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Jussi Seppälä

Depressive Symptoms, Metabolic Syndrome and Diet

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JUSSI SEPPÄLÄ

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ABSTRACT

The predictive value of the Beck Depression Inventory (BDI) for the detection of depression in the general population has not been extensively evaluated. Depression may be associated with an increased risk of the metabolic syndrome (MetS) and with a low folate intake or lower vitamin B_{12} levels. However, the impact of melancholic or non-melancholic depressive symptoms (DS) has not been examined.

The aims of this population-based study were to evaluate the value of the BDI as a screening instrument for depression, and to investigate the associations between predominantly melancholic or non-melancholic DS measured by the BDI and the MetS, folate intake, or serum vitamin B_{12} levels.

The study population (N = 2840) was selected from the National Population Register in 2007.

A score of 15 in the BDI simultaneously maximized the sensitivity and specificity of detecting depression.

The risk for the MetS was two-fold higher in subjects with predominantly non-melancholic DS.

On the other hand, the risk for melancholic DS was almost 50% lower for the high folate intake tertile versus the lowest.

The relative risk ratio for melancholic DS was almost three-fold higher in the lowest vitamin B_{12} level tertile when compared to the highest.

This study demonstrated that the BDI with a cut-off score of 15 is a valid instrument for screening depression in population-based subjects.

These results suggest that liability to the MetS is particularly associated with non-melancholic DS, which may suggest possible differences in susceptibility to the MetS in different types of DS. The findings of the present study also suggest that folate intake and vitamin B_{12} may contribute to the pathogenesis of DS, which may be associated with melancholic characteristics.

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TIIVISTELMÄ

Beckin depressioasteikon (BDI) ennustearvoa tunnistaa depressio väestötasolla ei ole tutkittu laajalti. Kohonnut metabolisen oireyhtymän (MBO) riski sekä alentunut foolihapon saanti tai matala B_{12} vitamiinin pitoisuus voivat liittyä masennukseen. Melankolisten tai ei-melankolisten masennusoireiden vaikutusta ei ole kuitenkaan tutkittu.

Tämän väestötutkimuksen tarkoituksena oli arvioida BDI:n kykyä seuloa masennusta sekä BDI:llä mitattujen pääosin melankolisten tai ei-melankolisten masennusoireiden ja MBO:n, foolihapon saannin sekä B_{12} vitamiinin pitoisuuden välisiä yhteyksiä.

Tutkimusaineisto (N=2840) kerättiin väestörekisteristä vuonna 2007.
BDI:n pistemäärä 15 maksimoi samanaikaisesti sekä sensitiivisyyden että spesifisyyden masennuksen toteamisessa.

MBO:n riski oli yli 2x korkeampi niillä, joilla oli pääosin ei-melankolisia masennusoireita. Toisaalta melankolisten masennusoireiden riski oli lähes 50 % alhaisempi korkean foolihapon saannin yhteydessä suhteessa matalimpaan.

Matalimman B_{12} vitamiinipitoisuuden ryhmässä melankolisten masennusoireiden suhteellinen riski oli liki kolminkertainen verrattuna korkeimpaan ryhmään.

Tämän tutkimuksen perusteella BDI:n pistemäärä 15 on perusteltu väestön depression seulonnassa. Näiden tulosten pohjalta voi olla mahdollista, että taipumus MBO:hon liittyisi erityisesti ei-melankolisiin masennusoireisiin. Tämä saattaa viitata siihen, että alttius MBO:hon on ehkä erilainen eri masennusoireissa.

Nykyisen tutkimuksen löydökset voivat myös tukea foolihapon ja B_{12} vitamiinin osuutta masennuksen patogeneesissä, mikä saattaa liittyä melankolisiin piirteisiin.

Luokitus:
Yleinen Suomalainen asiasanasto: B12-vitamiini; foolihappo; masennus; melankolia; metabolinen oireyhtymä; ruokavaliot

To my family

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Contents

Abbreviations

AHA	American Heart Association
APA	American Psychiatric Association
ANOVA	Analysis of covariance
ATP	Adult Treatment Panel
BDI	Beck Depression Inventory
BMI	Body Mass Index
BP	Blood pressure
CEG	Clinician Evaluation Guide
CES-D	Center for Epidemiologic Studies Depression Scale
CI	Confidence interval
CIDI	Composite International Diagnostic Interview
CRP	C-reactive protein
DIS	Diagnostic Interview Schedule
DS	Depressive symptoms
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
FFQ	Food Frequency Questionnaire
HAM-D	Hamilton Rating Scale for Depression
HDL	High-density lipoprotein
HPA	Hypothalamic-pituitary-adrenal
ICD-10	International Statistical Classification of Diseases and Related Health Problems
IDF	International Diabetes Federation
IDS	Inventory of Depressive Symptomatology
IDS-SR	Inventory of Depressive Symptomatology, Self-report version
IDS-C	Inventory of Depressive Symptomatology, Clinician-administered version
IL-6	Interleukin 6
IL-I beta	Interleukin 1 beta
IO&NS	oxidative and nitrosative stress
LC	low-carbohydrate diet
LDL	Low-density lipoprotein
LF	high-carbohydrate diet
LR	Likelihood ratio
LR+	Likelihood ratio for positive result
LTPA	Leisure time physical activity
MADRS	Montgomery-Åsberg Depression Rating Scale
MDS	Melancholic depressive symptoms

