted for age and examination year.
[4]Model 2 is adjusted for age, examination year, body mass index, smoking, alcohol consumption, education, marital status, leisure-time physical activity, history of mental illnesses and history of cardiovascular diseases.
[5]Model 2 is adjusted for age, examination year, education, history of mental illnesses and four-year HPL depression score.

10.5 THE EFFECT OF LIFESTYLE INTERVENTION ON DEPRESSIVE SYMPTOMS (V)

At study entry, the mean BDI scores (*SD*) of the participants were 6.8 (5.5). The changes in the BDI scores and other variables over the follow-up period of three years are presented in **Table 20**. The BDI scores were reduced during the study by 0.82 (4.49) scores (P=0.006). The mean (*SD*, 95% *CI*) reduction in the BDI scores was 0.90 (4.54, -1.99 to -0.19) in the intervention group (P=0.033) and 0.75 (4.47, -1.80 to 0.31) in the control group (P=0.076) There was no statistically significant difference in the changes of BDI scores between the study groups (P=0.965). The use of antidepressant medication was uncommon in our study population both at the beginning (n=1 and n=2 in the intervention and control groups, respectively) and at the end of the intervention (n=2 and n=2 in the intervention and control groups, respectively). The mean energy intake and intake of SFAs decreased statistically significantly more in the intervention group compared to the control group. The weight and BMI of the participants also decreased more in the intervention group than in the control group.

Altogether 30 participants (21.4%) had elevated depressive symptoms (BDI≥11) at baseline and 22 (15.7%) after three years of the study entry. The decrease in the prevalence of elevated depressive symptoms was 2.9% in the intervention group, 8.5% in the control group and 5.7% in all participants with the BDI data available. When analyzing separately the participants with elevated depressive symptoms at baseline, the mean reduction of depressive symptoms during the study was -2.80 (5.83) points (P=0.015). In the intervention group the reduction was -2.00 (6.16) points (P=0.248) and in the control group -3.50 (5.63) points (P=0.031) (P=0.307 for the difference). When excluding those who had elevated depressive symptoms at baseline, BDI scores decreased by 0.62 (4.06) points (P=0.071) in the intervention group and increased with 0.06 (3.77) points (P=0.738) in the control group (P=0.321 for the difference).

In a stepwise linear multivariate regression model, the variables with the strongest associations with the change in BDI scores during the three-year study were baseline BDI scores (standardized coefficient - 0.392, P<0.001), weight change (0.194, P=0.024) and marital status (0.196, P=0.025). This model explained 20% of the change in BDI scores (R^2=0.204, P<0.001, n=140), indicating that higher BDI scores at the baseline, greater weight reduction and being married were associated with greater decrease in BDI scores.

Variables with the strongest associations with the change in BDI scores in those with elevated depressive symptoms at baseline (n=30) were baseline BDI score (-0.762, P=0.010), change in total energy intake (0.341, P=0.042), education (0.476, P=0.086) and weight change (0.190, P=0.268) (R^2=0.378, P=0.002). When specifically examining those who had no elevated depressive symptoms at baseline (n=110), the strongest determinants of the change in BDI scores during the three-year follow-up were almost the same (baseline BDI score, -0.685, P<0.001; marital status, 0.267, P=0.101; baseline BMI, 0.331, P=0.133; and weight change, 0.130, P=0.179; R^2=0.188, P<0.001). Thus, higher baseline BDI scores, greater decrease in energy intake, higher education and weight reduction were associated with greater decrease in the BDI scores.

Table 20. Changes in selected variables from baseline to year three according to the study group in the Finnish DPS[1]

	Intervention group (*n*=69)		**Control group (*n*=71)**		
	Mean (*SD*)	**95 % *CI***	**Mean (*SD*)**	**95 % *CI***	***P*-value[2]**
Change in BDI scores (points)	-0.90 (4.54)	-1.99, -0.19	-0.75 (4.47)	-1.80, 0.31	0.965
Change in weight (kg)	-3.14 (4.52)	-4.23, -2.05	-1.18 (5.32)	-2.44, 0.08	0.021
Change in body mass index (kg/m^2)	-1.16 (1.74)	-1.58, -0.74	-0.45 (1.90)	-0.90, -0.002	0.024
Change in physical activity (min/wk.)	56.3 (381.2)	-36.0, 148.5	66.7 (461.6)	-44.1, 177.6	0.885
Change in energy intake (kcal)	-223 (352)	-309, -137	-38 (492)	-156, 80	0.013
Change in consumption of					
PUFAs (E%)	-1.25 (3.89)	-2.19, -0.31	-0.64 (4.38)	-1.69, -0.24	0.389
SFAs (E%)	-9.06 (8.84)	-11.22, -6.91	-2.85 (13.44)	-6.08, 0.38	0.002
Fish (g)	3.65 (61.89)	-11.44, 18.75	-15.88 (58.33)	-29.89, 1.89	0.060
Fibre (g)	1.76 (6.88)	0.09, 3.04	-0.69 (2.71)	-156, 80	0.530
Rye (g)	-3.08 (33.90)	-5.19, 11.35	-6.34 (50.99)	-18.60, 5.90	0.208
Folate (µg)	-2.64 (74.22)	-20.74, 15.47	1.18 (87.45)	-19.83, 22.19	0.784
Depressive symptoms at baseline	**Intervention group[3] (*n*=14)** **Mean ± *SD***	**95 % CI**	**Control group[3] (*n*=16)** **Mean ± *SD***	**95 % CI**	***P*-value[†]**
Change in BDI scores (points)	-2.00 (5.91)	-5.56, 1.56	-3.50 (5.63)	-6.50, -0.50	0.307
Change in weight (kg)	-3.51 (5.91)	-6.93, -0.10	-0.83 (6.04)	-4.05, 2.39	0.230

Abbreviations: BDI, Beck Depression Inventory; *CI*, confidence interval; PUFAs, polyunsaturated fatty acids; SFAs, saturated fatty acids; *SD*, standard deviation
[1]Data are expressed as the mean (*SD*) unless otherwise indicated.
[2]Significance for the difference between the groups was assessed by Student's *t* test, Mann-Whitney *U*-test and χ^2 test
[3]Excluding participants without depressive symptoms at baseline (BDI score≥11)

10.6 SUMMARY OF THE RESULTS

The summary of the main results is presented in **Table 21**.

Table 21. Summary of the results.

Sub-work	Design	Study	*n*	No of cases	The main results
Work I	Prospective	KIHD	2313	47 and 58	Low dietary intake of folate was associated with an elevated risk of getting a hospital discharge diagnosis of depression both during 13.6 and 18.8 years of follow-up. Vitamin B_{12} intake was not associated with the risk of depression.
Work II	Prospective	KIHD	2077	46	No observed associations between serum concentrations of total long-chain n-3 PUFAs, individual serum PUFAs or the serum ratio of n-6 to n-3 PUFAs and the risk of depression.
Work III	Prospective	KIHD	2232	49	Coffee consumption was non-linearly associated with the decreased risk of depression, whereas tea or caffeine intake showed no associations.
Work IV	Cross-sectional	KIHD	1003	72	Healthy, prudent dietary pattern was associated with lower prevalence of depressive symptoms. Unhealthy Western-type dietary pattern was associated with elevated prevalence of depressive symptoms.
	Prospective			28	Prospective analyses showed an inverse association between adherence to the healthy dietary pattern and the risk of depression.
Work V	Intervention	DPS	140	-	The BDI scores decreased in both the intervention and the control group during three years of intervention study. However, there was no difference between the groups in the magnitude of the change, which was clinically non-significant.

Abbreviations: BDI, Beck Depression Inventory; DPS, Finnish Diabetes Prevention Study; KIHD, Kuopio Ischemic Heart Disease Risk Factor Study; PUFA, polyunsaturated fatty acid

11 Discussion

11.1 METHODOLOGICAL CONSIDERATIONS

11.1.1 Study populations and designs

*The KIHD study (**works I-IV**)*

The KIHD study population is a relatively large and representative population-based sample of middle-aged or older men in Finland. High participation rate (83%) is a strength and there were practically no losses to follow-up. Controlling of confounding factors was possible due to numerous measurements carried out and questionnaires filled in at baseline. Baseline and four-year subjects of the KIHD study population consisted only of men and hence, the results can only be generalized to male populations. In addition, the KIHD participants were middle-aged or older and thus, generalization into younger age groups should be done in caution.

The main strength of **works I-III** is the use of a prospective follow-up setting with population-based recruitment. Compared to cross-sectional studies, prospective studies give more reliable information on the relationship as dietary exposures have been measured before observed depression. We were able to exclude those with current elevated depressive symptoms and those with a history of mental illness, to avoid reverse causation.

*The DPS (**work V**)*

The DPS population consisted of both women and men, which makes the results more generalizable. However, the DPS participants were overweight and had IGT, which is why generalization to general population must be done with caution. The study population was recruited through local advertisements. It is possible that people who were more interested in health-relating issue, or had higher education may have been selected more often to participate compared to others. The DPS participants have been shown more likely to be women and non-smokers compared to general Finnish population (337). The drop-out from the follow-up in the DPS was very low (9% for intervention and 7% for the control group), which is a strength (338). In addition, the duration of the intervention in the DPS was three years, which is considered a long period for commit oneself to an intensive intervention.

11.1.2 Assessment of dietary intake and serum concentrations

As suggested earlier (269), discussion of the association between diet and disease should include evidence from many different types of studies and should not focus on only one method to assess dietary exposure. The works in this thesis utilized different types of methods in assessing dietary intakes.

Food records were collected during four consecutive days. Total energy intake was calculated from food records and was used as a potential confounder in **works I-III**, which is a certain strength. With four days of recording, the burden to the participants is modest. Unlike the FFQ method, food records are based on the actual intake of foods and beverages, and do not rely on memory, which is a strength of this method. However, if delaying recording for several hours or more, food records also rely on memory. Pictures of portions were used to ease the assessment of portion sizes. In addition, a qualified nutritionist provided the necessary instructions and checked the completed food records with the study participants, which added validity. Changes in eating while keeping a food record, reactivity, is usually caused by participants' wish to minimize the burden of reporting

(136). In addition, a tendency to fill records in a manner that will be viewed favorably by others may cause social desirability bias. Only highly motivated participants may keep accurate records. Therefore, in our dietary assessments, under-reporting may have been present. In addition, day-to-day variation in food intake may be large in individuals, and four days is not enough for accurate estimation of long-term mean intake on an individual level (136). However, it is probable that four consecutive days are enough to reliably detect differences in intake between individuals.

In **work I**, as folate is present in food items that are usually consumed daily (vegetables, fruits, whole-grain products), four-day food recording may reflect properly the differences in folate intake between individuals (136). The energy-adjustment of dietary folate intake is a certain strength, as it takes into account the differences in energy requirements among individuals. The evidence suggests that error by under- and over-reporting can also be at least partly cancelled by adjustments for energy intake (136,339). The Nutrica® software, used in the calculations of folate intake, takes into account the losses of folate during food preparation, which increases the reliability of the results. Assessment of dietary folate intake instead of serum or red-cell concentrations of folate is justified, as serum concentrations of vitamins are known to be affected by fluctuations in daily intake, smoking, alcohol consumption and physical activity (123,340).

In **work II**, we measured serum concentrations of long-chain n-3 PUFAs, which is a proper method for assessing the short-term intake of these fatty acids. Serum concentrations of long-chain n-3 PUFAs correlate well with fish and fish oil intake, reflecting dietary intake over several weeks (341). Generally, food records are suggested as a golden standard of dietary intake assessment. However, in our study, using the four-day food records to assess intake of long-chain n-3 PUFAs may not have been a proper method, as the most important source, fish, is usually not eaten on a daily basis, and day-to-day variation is large. Therefore, a four-day food record may not conclusively assess the intake of long-chain n-3 PUFAs. Moreover, serum concentrations reveal not only the actual intake of n-3 PUFAs but also reflect individual differences in fatty acid metabolism and storage. Sub-group analyses (31% of the study population) at the 11-year examination showed that fatty acid concentrations remained relatively similar to the baseline values, suggesting that the fatty acid concentrations are fairly stable even during longer follow-up periods.

In **work III**, the reliance on four-day food records on coffee consumption may be justified, as for foods or drinks typically consumed daily, such as coffee, a limited number of days is enough for estimating usual consumption (136). In addition, it has earlier been suggested that Finnish individuals usually report accurately their habits concerning coffee consumption (342). In addition, it is unlikely that possible misclassification of the exposure would be systematical. The volume of the cup mainly used by each participant was estimated by showing photographs of four different cup sizes generally available in Finland.