MDP	Mediterranean Diet Pattern
M.I.N.I.	The Mini-International Neuropsychiatric Interview
MetS	Metabolic syndrome
MONICA	Monitoring trends and determinants in cardiovascular disease
NCEP	National Cholesterol Education Programme
NmDS	Non-melancholic depressive symptoms
NPV	Negative predictive value
OR	Odds ratio
PPV	Positive predictive value
PRIME-MD	Primary Care Evaluation of Mental Disorders
PQ	Patient Questionnaire
ROC	Receiver operating characteristic
RRR	Relative risk ratio
SADS	Schedule for Affective Disorders and Schizophrenia
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SCID-I	Structured Clinical Interview
SCID-I/P	Structured Clinical Interview; Patient edition
SCID-I/NP	Structured Clinical Interview; Nonpatient edition
SCID-CV	Structured Clinical Interview; Clinical version
SD	Standard deviation
SDDS-PC	Symptom-Driven Diagnostic System for Primary Care
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TG	Triglycerides
Zung	SDSZung Self-Rating Depression Scale
WAT	White adipose tissue
WHO	World Health Organisation

1 INTRODUCTION

Major depression is a common disorder in the general population (Ayoso-Mateos et al. 2001, Kessler et al. 1994, Kessler et al. 2003). It frequently has a tendency towards a recurrent or chronic course, significantly impairing the quality of life and being among the most important causes of the disease burden and years lost due to disability (Murray et al. 1996). In the Finnish population, the 12-month prevalence of major depressive episodes was reported to be 9.3% (Lindeman et al. 2000). Depressive disorders were found in 6.5% of the subjects in the Finnish Health 2000 Study (Pirkola et al. 2005). The lifetime prevalence of depressive disorders was almost 18% in the latest Finnish study among younger population subjects (Suvisaari et al. 2009).

The Beck Depression Inventory (BDI) is the most commonly used self-rating scale for depression, and the literature on the psychometric properties of the BDI in both clinical and non-clinical samples/settings as well as across different countries is extensive (Beck et al. 1988). The cut-off score of 10 points in the BDI has been shown to be useful for detecting depressive symptoms in various adult populations (Timonen et al. 2006, Räikkönen et al. 2007, Vanhala et al. 2009, Koponen et al. 2010, Korniloff et al. 2010, Mäntyselkä et al. 2011). In order to examine the impact of the subtype of depressive symptoms (DS), a DSM-IV criteria-based summary score of melancholic symptoms in the BDI has been applied to divide the participants with increased DS into melancholic and non-melancholic subgroups (Sheehan et al. 1994, Steer et al. 1999, Ovaskainen et al. 2009, Vanhala et al. 2009). However, only two studies have examined the predictive value of the BDI for the detection of depression in a representative sample of the general population and have applied a reliable psychiatric interview as a validation instrument (Lasa et al. 2000, Nuevo et al. 2009).

The metabolic syndrome (MetS) is a cardio metabolic risk cluster comprising abdominal obesity, altered glucose and lipid metabolism, and elevated blood pressure (Expert panel, 2001, Alberti et al. 2005, Grundy et al. 2005, Alberti et al. 2006). Applying the criteria based on the National Cholesterol Education Programme (NCEP), the age-adjusted prevalence of the MetS has been estimated to be approximately 35% in the US population and 37% in Eastern Finland (Ford 2005, Miettola 2008). It has been shown to associate with an increased risk of cardiovascular diseases, type 2 diabetes mellitus and all-cause mortality (Lakka et al. 2002, Ford 2005). Most previous cross-sectional studies have demonstrated that the MetS is more common in those with major depression or DS than in non-depressed subjects, and the observed prevalence rates have varied from 8% to 38% (Kinder et al. 2004, Heiskanen et al. 2006, Räikkönen et al. 2007, Skilton et al. 2007). However, two recent studies have found no correlation between depression and the MetS (Hildrum et al. 2009, Foley et al. 2010). Depression may also be a risk factor for several components of the MetS. On the other hand, only a few studies have evaluated the relationship between the MetS and its components and subtypes of DS (Lamers et al. 2010, Vanhala et al. 2009). The only longitudinal study reporting the risk of metabolic syndrome in various subtypes of DS has been the subgroup analysis of Vanhala and co-workers, who detected the highest risk for the MetS among women only in a subgroup with more melancholic DS (Vanhala et al. 2009).

Only a few cross-sectional studies have reported an association between a low folate intake and depression (Tolmunen et al. 2003, Sanchez-Villegas et al. 2009, Murakami et al. 2010). Of the three published prospective studies, one reported a 3-fold increased risk of depression in men with a low folate intake (Tolmunen et al. 2004), and another demonstrated a 75% reduced risk of recurrent depression among middle-aged men with an increased folate intake (Astorg et al. 2008). On the other hand, a recent U.S. population-based study reported that the intake of folate was not associated with DS (Skarupski et al.

2010). No studies have evaluated the correlation between folate intake and subtypes of depression.

Vitamin B_{12} levels and DS or depressive disorders have been associated in some studies (Penninx et al. 2000, Tiemeier et al. 2002, Kim et al. 2008, Ng et al. 2009), but inconsistent results exist (Lindeman et al. 2000, Morris et al. 2003, Bjelland et al. 2003, Sachdev et al. 2004, Beydoun et al. 2010). The relationship between vitamin B_{12} levels and different subtypes of DS has not been evaluated in previous studies.

This population-based study was undertaken to evaluate the value of the BDI as a screening instrument for depression and the depressive symptom profile, using the clinical Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)-based Mini-International Neuropsychiatric Interview (MINI) as a validating measure. It further aimed to investigate the associations between predominantly melancholic or non-melancholic DS measured by the BDI and the MetS or folate intake and serum vitamin B_{12} levels in a population-based study. The study population was selected from the National Population Register of Finland in August 2007, and comprised subjects aged 45–74 years, stratified according to gender and 10-year age groups (45–54, 55–64 and 65–74 years), from the hospital districts of Pirkanmaa, Southern Ostrobothnia and Central Finland.

2 REVIEW OF THE LITERATURE

2.1 Terminology

In the following review of the literature and discussion sections, the term depression covers both studies on depressive disorders and patients with increased depressive symptoms (DS).

2.1.1 Screening of depression

2.1.1.1 Diagnostic psychiatric interviews for adults

Besides depression-rating scales, several diagnostic interviews were initially developed to provide reliable diagnoses for clinical research on patients with particular mental disorders. Later, to obtain reliable data on the prevalence of mental disorders in the general population, interviews were more focused on being useful in epidemiological community studies. Today, most patients with psychiatric disorders are treated in primary care. Therefore, two of the interviews included here, the Primary Care Evaluation of Mental Disorders (PRIME-MD) and the Symptom-Driven Diagnostic System for Primary Care (SDDS-PC), were developed to address the need for better recognition of mental disorders among primary care physicians. Their main output is a determination of whether the patient's clinical picture meets the diagnostic criteria for one of the psychiatric disorders covered by the instrument (Handbook of Psychiatric Measures 2000). The characteristics of the most common diagnostic interviews are presented in Table 1.

Table 1. Diagnostic interviews

Diagnostic interview instrument	**Disorder assessed**	**Format**
Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), Patient edition (SCID-I/P), Nonpatient edition (SCID-I/NP), Clinical version (SCID-CV) (Handbook of Psychiatric Measures 2000).	Psychiatric disorders according to the DSM-IV	Clinician-administered, semistructured interview with seven diagnostic modules
Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (World Health Organisation 1994)	Psychopathology and behaviour associated with a broad range of major psychiatric disorders of adult life, including the ICD-10 and DSM-IV, among others	SCAN interview text, Item Group Checklist, and Clinical History Schedule, glossary of differential definitions, and CATEGO-5 computer program
Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer 1978, Spitzer et al. 1978)	Mental disorders as defined by Research Diagnostic Criteria (RDC)	Clinician-administered interview, first part on symptoms and second part on the history of mental disorders
Diagnostic Interview Schedule (DIS) (Robins et al. 1981) Composite International Diagnostic Interview (CIDI) (Robins et al. 1988)	Current and lifetime psychiatric disorders according to the DSM-IV Expanded DIS for use across cultures according to the DSM-IV and ICD-10	Highly structured interview containing both a demographic section and diagnostic modules for administration by laypersons
Primary Care Evaluation of Mental Disorders (PRIME-MD) (Spitzer et al. 1994)	For primary care doctors in diagnosing the most commonly seen adult mental disorders such as depression or anxiety in primary health care settings	1-page Patient Questionnaire (PQ) and 9-page Clinician Evaluation Guide (CEG)
Symtom-Driven Diagnostic System for Primary Care (SDDS-PC) (Olfson et al. 1995, Weissman et al. 1995)	Computerized tool for the detection, diagnosis and management of mental disorders such as depression or anxiety in primary health care settings	29-item patient self-report screening questionnaire, a diagnostic interview guide containing an extra module for suicide risk, and a longitudinal tracking form

2.1.1.2 Depression scales

The most common goal of assessment is to measure the severity of depressive symptoms, in terms of both the severity of individual symptoms and the total number of mood-related symptoms that have been present. Depression scales are also used to detect or exclude depressive disorders, as well as for the follow-up of recovery after treatment interventions. They can be divided into self- or observer-rated scales (Table 2) (Handbook of Psychiatric Measures 2000). The Hamilton Rating Scale for Depression (HAM-D) was originally described for use in assessing the symptoms of patients diagnosed as suffering from depressive states. It has 17 to 21 items, depending on the version, that are rated according to intensity and frequency within the previous few days. The scores for each item range from 0 to 2 or from 0 to 4 (Hamilton 1960). It includes somatic manifestations of depression, and is the most widely used scale in treatment studies on depression (Kaplan and Sadock 2009).

The Montgomery-Åsberg Depression Rating Scale (MADRS) contains 10 items, each of which is scored from 0 to 6 (overall range 0–60 points) (Montgomery and Åsberg 1979). The MADRS was specifically designed to be sensitive to changes over time (Montgomery and Åsberg 1979). It is a widely used scale with high face validity. In addition, its validity has been demonstrated by its high correlations with the HAM-D (Kaplan and Sadock 2009). In the Center for Epidemiologic Studies Depression Scale (CES-D), scores range from 0 to 60, and higher scores indicate more severe depressive symptoms (Radloff 1977). In the Raskin Scale the total depression severity score may range from 3 to 15 (Raskin 1988).

The Zung Self-Rating Depression Scale (Zung SDS) includes 20 items that are rated according to their frequency of occurrence (Zung 1965). The Inventory of Depressive Symptomatology (IDS) is unique among depression rating scales in that a self-report form (IDS-SR) and a clinician-administered form (IDS-C) were developed simultaneously (Rush et al. 1985).

Table 2. Depression rating scales

Instrument	Rater	Disorder or construct assessed
Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960)	Professional, 17 items	Severity of depressive symptoms in patients with primary depressive illness
Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg 1979)	Professional, 10 items	Severity of depressive symptoms
Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff 1977)	Self, 20 items	Severity of depressive symptoms in community populations
Raskin Scale (Three-Area Severity of Depression Scale) (Raskin 1988)	Professional, 3 items	Severity of depression in three domains: subjective experience, behavioural manifestations, and secondary signs of depression
Zung Self-Rating Depression Scale (Zung SDS) (Zung 1965)	Self, 20 items	Severity of depressive symptoms
Beck Depression Inventory (BDI) (Beck et al. 1961)	Self, 21 items	Severity of depressive symptoms.
Inventory of Depressive Symptomatology (IDS) Self-report version (IDS-SR) Clinician-administered version (IDS-C) (Rush et al. 1985)	Self (IDS-SR) or professional (IDS-C), 28- and 30-item versions	Severity of signs and symptoms of depression including all DSM-IV criteria items

Three of the scales presented in this table (the BDI, CES-D and Zung SDS) are also targeted for screening depressive disorders among in the community or in general medical populations. This strategy requires a two-stage approach: the first-stage screen identifies persons likely to have a mood disorder, and those patients screened then will be evaluated in a second clinical diagnostic interview (Handbook of Psychiatric Measures 2000).