In **work IV**, the FFQs were utilized in the assessment of food intake and in evaluating the dietary patterns. The FFQs were filled at one time-point only, year four in the KIHD study. The FFQ was planned especially for the KIHD study cohort and it was not validated. The FFQ was relatively short, including only 38 food and beverage items, and the consumption frequency of most of the food groups was measured mainly by frequencies. However, quantitative assessment of consumption of foods and beverages was committed for a few items, such as coffee, tea and eggs. In addition, information on total energy intake, a potential confounder, was not available at four-year examinations, which is a limitation.

The general advantages of FFQ include the ability to assess longer-term food consumption. In addition, the advantages include self-administration and a modest burden on individuals (136). Moreover, as measured food consumption in preceding 12 months, seasonal variation is unlikely to bias the results, though the seasonal point of filling the FFQs may affect the retention of foods consumed. The largest challenge of the FFQ is that it

is based on memory and is not the best method for assessing the absolute intakes, as it may not accurately reflect portion sizes. However, there is no given method for measuring long-term food consumption available that could avoid the possibility of under- or over-reporting. In **work IV** the main aim was, however, not to measure the accurate intakes, but instead, to categorize participants according to the frequencies of their food consumption and to determine dietary patterns. The FFQ method usually properly divides the participants on a relative scale according to food consumption, and relative rankings are considered adequate for determination of relative risks (136). In addition, concerning the dietary patterns, it may be advantageous to sacrifice precise intake measurements in exchange for more crude information relating to an extended period of time, as suggested before (136). The FFQ method is known to associate with substantial measurement error and these errors may seriously attenuate the power of studies in nutritional epidemiology (343). The dietary measurement error associated with the FFQs is, however, suggested to lead to an underestimation rather than overestimation of the true association (343).

The FFQ is considered a good and generally used measurement of food consumption for factor analyses (269). *A posteriori* dietary pattern analysis allows investigation of food consumption as it exists within the sample data, using validated methods (344). Factor analysis is the most commonly used analysis in the nutritional epidemiology literature demonstrating dietary patterns, and it has been shown to perform reasonably well (269). Nevertheless, the challenges of dietary pattern analyses include data-based interpretation and challenge in objectivity. In addition, based on the results of dietary pattern analyses, it is difficult to give recommendations concerning the quantitative consumption of foods and beverages.

11.1.3 Measurements of outcome events

The outcomes in **works I-III** were limited to participants with severe depression requiring hospitalization and therefore, the number of outcomes was low, about 2% of the whole KIHD study population. Unfortunately, we had no national register of outpatients with depression available in Finland during the follow-up. The National Hospital Discharge Register covers the treatment periods in general and psychiatric hospitals, as well as in military, prison and private hospitals. The register data have been shown to be reliable, as 95% of the primary diagnoses were identical compared to medical records (345). The use of the discharge register guaranteed that we were able to detect severely depressed patients, but due to overlapping, it simultaneously led to not detecting some of the cases with milder depression. Hence, it is a limitation of the register data that though specificity of the outcome is excellent, sensitivity is low. Therefore, our findings may be applicable to the more serious portion of the wide range of depressive symptoms. Especially, regarding the n-3 PUFAs, although we found no statistically significant associations between n-3 PUFAs and the risk of depression (**work II**), we cannot fully exclude the possibility that non-significance is due to the relatively small number of hospitalizations, or in other words, the lack of power in the study (type II error). In addition, due to the low number of cases, it is possible that our results considering the association between coffee drinking and the risk of depression (**work III**) may be due to chance (type I error). Moreover, since there were 1,003 participants present in the four-year re-examination, out of whom only 28 participants received a discharge diagnosis of depression, the power of the prospective analyses was modest (**work IV**).

In the cross-sectional analyses of **work IV**, we used the HPL depression scores to measure depressive symptoms. The HPL depression scale is not commonly used outside the KIHD study cohort, but several studies based on this cohort have used this scale to assess depressive symptoms (119,155,327). Clinical cases of depression were not identified, which can be regarded as a limitation. The challenges in the use of self-rating depression scale include social desirability bias, which may lead to under-reporting of depressive

symptoms. Nevertheless, several previous studies have demonstrated the validity of self-demonstrated scales, and potential misclassifications usually bias the association towards the null (123). The prevalence of elevated depressive symptoms was 7.2% at four-year examinations, which is slightly lower compared to a previous Finnish study estimating the prevalence of clinical depressive symptoms to be 10.4% in men (346).

In **work V** based on the Finnish DPS, there was a limited number of study participants with the BDI scores available, as the BDI questionnaires were filled only at two study centers out of five both at baseline and at the three-year examination. Furthermore, there were no clinical interview-based diagnoses of depressive symptoms available. However, it has been shown that the BDI is a valid tool especially in assessing the change in depressive symptoms and that mean BDI scores correlate well with the prevalence of depression assessed by clinical interviews (335).

The Finnish DPS intervention was not designed to prevent or diagnose depression. However, in this study the prevalence of elevated depressive symptoms at the baseline (21.4%) was higher than the prevalence of depressive symptoms in the previous Finnish study (10.4% in men, 16.5% in women) (346). The DPS participants were overweight and they had IGT, and therefore at higher risk for depressive symptoms, which may partly explain the relatively high prevalence. In addition, the cut-off point used in the DPS (10/11) is also relevant for screening sub-clinically depressed individuals, which probably explains the relatively high prevalence of depressive symptoms. Originally, Beck suggested that a cut-off point of 12/13 would be suitable to detect depression among psychiatric patients, while 9/10 should be used among medical non-psychiatric patients (42). In addition, in **work V**, the strengths include the fact that information on both depressive symptoms and antidepressant medication use was available. It has previously been recommended that the use of both markers could be a sufficient estimate of overall depression rates (303). However, the number of participants using antidepressant medication in the DPS was very low, only one participant in the intervention group and two participants in the control group at the baseline.

11.2 DIETARY FOLATE AND THE RISK OF DEPRESSION (I)

We found that low folate intake was associated with an elevated risk of depression. In addition, the inverse association was strongest in the follow-up years 13 to 19, after which period the association still existed, but became weaker. Finally, the association did not reach a statistically significant level after 20 years of follow-up.