2.1.1.3 Mini

The Mini-International Neuropsychiatric Interview (MINI) is a short structured widely used diagnostic interview, jointly developed by psychiatrists and clinicians in the United States and Europe. It is validated for the diagnosis of DSM-IV and ICD-10 psychiatric disorders (Sheehan et al. 1994, Sheehan et al. 1998).

2.1.1.4 Beck Depression Inventory

The Beck Depression Inventory (BDI) is probably the most commonly used self-rating scale for depression. In the planning of the research design of a project aimed at testing certain psychoanalytic formulations of depression, the necessity for establishing an appropriate system for identifying depression was recognized (Beck et al. 1961). In its original version, subjects were asked to rate 21 items (Table 3) according to how they feel at the present time. Items were then scored from 0 to 3 and summed to obtain a total score for depressive symptom severity (range from 0 to 63) (Beck et al. 1961, Beck and Beamesderfer 1974).

Table 3. The symptom-attitude categories of the BDI (Beck et al. 1961)

a. Mood	l. Social Withdrawal
b. Pessimism	m. Indecisiveness
c. Sense of Failure	n. Body Image
d. Lack of Satisfaction	o. Work Inhibition
e. Guilty Feeling	p. Sleep Disturbance
f. Sense of Punishment	q. Fatigability
g. Self-Hate	r. Loss of Appetite
h. Self-Accusations	s. Weight Loss
i. Self-Punitive Wishes	t. Somatic Preoccupation
j. Crying Spells	u. Loss of Libido
k. Irritability	

The primary clinical use of the BDI is to assess the severity of depressive symptoms in patients with previously diagnosed depressive illness. A second use of the BDI is to screen subjects who may have depressive illness or may need intervention, but in this case it should be followed up with a diagnostic instrument or a clinical interview (Handbook of Psychiatric Measures 2000).

The BDI has several advantages: it is easy and quick to use (self-administered), uses simple language and is easy to score. A disadvantage is that biases have been reported (e.g. women, the less-educated, adolescents, elderly people and individuals with certain comorbid psychiatric diagnoses such as prominent anxiety tend to show higher scores) (Handbook of Psychiatric Measures 2000).

2.1.1.5 Psychometric properties of the BDI

The term 'psychometric' is used to describe the performance characteristics of many types of measures. The two principal psychometric properties of a measure are reliability and validity. The reliability of a test is the consistency or precision with which it can discriminate one subject from another, while the validity of a measure is the degree to which the diagnosis, category, rating or score it yields is a reflection of the true state. When evaluating the reliability of a test, internal consistency and joint and test-retest reliability are assessed (Handbook of Psychiatric Measures 2000).

On the other hand, sensitivity and specificity are the statistics of choice when a measure's ability to evaluate categorical variables such as diagnoses has to be assessed (Hulley and Cummings 1988, Zarin and Earls 1993).

Sensitivity refers to a test's ability to identify true cases, or its true positive rate. Specificity is the test's accuracy in identifying noncases, or one minus the false-positive rate. The other key terms to take into account concerning a measure's validity against a gold standard are PPV (positive predictive value) and NPV (negative predictive value). PPV is the probality (in a given population) that a positive test result corresponds to a true case, and NPV is the probality (in a given population) that a negative test result corresponds to a noncase (Handbook of Psychiatric Measures 2000).

The BDI shows high internal consistency among different study populations (Beck et al. 1988). Assessments of BDI test-retest reliability are problematic because repeated testing

has often involved comparing questionnaires repeated outside the time frame mandated by the first administration of the questionnaire. To assess the stability of one-week assessments, repeated measurements must be carried out using the same unit of observation but varying the time of administration (e.g., morning and afternoon). The correlation between the BDI and other standard measures of depressive symptom severity demonstrates high, but not complete, concordance across measures. Correlations between observer-rated scales of depression such as the HAM-D or MADRS and the BDI for psychiatric patients range from 0.55 to 0.96, with a mean of 0.72. For nonpsychiatric subjects, correlations range from 0.55 to 0.73, with a mean of 0.60 (Handbook of Psychiatric Measures 2000).
Higher sensitivity scores have been reported in nonpatient populations. The BDI also shows high concurrent validity with other measures of depressive symptom severity, such as the Ham-D and the Zung SDS (Handbook of Psychiatric Measures 2000).

2.1.1.6 The BDI and screening of depression

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 (Beck et al. 1961). Two previous Finnish studies have suggested different cut-off points: 14/15 in a clinical sample and 17/18 in a population-based but geographically highly selected sample were found to maximize sensitivity and specificity in detecting depression (Viinamäki et al. 2004, Nuevo et al. 2009). The optimal cut-off point of the BDI seems to be dependent on the reference group and on the method applied to confirm the diagnosis of depression. Therefore, a wide range of cut-off points (from 10 to 23) have been suggested in the literature (for a review, see Viinamäki et al. 2004). For example, in a study among young adults (outpatient ages 18–37 years), a BDI cut-off score of 18 was recommended for maximal efficiency (sensitivity 66.88%, specificity 58.90%) (Rudd and Rajab 1995). On the other hand, the mean BDI score correlated well with the prevalence of depression determined by clinical interviews (Veerman et al. 2009). A recent study using the Composite International Diagnostic Interview as the gold standard reported that the BDI might be useful in detecting depressive disorders in the general population (Aalto et al. 2012).