Folate intake in the KIHD cohort was earlier found to have an inverse association with depressive symptoms in cross-sectional analyses (119). The present study was the first prospective study to show an association between dietary intake of folate and increased risk of depression. There are four prospective studies published since on blood concentrations of folate, and two studies published on the relation between intake of folate and the risk of depression. The prospective studies have shown a similar inverse association in some studies assessing dietary intake (9) or blood concentrations (7,8) of folate, but not in other studies assessing dietary intake (10) or blood concentrations (11,12) of folate. In addition, in a French study, folate deficiency was not associated with the depression prevalence in cross-sectional analyses, whereas lower blood concentrations of folate were associated with a higher likelihood of depression two years later (9), suggesting that folate concentrations could affect the onset of depression, not vice versa.

It has previously been suggested that only low blood concentrations of folate may increase the risk of depression, and once a minimal safety level is reached, further elevations in intake do not lead to further reduction in the risk of depression (123). In our

study population, only 25% of the participants attained the recommended intake level of 300 μg of folate, which is in line with this hypothesis. Similarly, in the previous prospective study in the elderly participants from the U.S., intakes of folate were much higher (second tertile of folate intake from food and supplements was 263 to 397 μg/day) compared to our study population (10). The study showed no association between folate and the risk of depression, and also suggested that folate may be associated with the risk of depression only at insufficient concentrations. However, in the U.S., all grain products and cereals are nowadays fortified with folic acid (140 μg of folic acid per 100 g). Moreover, as the use of vitamin supplements is more common in the U.S., the mean intake of folate is likely to be higher compared to Finland. In the French prospective study with no association between folate intake and risk of any or single depressive episodes (9), the intake of folate was also higher compared to our population (the mean for the first, second and third tertiles of folate intake was 243 μg/day, 336 μg/day and 441 μg /day, respectively). However, an inverse association was observed only with the risk of recurrent depression, only in men. Moreover, the prospective studies on blood concentrations of folate and risk of depression partly support the hypothesis. In a multinational prospective European study, only 0.3% of the participants had deficiency of folate and no associations were detected (12). However, in a Korean study, an inverse association was found even though the mean serum concentrations of folate were relatively high (mean 24.4 nmol/L) and deficiency of folate was uncommon (4.0%) (7). Thus, this hypothesis may not entirely explain the differences.

Some individuals may be deficient of folate regardless of adequate dietary intake because of genetic polymorphisms, diseases or drugs that may cause improper absorption and utilization (97). As polymorphisms in the *MTHFR* gene needed in the metabolism of folate have previously been found to associate with depressive symptoms, stratified analyses by genotype would give more information on the association between folate intake and depression (85). In the KIHD study population, we have information on *MTHFR* genotypes available. Unfortunately, due to the low number of participants stratified analyses according to genotype could not be performed.

We found no association between vitamin B_{12} intake and the risk of depression. Sufficient intake for nearly everyone may affect the results, as 99.9% of the study participants reached the recommended Finnish daily vitamin B_{12} intake of 2.0 μg/day (102). As the intake of B_{12} was sufficient in almost all of the KIHD participants, it leads to a more dense value distribution and differences in the outcome are less likely observed. Nevertheless, as previously suggested, B_{12} may not be linearly associated with depression, but the association may be observed only at low levels (114).

We are not able to fully exclude the possibility that the relationship between dietary folate and depression is explained by other healthy features of a folate-rich diet. Main sources of folate in KIHD cohort, vegetables, fruits, berries and whole-grains, are rich in many other essential nutrients, and folate intake may be a proxy for other unmeasured factors, such as a healthy overall diet. However, adjustment for the intake of vitamin C and fiber, which are considered good markers of an overall healthy diet, did not change the results. Similarly, poor eating habits easily cluster with other unhealthy habits, such as low physical activity, smoking and alcohol consumption, and these factors may confound the association (123,340). We tested for total energy intake as being a potential confounder, but it did not attenuate the association. Smoking may be an effect modificator, as in a cross-sectional study with over 9,000 individuals an inverse association between intake of folate and prevalence of depressive symptoms was found only among men who were current smokers and had lower levels of anxiety symptoms (123). Smokers may be vulnerable to a selective folate deficiency as cigarette smoking increases folate requirements by interfering with the metabolism of folate and reducing folate utilization (347). Nevertheless, adjustments with several possible risk factors associated with lifestyle, including smoking, did not alter the main results of our study.

11.3 SERUM N-3 FATTY ACIDS AND THE RISK OF DEPRESSION (II)

We found no association between serum concentrations of total long-chain n-3 PUFAs, total n-6 PUFAs, individual fatty acids or the ratio of n-6 to n-3 PUFA and the risk of getting a hospital discharge diagnosis of depression. The results are congruent with other prospective studies, a Finnish study (90), a North-American study (88) and two French studies (19,87), in which no association was found between the intake or serum concentrations of n-3 PUFAs and the risk of depression. The NHS (88) may present valid research, as the study was carried out with repeated measurements of dietary intake during the ten years of follow-up, as well as a rigorous definition of clinical depression. In the other French study, however, also cross-sectional analyses showed that higher n-3 PUFA consumption associated with lower likelihood of depressive symptoms (87). This reinforces the theory that depressive symptoms affect n-3 PUFA intake, rather than the opposite.

The concentrations of serum n-3 PUFAs were relatively low (mean 4.7%) in our study population, which reflects relatively low fish consumption and may affect our results. However, previously in the KIHD cohort an inverse association was found between serum long-chain n-3 PUFA concentrations and CVD and inflammation-related conditions (223,348). In a recent Finnish cross-sectional study combining three different data sets with a very wide range of fish consumption and n-3 PUFA intake including the extreme ends, the results showed no association between fish consumption and psychological stress in either high or low fish consumption categories (178). Therefore, it is probable that our results would be similar regardless of the concentrations of serum PUFAs. The potential association between n-3 PUFAs and depression is suggested to be non-linear (15,18,178,349). Extremely high concentrations of n-3 PUFAs may not show advantages but disadvantages, as in the cross-sectional Finnish Fishermen Study, when serum concentrations of DHA reached 6%, there was an increase in scores of psychological stress (178). Similarly, in a prospective study in Spanish men and women, those with high baseline fish consumption and increased consumption during the follow-up had elevated risk of depression (18). Further, in a prevention trial, supplementation with EPA and DHA, 600 mg at a 2:1 ratio, for almost five years elevated depressive symptoms, but in men only (137).