The literature on the psychometric properties of the BDI in both clinical and non-clinical samples/settings as well as across different countries is extensive. There have only been two published studies examining the predictive value of the BDI for the detection of depression in a representative sample of the general population that have applied a reliable psychiatric interview as a validation instrument (Lasa et al. 2000, Nuevo et al. 2009). They suggested different cut-off points in the BDI, 12/13 and 17/18 respectively, to obtain maximal sensitivity and specificity. The cut-off of 10 points in the BDI has been shown to be useful for detecting depressive symptoms in various adult populations (Timonen et al. 2006, Räikkönen et al. 2007, Vanhala et al. 2009, Koponen et al. 2010, Korniloff et al. 2010, Mäntyselkä et al. 2011).

2.1.2. Subtypes of depression according to the DSM-IV

According to the DSM-IV, mood episodes and mood disorders can be distinguished. An episode is a period lasting at least 2 weeks during which there are enough symptoms for the full criteria to be met for the disorder. Furthermore, depressive disorders take one of three forms: a major depressive episode, a dysthymic disorder or "depression not otherwise specified", which includes several forms of briefer or milder periods of depression.

Patients with or without a history of mania may have a major depressive episode if they fulfil these criteria, but major depressive disorder refers to one or more episodes of major depression in the absence of mania or hypomania. Dysthymic disorders in the DSM-IV

consist of chronic but milder symptoms than major depressive episode (American Psychiatric Association (APA) 1994).

According to the DSM-IV, other subtypes of depression are also categorized, for example recurrent brief depressive disorder or seasonal pattern depressions (APA 1994, Angst and Hochstrasser 1994, Partonen and Lönnqvist 1999,Westrin and Lam 2007).

2.1.2.1. The prevalence of major depressive episode or depressive disorders

Numerous studies have shown that major depression is a common disorder in the general population (Ayoso-Mateos et al. 2001, Kessler et al. 1994, Kessler et al. 2003). It frequently has a recurrent or chronic course, significantly impairing the quality of life and being among the most important causes of the disease burden and years lost due to disability (Murray et al. 1996). In the Finnish population, the 12-month prevalence of major depressive episode was 9.3% (Lindeman et al. 2000). Depressive disorders were found in 6.5% of the subjects in the Finnish Health 2000 Study (Pirkola et al. 2005). An even higher rate has been reported in primary care, as the 12-month prevalence of clinical depression was 20% (Salokangas et al. 1996). The lifetime prevalence of depressive disorders was almost 18% in the latest Finnish study among the younger population (Suvisaari et al. 2009). Published prevalence rates may vary due to differences in samples and methods applied. Controversial results have been published when evaluating the differences in depression prevalence over time. A study using identical diagnostic criteria at both time points reported an increase of over two-fold in the 12-month prevalence of depression during a 10-year period (Compton et al. 2006). However, subsequent reports have failed to confirm the often publicly presented hypothesis that depression is more common at present (Hawthorne et al. 2008, Patten 2008).

On the other hand, 11–21% of persons in Finland have an elevated number of depressive symptoms (DS) assessed according to the Beck Depression Inventory (BDI ≥ 10 points) (Vaananen et al. 2008, Vanhala et al. 2009).

2.1.2.2. Diagnosis and symptoms of major depressive episode

Major depression is clinically the most important entity among the spectrum of depressive disorders. Besides defining the traditional major depressive episode, it can be typed by the presence of the most prominent symptoms, such as the melancholic or atypical features.

The fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) published in 1994, and the text revision in 2000, is the latest and most up-to-date classification of mental disorders (APA 1994, APA 2000). The fourth edition correlates with the 10th revision of the World Health Organisation's International Classification of Diseases and Related Health Problems (ICD-10) (WHO 1992). A definition of a major depressive episode is provided in Table 4.

Table 4. DSM-IV criteria for a major depressive episode (American Psychiatric Association 1994)

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is (1) depressed mood or (2) a loss of interest or pleasure:

   (1) depressed mood most of the day, nearly every day, as indicated by either subjective report or observation by others

   (2) markedly dimished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation by others)

   (3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or an increase in appetite nearly every day

   (4) insomnia or hypersomnia nearly every day

   (5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

   (6) fatigue or loss of energy nearly every day

   (7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

   (8) a diminished ability to think or concentrate, or in decisiveness, nearly every day (either subjective account or as observed by others)

   (9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet the criteria for a mixed episode

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

D. The symptoms are not due to the direct physiological effects of a substance or a general medical condition

E. The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation

2.1.2.3. Melancholic depression

In contrast to reactive depression, melancholic depression, as also referred to as endogenous depression in the German literature, is characterised by greater severity, more considerable guilt and loss of interest, typical vegetative symptoms such as decreased appetite and sleep, and other physical symptoms such as difficulty concentrating, early morning awakening, and a diurnal mood swing (depression is worse in the morning) (Tsuang and Faraone 1996). Melancholic depression has a lower rate of response to psychotherapy and placebo when compared to reactive depression (Tsuang and Faraone 1996).

The DSM-IV defines a major depressive episode with melancholic features in a manner that covers most of the features of endogenous depression (Table 5).