Our study population consisted of men only, and no association was found between n-3 PUFAs and the risk of depression. Gender has been suggested to be a possible confounder as in previous studies, the association between n-3 PUFAs and depression has been observed in two prospective studies in women only (17,18). Two Finnish cross-sectional studies have also shown a similar gender difference (172,173). In contrast, in a French prospective study (15) and in a Finnish cross-sectional study (349), fish consumption associated with recurrent depression and MDD, respectively, in men only. Unfortunately, none of the RCTs have reported results stratified by gender. The potential gender difference might be explained by the differences in neurotransmitter metabolism between the genders (173) or by gender-mediated differences in oxidative stress or inflammation (350). However, the concentrations of endogenous n-3 PUFAs, especially DHA, are higher in women than in men, even when fed identical diets (351). Also other confounders have been suggested, as the beneficial effects of fish consumption or intake of n-3 PUFAs may manifest mainly in individuals with a harmful lifestyle and health behaviors, such as a sedentary lifestyle, high alcohol consumption or smoking (178,349). In contrast, risk of self-reported depressed mood was elevated with increased fish consumption in smoking men in the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study (90), and strong interaction between fatty fish consumption and smoking on recurrent depression risk was also found in the SU.VI.MAX cohort, especially in women (15).

Total energy intake should also be taken into account as a potential confounder. Men usually eat more and get more energy and n-3 PUFAs from food compared to women and

depressed individuals may eat less than non-depressed persons, which may affect their n-3 PUFA status (178,352). However, in our study, those who became depressed during the follow-up actually obtained more energy from the diet at baseline than those who remained non-depressed. We repeated the analyses adjusting for baseline energy intake, but the results remained unaltered.

We observed no statistically significant differences in the ratio of n-6 to n-3 PUFAs between the participants who received a hospital discharge diagnosis for depression and those who did not. The main dietary sources of the long-chain n-3 PUFAs are fish and seafood, whereas the n-6 PUFAs are mainly derived from vegetable oils (LA), but also from animal products (AA). In the early 1980s, the consumption of vegetable oils was relatively low in Finland, but has increased three-fold during the recent decades (353). Therefore, it may be possible that the serum ratio of n-6 to n-3 has changed during the follow-up time. However, the ratio of n-6 to n-3 PUFAs was relatively similar in our study population at baseline (6.2:1) to the ratio reported previously in a cross-sectional study with a positive association (6.6:1 and 6.9:1 in non-depressed and depressed individuals, respectively) (169). In other cross-sectional studies with no association, the ratios were much higher (mean 8.5:1) in non-clinical population (190) and much lower in a study comparing non-depressed and depressed individuals (3.6:1 and 3.9:1, respectively) compared to our results (184). It is also possible that the small variation in the fatty acid ratios between the study subjects may have affected our finding towards the null.

11.4 COFFEE, TEA AND CAFFEINE AND THE RISK OF DEPRESSION (III)

We found that coffee consumption was associated with a decreased risk of hospitalization due to depression. However, the association was non-linear. According to our results, participants in the light and heavy drinkers' groups had a decreased risk of depression, while those in the group of moderate drinkers did not. Since our observation was the first one published in a prospective setting in a population sample and with adequate follow-up time, these findings need to be replicated. Recently, prospective work from the NHS population showed that coffee consumption decreased the risk of depression dose-dependently (250). There were only few participants with very high consumption of coffee; only 0.52% drank six or more cups (>900 mL) of caffeinated coffee daily. Therefore, they were unable to address the effects of high coffee or high caffeine consumption. In contrast, in our study, 17.5% of participants were heavy coffee drinkers (>813 mL/day) and they also had a decreased risk of depression compared to non-drinkers. This result gives a relevant reason to hypothesize that coffee drinking, also at high amounts, could be safe for mental health.

There were only few men (n=21) in our study sample who did not consume any caffeine. Therefore, it is possible that the lack of association is confounded by the relatively high caffeine intake observed also in the lowest quartile of our cohort (the mean intake of the lowest quartile was 274 mg/d). In the NHS, a decreasing risk of depression was seen with increased consumption of caffeinated coffee, but not with decaffeinated coffee (250). The mean caffeine intake in their cohort was a lot smaller than ours: 236 mg/day versus 607 mg/day, respectively. In contrast, an Australian longitudinal study reported that non-caffeine consumers had better mental well-being compared to regular caffeine consumers (249). Nevertheless, there was no quantitative assessment of caffeine intake in their study, thus no dose-response analysis were committed. Both of these studies (249,250) were conducted only in women, whereas our study population consisted of men only. The possible gender differences need further investigations.

Tea consumption was not associated with the risk of depression in our study, in contrast to previous studies. Although 43% of the participants in our study population drank tea, the mean tea consumption was quite low (105 mL/day). In addition, in the KIHD cohort, there were 907 participants (40% of the cohort) who consumed both coffee and tea during the four-day food recording (mean consumption was 496 mL/day for coffee and 227 mL/day for tea). Moreover, out of them, 314 men (14% of the cohort) drank more than 200 mL of both tea and coffee daily (mean for coffee 508 mL/day and for tea 382 mL/day). The tea consumed in our study population was mainly black tea. Most of the previous studies presenting the protective effect of tea were conducted with green tea and mostly in Asian countries, where the consumption of green tea is fairly high (264,265). There are several possible explanations for the more promising results for green tea compared to black tea. Green tea contains more catechins, has a higher level of antioxidant activity and, furthermore, green tea is usually consumed in higher amounts compared to black tea (354).

We found that the potential protective effect of coffee consumption is not accredited by caffeine consumption. Caffeine is traditionally considered to be responsible for the health effects of coffee. In a work from the NHS, caffeinated coffee consumption was associated with a decreased risk of depression, which gives good reason to presume that it may be the caffeine in coffee that is the affective substance (250). However, as presented earlier in this thesis (chapter 5.3.3), coffee contains plenty of other functional components with both anti-inflammatory and antioxidative effects. Therefore, these effects might, at least partly, explain our observations, especially in the heavy coffee drinkers´ group.

We did not have the information of other sources of caffeine than coffee and tea. However, it was highly uncommon to consume caffeine from other sources in the 1980s, especially on a daily basis. To minimize the reverse causation bias, we excluded the participants with elevated depressive symptoms at the baseline. The most worthy limitation is the low number of the cases. Secondly, a possibility of residual confounding cannot totally be excluded since coffee consumption is usually associated with other lifestyle factors, such as smoking, poor eating habits, low physical activity and higher alcohol consumption (355,356). In our study population, there were statistically significant differences in smoking, intake of folate and adulthood SES, but not in alcohol consumption between coffee drinkers and non-drinkers. However, adjustments for these factors did not alter the findings.

11.5 DIETARY PATTERNS AND DEPRESSION (IV)

In this study, it was observed that a healthy dietary pattern characterized by consumption of vegetables, fruits, berries, whole-grain bread, fish and low-fat cheese was associated with a decreased prevalence of elevated depressive symptoms in middle-aged men. In contrast, adherence to an unhealthy Western-type dietary pattern, characterized by higher consumption of sausages, processed meats, sweet snacks, sweet soft drinks, baked potatoes and French fries, wheat bread, cheese and manufactured foods, increased the likelihood of being depressed. In addition, prospective analyses showed an inverse association between a healthy dietary pattern and the risk of getting a hospital discharge diagnosis of depression during the average 16.5 years of follow-up.

Our results are in line with the previous studies, as it has been shown both in cross-sectional (95,281,285) and in prospective (24-26) studies that healthy dietary patterns – naturally not defined exactly similarly in the different studies – are associated with a lower prevalence or risk of depression. Our study population consisted of men only, and we found an inverse association. Interestingly, an inverse association between healthy dietary patterns and depression has been observed especially in women both in cross-sectional

(95,283,285) and in prospective studies (25). In addition, diet quality index also showed an inverse association with the incidence of depression only in women (286).

Total energy intake may be a potential confounder of the association. For example in Australian women, a statistically significant association between an unhealthy Western dietary pattern and depression was found only in unadjusted models, disappearing once overall energy intake was taken into account (285). Adjustments for total energy intake were performed in only six of the previous cross-sectional (95,280-283,285) and three of the prospective (24,25,284) studies, which may partly explain the inconsistency in the results. Unfortunately, in our study, we were not able to adjust for total energy intake, as we used the short FFQ, in which the quantitative assessment of total energy intake was impossible.

Several potential confounding factors were, however, assessed and adjusted for in the cross-sectional analyses. Physical inactivity is a potential confounding factor for the association between dietary patterns and depression. However, adjustments for leisure-time physical activity had only minor effect on our results. In addition, the association between dietary patterns and depressive symptoms could be attenuated by the fact that the study participants may have modified their diet and eating habits after developing a diet-related disease, such as CVD. To avoid this confounding, we adjusted for a history of CVD. Finally, dietary patterns reflect complex interactions between individuals and the culture and society in which they live; it is therefore possible and even probable that in addition to biological mechanisms, social and psychological mechanisms may be behind the associations found (357). These complex interactions could not be tested in our study.

Depression itself may affect appetite, change dietary patterns and lead to unhealthy eating habits. However, the association between dietary patterns and depressive symptoms may be bi-directional: dietary patterns affect mood and mood affects dietary patterns and eating behavior (357). Previous prospective studies on diet quality (24,284) did not, however, support the reverse causality as an explanation for the association. Prospective analyses to clarify the association can be considered as a strength. Results from prospective analyses support the hypothesis that a healthy dietary pattern may lead to reduced risk of depression. However, the Western dietary pattern did not associate with the risk of hospitalization due to depression in our prospective analyses, which supports the direction of the relationship to be reversed.

11.6 LIFESTYLE INTERVENTION AND DEPRESSIVE SYMPTOMS (V)

We found that participation in the intervention study lowered depression scores both in the intervention and the control groups, although the mean decreases were clinically non-significant. Furthermore, regardless of group status or the level of depression scores, the participants who succeeded in weight reduction showed greater reduction in the BDI scores.

Similar to the present results, the DPP found no association between participation in the intensive lifestyle modification group and changes in the levels of depression (358). It was reported that the median BDI score at the baseline was three points, whereas in our study it was six points. The mean BMI of the participants was over 30 kg/m^2 in both studies (358). A study in overweight women observed that diet alone or a combination of diet and exercise had identical benefits on depressive symptoms (307). The effect was not specific to the intervention type, and exercise did not produce any additional advantage, at least when the weight loss was about the same in all groups. In contrast, a trial with three treatment arms showed that a combination of diet and exercise was more effective than diet alone in overweight women (311). Unfortunately, we were unable to differentiate between the specific effects of diet and exercise on depressive symptoms, because the dietary and

exercise interventions were combined in our study. However, it seems that rather than the content of the intervention, participation and achieving social support are the key issues.

Obesity is a commonly distinguished risk factor for depression especially in women (359) and there is also a positive association between weight and depression (360). A reciprocal link between depression and obesity was confirmed by a recent meta-analysis (361). The DPS participants were mostly obese at baseline and therefore, they were high-risk subjects for depressive symptoms. In previous intervention studies, weight change has been suggested to be a mediator of the treatment effects on the BDI score (308) and to be associated with a small but statistically significant reduction in the risk of elevated depressive symptoms (303). Weight change was one of the strongest determinants of the change in the BDI scores also in the DPS. However, the studies described above mainly aimed at weight reduction, whereas the intervention program in the DPS focused on the quality of diet in general, combined with weight reduction and physical exercise.

The prevalence of elevated depressive symptoms decreased both in the intervention and the control groups. Moreover, among those who had the elevated depressive symptoms at baseline, we found a reduction of depressive symptoms in both groups, but the reduction was statistically significant only in the control group. This may be due to chance because of the small sample size, or it may reflect the benefit from meeting with health care professionals without the need of more intensive intervention. Actually, an intensive lifestyle intervention may be even more demanding for individuals with depressive symptoms, and general lifestyle advice or a mini-intervention may be more beneficial in these cases. In line with this, it was found in the Look AHEAD trial that individuals who reported incident symptoms of depression had more than seven points of increase in the BDI scores during the trial (309), which is regarded as a clinically significant change. Weight loss aim was the main focus of the study.

It is a commonly known phenomenon that in lifestyle intervention studies both the intervention and the control group benefit from participation (337). The Hawthorne effect (362), which reflects the magnitude of regular follow-up and appointments with health care professionals, may affect our results and narrow the differences. Participants in the DPS control group gave blood samples and were examined by the study physician annually. They also received general health advice due to ethical reasons (330). Thus, they might also have benefited from lifestyle advice.