Table 5. The DSM-IV melancholic features specifier (American Psychiatric Association 1994)With melancholic features (can be applied to the current or most recent major depressive episode in major depressive disorder and to a major depressive episode in bipolar I or bipolar II disorder only if it is the most recent type of mood episode)

A. Either of the following, occurring during the most severe period of the current episode:

   (1) loss of pleasure in all, or almost all, activities

   (2) lack of reactivity to usually pleasurable stimuli (does not feel much better, even temporarily, when something good happens)

B. Three (or more) of the following:

   (1) distinct quality of depressed mood (i.e., the depressed mood is experienced as distinctly different from the kind of feeling experienced after the death of a loved one)

   (2) depression regularly worse in the morning

   (3) early morning awakening (at least 2 hours before usual time of awakening)

   (4) marked psychomotor retardation or agitation

   (5) significant anorexia or weight loss

   (6) excessive or inappropriate guilt

2.1.2.4 Atypical depression

Atypical depression is distinguished by mood reactivity (i.e., the capacity to be cheered up temporarily by positive experiences or events) as well as by severe fatigue (so-called leaden paralysis), sensitivity to rejection, self-pity, a reverse diurnal mood swing (depression is worse later in the day), and reverse vegetative symptoms (e.g., increased instead of decreased appetite and sleep (Stung and Forgone 1996). About 15% of depressive episodes have atypical features. Atypical depression has traditionally had a better response to monoamine oxidase inhibitor antidepressants than to other antidepressants (Textbook of Psychiatry 2005). However, antidepressive medication of this particular mechanism of action is very seldom used in the treatment of depression in Finland. A major depressive episode with atypical features is defined by the DSM-IV (Table 6).

Table 6. DSM-IV atypical features specifier (American Psychiatric Association 1994)
With atypical features (can be applied when these features predominate during the most recent 2 weeks of a major depressive episode in major depressive disorder or in bipolar I or bipolar II disorder when the major depressive episode is the most recent type of mood episode, or when these features predominate during the most recent 2 years of dysthymic disorder)

A. Mood reactivity (i.e., mood improves in response to actual or potential positive events

B. Two (or more) of the following features:

   (1) significant weight gain or increase in appetite

   (2) hypersomnia

   (3) leaden paralysis (i.e., heavy, leaden feelings in arms or legs)

   (4) long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) that results in significant social or occupational impairment

C. Criteria are not met with melancholic features or catatonic features during the same episode.

2.2.2.5. Other proposed subtypes of depression
Besides those mentioned above, some other subtypes of depression have also been proposed, such as non-melancholic depression, metabolic depression and vascular depression, that are not included in the DSM-IV.
Compared to melancholic depression, non-melancholic depression can be defined as a major depressive episode not having the DSM-IV-based melancholic symptoms included in the definition of melancholic depression (Rush and Weissenburger 1994, Whithall et al. 2010).

The definition of metabolic depression is based on the connection between the MetS and depression (Vogelganzs et al. 2011). Depressed patients with the MetS are reported to be more likely to have persistent or recurrent depression. The latter may suggest that depression with metabolic abnormalities, which could be labelled as metabolic depression, identifies a chronic subtype of depression (Vogelganzs et al. 2011).

The concept of vascular depression has also been presented. The vascular depression hypothesis was proposed as a subtype of depression late in life (Alexopoulos et al. 1997, Steffens et al. 1998, Hickie et al. 1995, Krishnan et al. 1995). During the history of the vascular depression hypothesis, several researchers have proposed different diagnostic criteria (Alexopoulos et al. 1997, Steffens et al. 1998, Krishnan et al. 2004, Alexopoulos et al. 2001, Sneed and Culang-Reinlieb 2011). Chronic inflammation may also underlie many forms of depression associated with vascular disease and the metabolic syndrome (Viscogliosi et al. 2011). Finally, to make progress regarding the validity of vascular depression as a subtype of depression, its longitudinal course needs to be chararacterized (Sneed et al. 2008).

2.2 The metabolic syndrome (MetS), proinflammation and depression
2.2.1 MetS and depression
2.2.1.1 Definitions and prevalence of the MetS
The metabolic syndrome (MetS) is a cardiometabolic risk cluster comprising abdominal obesity, altered glucose and lipid metabolism and elevated blood pressure (Expert panel 2001, Alberti et al. 2005, Grundy et al. 2005, Alberti et al. 2006). It is associated with an increased risk of cardiovascular diseases, type 2 diabetes mellitus and all-cause mortality (Lakka et al. 2002, Ford 2005). Although generally recognized, there has not been a uniform

definition or diagnostic criteria for the MetS. The World Health Organization (WHO) proposed the first commonly accepted criteria for the MetS in 1998: insulin resistance and hyperinsulinemia are the core of the syndrome, as well as central obesity. In addition, dyslipidemia, elevated blood pressure and glucose intolerance are included (World Health Organisation 1999). The National Cholesterol Education Program (NCEP) – Adult Treatment Panel III established a set of criteria for the MetS in 2001 (Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults 2001). Later, the modified National Cholesterol Education Program (NCEP-ATPIII) introduced a lower criterion of 5.6 mmol/l (100 mg/dL) for the fasting serum glucose cut-off point (Grundy et al. 2005).

Since then, an internationally accepted definition for the MetS has been proposed by the International Diabetes Federation (IDF) (The IDF consensus worldwide definition of the metabolic syndrome 2006). The latest proposition to harmonize the criteria for the MetS was published by the IDF and the American Heart Association (AHA) (Alberti et al. 2009). When applying the NCEP criteria, the age-adjusted prevalence of the MetS is estimated to be approximately 35% in the US population and 37% in Eastern Finland (Ford 2005, Miettola 2008). Research into the mechanisms involved in the MetS is of great importance due to the increasing occurrence of obesity and the growing prevalence of MetS.

Criteria for the metabolic syndrome according to NCEP, NCEP-modified, IDF and IDF/AHA definitions are presented in Table 7.

Table 7. Criteria for the metabolic syndrome according to NCEP, NCEP-modified, IDF and IDF/AHA definitions.