In the previous lifestyle intervention studies demonstrating the effect on depressive symptoms, the time period has varied from 20 weeks up to four years (303,307,308). In the shortest study (307), depressive symptoms decreased statistically significantly during the first ten weeks, but increased during the next ten weeks, even though weight reduction continued until 20 weeks of the study. In the DPS, measurements of depressive symptoms were available at baseline and at three-year examination. It should, however, be noticed that earlier assessment may be biased as a result of changes made only because participants are conscious of being studied (331). In addition, as was recommended earlier, longer study periods are needed to observe the stability of improvements, especially when it is probable that participants will regain some weight during long follow-up studies (308).

The DPP showed that while the prevalence of elevated depressive symptoms decreased from 10.3% at baseline to 8.4% at year three, the proportion of antidepressant medicine users increased from 5.7% to 8.7% (303). In the DPS, with the same cut-off (BDI≥11), the prevalence of elevated depressive symptoms was higher both at baseline (21.4%) and at year three (15.7%), and use of antidepressants was uncommon both at baseline (2.3%) and at three-year visit (3.6%). As the use of antidepressants was uncommon in our study population, it was not possible to examine the association between intervention and the use of antidepressants. It is also very unlikely that the use of antidepressant medication has affected our results. In addition, the use of antidepressants was uncommon compared to the number of those who had depressive symptoms at baseline (21.4%). Low rates of

antidepressant treatment can be explained by the fact that it was fairly uncommon to treat mild depression with drugs during the DPS in the 1990s in Finland.

Even though in the DPS, based on the range of the reported BDI values, some of the individuals shifted from the category of severe depression to mild or non-depressed, and the proportion of participants with elevated depressive symptoms decreased from 21.4% to 15.7%, we cannot draw reliable conclusions about the clinical significance on group level. However, the clinical meaning of our observations remains suggestive regarding the clinical benefits. Nevertheless, the mean reductions of the BDI scores during the three-year intervention (-0.90 points in the intervention group, -0.75 points in the control group) are not regarded as clinically significant.

12 Conclusions

Based on the findings in the works I to V, the following five conclusions can be drawn:

1. Low intake of folate increases the long-term, up to 20 years, risk of getting a hospital discharge diagnosis of depression in middle-aged men, at least in a population with generally low mean intake of folate and a large variance in it. Therefore, improving folate status could be beneficial in the prevention of depression. Dietary intake of vitamin B_{12} is not related to the risk of depression in men whose intake of vitamin B_{12} is sufficient.

2. Serum concentrations of the long-chain n-3 PUFAs, single fatty acids or the ratio of n-6 to n-3 PUFAs are not associated with the risk of depression in middle-aged men. These results support the hypothesis that the prevention of depression with long-chain n-3 PUFAs may prove unsuccessful.

3. Coffee consumption, but not tea consumption or caffeine intake as such, may be preventive against depression.

4. Adherence to a healthy dietary pattern associates with a lower prevalence of depressive symptoms, whereas adherence to an unhealthy dietary pattern associates with elevated depressive symptoms in middle-aged men. Moreover, adherence to a healthy dietary pattern reduces the risk of depression requiring hospital treatment.

5. Participation in the lifestyle intervention study improves the BDI scores with no specific group effect, although not clinically significantly. Therefore, regardless of the intensity of the treatment, participation and success in executing alterations in one's lifestyle and behavior is associated with beneficial changes in mood. Among the lifestyle changes in intervention study, successful reduction of body weight associates particularly with a greater reduction of depressive symptoms.

13 Implications

13.1 IMPLICATIONS FOR PREVENTION AND CLINICAL PRACTICE

Our results indicate that diet may have a role in the prevention of depression. On the basis of this work and previously published studies it can be stated that eating a healthy diet rich in folate sources, such as vegetables, fruits, berries and whole-grains is beneficial in the prevention of depression. In addition, a dietary pattern characterized by consumption of vegetables, fruits, berries, whole-grains, poultry, fish and low-fat cheese may be protective against depression.

Generally, primary prevention strategies of depression should include lifestyle choices, including a healthy diet. Sufficient intake of folate is recommendable as low intake of folate may be an independent risk factor for depression. An increase in the consumption of especially vegetables, fruits and berries that may elevate the dietary intake of folate and various other nutrients is recommended. Our results suggested no benefit of n-3 PUFAs in the prevention of depression, at least in middle-aged men with generally low circulating concentrations of n-3 PUFAs. Nevertheless, there is no need to change the current dietary guidelines that recommend eating fish at least twice a week, as fish consumption is beneficial, especially for cardiovascular health. In the light of the evidence, it is probable that coffee drinking may have advantages, but not as many harmful effects on mood as previously thought. Still, it is far too premature to recommend coffee consumption for the prevention of depression.

Based on the literature, dietary habits among depressed individuals are often poor and dietary intakes insufficient, which may cause deficiencies. Therefore, continuous nutrition education and counseling for healthy dietary patterns and balanced nutrition status are needed. Sufficient intake of folate and long-chain n-3 PUFAs is especially important for depressed individuals. Folate or EPA and DHA augmentation may enhance the efficacy of antidepressant medication in non-responders, to enable those who partially respond to antidepressant monotherapy to achieve remission, or to alleviate residual symptoms during antidepressant treatment. However, there are no specific unanimous augmentation guidelines for clinical practice. Although a healthy diet is naturally the most recommendable option, supplements should not be avoided if needed.

13.2 IMPLICATIONS FOR FUTURE RESEARCH

The possibilities to prevent depression by healthier dietary patterns or elevated intake of healthy foods and nutrients should be studied more extensively. Firstly, more well-designed, large, population-based prospective studies with long follow-up periods are warranted. In prospective designs, multiple exposure assessments throughout the follow-up period and evaluation of depression status both at baseline and during the follow-up should be emphasized. Secondly, population-based RCTs in non-depressed or high-risk participants are warranted, as previous studies have mainly consisted of clinically depressed patients. However, the effects of diet on the prevention of recurrent depression should also be investigated, as there may be differences in the effects of diet between the first episode of depression and recurrent depression. Studies with stratified age groups and gender groups should be emphasized, as there may also be differences in the effects of diet depending on age or gender. Lifestyle factors, especially total energy intake and smoking,

should be more often taken into account as potential confounders. Moreover, RCTs investigating the differences in the effects of elevated intakes of nutrients from dietary sources compared to supplementation with nutrients are warranted. Finally, specific diet-related randomized interventions with interventions based on the changes in the overall dietary pattern are needed to form primary prevention strategies for depression. As depression is a systemic disease and diet may affect several pathways in the pathogenesis of depression, the mechanisms behind the possible predisposing or protecting effects of dietary factors require further investigations. Individual differences and genetic background behind the sensitivity to the effects of diet should especially be studied in more detail.

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APPENDICES

APPENDIX 1. Beck Depression Inventory (BDI) depression scale (version Ia)

1 (Mood)	0	I do not feel sad.
	1	I feel blue or sad.
	2	I am blue or sad all the time and I can't snap out of it.
	3	I am so sad or unhappy that I can't stand it.
2 (Pessimism)	0	I am not particularly pessimistic or discouraged about the future.
	1	I feel discouraged about the future.
	2	I feel I have nothing to look forward to.
	3	I feel that the future is hopeless and that things cannot improve.
3 (Sense of Failure)	0	I do not feel like a failure.
	1	I feel I have failed more than the average person.
	2	As I look back on my life all I can see is a lot of failures.
	3	I feel I am a complete failure as a person.
4 (Lack of Satisfaction)	0	I am not particularly dissatisfied..
	1	I don't enjoy things the way I used to.
	2	I don't get satisfaction out of anything anymore.
	3	I am dissatisfied with everything.
5 (Guilty Feeling)	0	I don't feel particularly guilty.
	1	I feel bad or unworthy a good part of the time.
	2	I feel bad or unworthy practically all the time now.
	3	I feel as though I am very bad or worthless.
6 (Sense of Punishment)	0	I don't feel I am being punished.
	1	I have a feeling that something bad may happen to me.
	2	I feel I am being punished or will be punished.
	3	I feel I deserve to be punished.
7 (Self Hate)	0	I don't feel disappointed in myself.
	1	I am disappointed in myself.
	2	I am disgusted with myself.
	4	I hate myself.
8 (Self Accusations)	0	I don't feel I am any worse than anybody else.
	1	I am very critical of myself for my weakness or mistakes.

	2	I blame myself for my mistakes.
	3	I blame myself for everything that goes wrong.
9 (Self-punitive Wishes)	0	I don't have any thoughts of harming myself.
	1	I have thoughts of harming myself but I would not carry them out.
	2	I feel I would be better off dead.
	3	I would kill myself if I could.
10 (Crying Spells)	0	I don't cry any more than usual.
	1	I cry more now than I used to.
	2	I cry all the time nowadays.
	3	I used to be able to cry but now I can't cry at all even though I want to.
11 (Irritability)	0	I am no more irritated now than I ever am.
	1	I get annoyed or irritated more easily than I used to.
	2	I feel irritated all the time.
	3	I don't get irritated at all at the things that used to irritate me.
12 (Social Withdrawal)	0	I have not lost interest in other people.
	1	I am less interested in other people now than I used to be.
	2	I have lost most of my interest in other people and have little feeling for them.
	3	I have lost all my interest in other people and don't care about them at all.
13 (Indecisiveness)	0	I make decisions about as well as ever.
	1	I am less sure of myself now and try to put off making decisions.
	2	It is very difficult to me to make any decisions.
	3	I can't make any decisions at all anymore.
14 (Body Image)	0	I feel my appearance hasn't changed.
	1	I am worried that I am looking old or unattractive.
	2	I feel that there are permanent changes in my appearance and they make me look unattractive.
	3	I feel that I am ugly or repulsive looking.
15 (Work Inhibition)	0	I can work about as well as before.
	1	It takes extra effort to get started at doing something.
	2	I have to push myself very hard to do anything.
	3	I can't do any work at all.

16 (Sleep Disturbance)

0 I can sleep as well as usual.
1 I wake up more tired in the morning than I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than before and can't get myself back to sleep.

17 (Fatigability)

0 I don't get any more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing anything.
3 I get too tired to do anything.

18 (Loss of Appetite)

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19 (Weight Loss)

0 I haven't loss much weight, if any, lately.
1 I have lost more than 3 kilograms.
2 I have lost more than 5 kilograms.
3 I have lost more than 8 kilograms.

I am trying to lose my weight on purpose by eating less
Yes_____ No_____

20 (Somatic Preoccupation)

0 I am no more concerned about my health than usual.
1 I am concerned about aches and pains *or* upset stomach *or* constipation.
2 I am so concerned with how I feel or what I feel that it's hard to
think of much else.
3 I am completely absorbed in what I feel.

21 (Loss of Libido)

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

Modified from Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961) An Inventory for Measuring Depression. Archives of General Psychiatry 4: 561-571 and Beck AT, Rush AJ, Shaw BF, Emery G. Cognitive therapy of depression. New York: Guilford 1979.

APPENDIX 2. Human Population Laboratory (HPL) depression scale SCALE

Items of HPL depression scale. Possible answers were “never”, “sometimes” and “often”. Answers “never” or “often” (whichever is appropriate) were considered to be indicative of a depressed response.

Felt depressed or very unhappy

Appetite poor

Trouble getting to sleep or staying asleep

Felt lonely or remote from other people

Felt happiness

Little enjoyment from leisure time

Less energy than other people

Felt pleased about accomplishing something

Felt bored

Felt so restless than could not sit still long

Felt excited or interested in something

Cannot relax easily

Felt vaguely uneasy without knowing why

Feeling too tired to do the things wishing to

Social withdrawal even from the people who also close to

Difficulties while being with others

Never satisfied with things which one has done

Getting tired easily

Modified from Kaplan GA, Roberts RE, Camacho TC, Coyne JC. Psychosocial predictors of depression. Prospective evidence from the human population laboratory studies. Am J Epidemiol. 1987 Feb;125(2):206-20.

Anu Ruusunen

Diet and Depression

An Epidemiological Study

Depression is one of the leading health concerns worldwide, and it significantly affects public health, quality of life and economics. Diet influences the risk of many non-communicable diseases, but there is limited evidence on the association between diet and the risk of depression in general population. This is an epidemiological study that aims to clarify the association between diet and depression in cross-sectional, prospective and intervention settings.

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