	NCEP ATP III (2001)	NCEP modified (2005)	IDF (2005)	IDF/AHA(2009)
Number of criteria needed for diagnosis	Three or more of the following	Three or more of the following	The first plus any two of the following	Three or more of the following
Waist circumference (males)	>102 cm	>102 cm	>94 cm	Population- and country-specific definitions
Waist circumference (females)	>88 cm	>88 cm	>80 cm	Population- and country-specific definitions
Hypertension	BP ≥130/85 mmHg or specific medication	BP ≥130/85 mmHg or specific medication	BP ≥130/85 mmHg or specific medication	Systolic ≥130 and/or diastolic ≥85 mmHg or specific medication
Trigycerides	≥150 mg/dL or ≥1.7 mmol/L or specific medication	≥150 mg/dL or ≥1.7 mmol/L or specific medication	≥150 mg/dL or ≥1.7 mmol/L or specific medication	≥150 mg/dL or ≥1.7 mmol/L or specific medication
HDL cholesterol (men)	<40 mg/dL or <1.03 mmol/L or specific medication	<40 mg/dL or <1.03 mmol/L or specific medication	<40 mg/dL or <1.03 mmol/L or specific medication	<40 mg/dL or <1.0 mmol/L or specific medication
HDL cholesterol (women)	<50 mg/dL or <1.29 mmol/L or specific medication	<50 mg/dL or <1.29 mmol/L or specific medication	<50 mg/dL or <1.29 mmol/L or specific medication	<50 mg/dL or <1.3 mmol/L or specific medication
Fasting plasma glucose	≥110 mg/dL or ≥6.1 mmol/L or specific medication	≥100 mg/dL or ≥5.6 mmol/L or specific medication	≥100 mg/dL or ≥5.6 mmol/L or specific medication	≥100 mg/dL or ≥5.6 mmol/L or specific medication

AHA = American Heart Association
ATP = Adult Treatment Panel
BP = blood pressure
HDL = high-density lipoprotein
IDF = International Diabetes Federation
NCEP = National Cholesterol Education Programme

2.2.1.2 Association between the MetS and depression

Most previous cross-sectional studies have demonstrated that the MetS is more common in depressed than in non-depressed subjects, and the observed prevalence rates have varied from 8% to 38% (Kinder et al. 2004, Heiskanen et al. 2006, Räikkönen et al. 2007, Skilton et al. 2007). In a recent study by East et al. (2010), women and men who exhibited depressive symptoms had a higher prevalence of the MetS compared to those who did not (15.4% versus 7.2% for women; 31.6% versus 22.8% for men). In a study by Laudisio and coworkers, the MetS was independently associated with depressive symptoms in community-dwelling elderly women, but not in men (Laudisio et al. 2009). In a 15-year follow-up study, depressive symptoms and stressful life events at baseline were predictive of the metabolic syndrome in a sample of females (Räikkönen et al. 2007). Psychological distress may also increase the risk of later MetS (Puustinen et al. 2010).

On the other hand, a two-way connection may exist between depression or DS and the MetS (Pan et al. 2012). The MetS predisposed to DS in a population-based 7-year follow-up

(Koponen et al. 2008). Another longitudinal 6-year follow-up study examined the same phenomena. In that study, at baseline, 235 out of 823 persons had metabolic syndrome and 168 were depressed (CES-D score ≥ 20). Among those not depressed at baseline, 26.0% developed depression. A higher waist circumference increased the odds of depression onset, but there was no association between other metabolic syndrome components or the MetS and the onset of depression. Among persons depressed at baseline, depression had a chronic character in 69.0% of those without and 88.5% of those with the metabolic syndrome. The chronicity of depression was defined by a CES-D score ≥20 both at baseline and after 3 or 6 years. Metabolic syndrome was associated with an almost 3-fold increase in the odds of chronicity of depression (Vogelganzs et al. 2011).

The association between depression and the MetS may not, however, be unequivocal, as the largest published cross-sectional study to date (n = 9571) detected no association between depression or anxiety and the MetS (Hildrum et al. 2009). Another large study also revealed no association between a lifetime history of major depression and the presence of the MetS (Foley et al. 2010).

Depression may be a risk factor for several components of the MetS. A tendency towards dyslipidemias and visceral fat accumulation is also associated with depression (Weber-Hamann et al. 2006). In a study by Richter et al. (2010), a correlation between triglyceride levels and the severity of depression was observed in both the acute stage as well as in remission in a group of acutely depressed in-patients with the MetS. Depression in women, but not in men, was associated with a two-fold higher risk of having the MetS (Toker et al. 2008). In both men and women, depression was associated with an increased waist circumference (Toker et al. 2008). In addition, low HDL cholesterol associated with major depression in a sample with a 7-year history of DS (Lehto et al. 2008).

2.2.1.3 The MetS and subtypes of depression

A recent study categorized depression into a severe melancholic depressive class, a severe atypical depressive class and a depressive class of moderate severity. The atypical class showed more MetS than the melancholic class (Lamers et al. 2010). A higher prevalence of abdominal obesity and hypertriglyceridemia was also identified among subjects in the severe atypical depressive class than in the severe melancholic class (Lamers et al., 2010). Furthermore, melancholic features were independently associated with lower HDL cholesterol, and atypical depression was independently associated with higher total and LDL cholesterol (van Reedt Dortland et al. 2010). Another study by Luppino and coworkers demonstrated a strong association of waist circumference, triglyceride levels and blood pressure with the somatic arousal symptom dimension assessed by the Mood and Anxiety Symptom Questionnaire (Luppino et al. 2011). In a recent study, women with undifferentiated and atypical features of major depressive disorder exhibited a greater BMI and higher whole body and abdominal fat mass compared to healthy controls (Cizza et al. 2012). The MetS may be also associated with seasonal changes in mood and weight (Rintamäki et al. 2008).

The only longitudinal study reporting the risk of metabolic syndrome in various subtypes of DS has been the subgroup analysis of Vanhala and co-workers. Females with DS at baseline, compared to those without DS, were shown to have a 2.5-fold higher risk of the MetS at the end of the 7-year follow-up The risk was highest in the subgroup with more melancholic symptoms. Among men there was no risk difference, and males had less severe DS than females, suggesting that the severity of DS may affect the prevalence of the MetS in DS (Vanhala et al. 2009). These findings suggest that the association between depression and the MetS may only be present in certain subtypes of depression.

2.2.1.4. Proposed mediating pathways between the MetS and depression

Underlying mechanisms that may explain the association between depression and the MetS include genetic factors (Zeman et al. 2009), low-grade inflammation and increased secretion

of proinflammatory cytokines (Ovaskainen et al. 2009, Zeugmann et al. 2010). In addition, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis resulting in inappropriate cortisol secretion (Bjorntop 2001, Muhtz et al. 2009, Vogelzangs et al. 2009) may play a role. An imbalance in autonomous neurotransmission may also contribute to persistent (over)activation of the autonomic nervous system, which could lead to metabolic alterations, but the underlying mechanisms are complex and not clearly understood (Tentolouris et al. 2008). Decreased parasympathetic nervous system activity and increased sympathetic nervous system activity were associated with the Mets and its components when the interbeat interval time, pre-ejection period and respiratory sinus arrhythmia were applied to reflect autonomous nervous system activity (Licht et al. 2010).
Leptin resistance may also contribute (Zeman et al., 2009). Leptin regulates dietary intake and appetite by acting on leptin receptors in the brain, particularly the hypothalamus (Brennan and Mantzoros 2006).

2.2.2. The role of proinflammation

2.2.2.1 Proinflammation and depression

The literature on cytokines and depression is abundant, and a large amount of evidence indicates that depressed patients exhibit increased levels of markers of innate immune system activation and inflammation (Miller et al. 2009, Raison and Miller 2011). In a meta-analysis of over 50 studies, the majority of studies reported depressed patients to have elevations in the proinflammatory cytokines interleukin (IL)-6, and IL-1 beta, as well as an acute phase protein, C-reactive protein (CRP) (Howren et al. 2009). While both positive and negative results have been reported in individual studies, a recent meta-analysis indicated that depression may be accompanied by activation of the inflammatory response system (Dowlati et al. 2010). According to Dowlati et al. (2010) and Maes (2011), major depression is characterized by an inflammatory response, such as with increased production of cytokines interleukin-6 and tumour necrosis factor-alpha. Besides this, Maes emphasized the role of cell-mediated immune activation that involves cellular interactions between T lymphocytes and monocytes, which is manifested by T cell activation in depression and may lead to serotonergic disturbances (Maes 2011). Thus, the lowered availability of plasma L-tryptophan (the precursor of serotonin) in the brain in depression is a marker of immune activation, indicating that lowered plasma L-tryptophan, and hence serotonin, are induced through the activation of indoleamine 2,3-dioxygenase (IDO) (Maes 2011). In this way, serotonin can play a role in the inflammatory system response in major depression (Song et al. 1998). Cell-mediated immune activation can also cause glucocorticoid resistance in immune cells, suggesting that HPA hyperactivity in depression is induced by pro-inflammatory cytokines (Maes 2011). Incongruent results nevertheless exist, since circulating cytokine concentrations were not associated with major depressive disorder in a community-based cohort in a recent study (Einvik et al. 2012). Cytokines may affect not only central monoamine synthesis, release and reuptake, but also neuroendocrine function and neural plasticity (Miller et al. 2009). Moreover, long-term exposure to cytokines may lead to depressive disorders. For example, 20% to 50% of patients receiving chronic interferon alpha therapy for the treatment of infectious diseases or cancer developed clinically significant depression (Musselmann et al. 2001, Capuron et al. 2002). A recent longitudinal study reported a correlation between the capacity of T-cells and monocytes to produce cytokines and the development of DS in response to a period of severe stress (van Zuiden et al. 2011).

2.2.2.2 Proinflammation and subtypes of depression

Research data on the association between inflammation and different subtypes of depression are scarce. A study by Kaestner and coworkers reported higher proinflammatory cytokines levels in patients with non-melancholic major depression, whereas in patients with melancholic depression the levels did not differ from the controls

(Kaestner et al. 2005). In the follow-up, the levels were normalized with remission. The incidence of immunoglobulin G/immunoglobulin M-mediated autoimmune responses directed against serotonin is significantly higher in depression, particularly in melancholia. Thus, autoimmune reactions against serotonin may play a role in the pathophysiology of depression and the onset of severe depression. These data may provide support for the notion that melancholia could be a valid subtype of depression (Maes et al. 2012).

2.2.2.3 Proinflammation and the MetS

The link between inflammation and depression may explain the frequent connection between medical illnesses and depression (Benton et al. 2007). While several medical conditions are associated with increased rates of depression, the majority of these illnesses are also linked with increased inflammation, including not only autoimmune and infectious diseases and cancer but also cardiovascular disease and diabetes, both of which are recognized to have an inflammatory component (Hevener and Febbraio 2010). Inflammation and the induction of oxidative and nitrosative stress (IO&NS) are connected with depression and may provide one possible explanation for the association between depression and various disorders such as the MetS, obesity and diabetes (Ames et al. 2011). Inflammation is not only a triggering factor of the MetS but also a consequence: inflammatory cytokines are produced by fat cells, and resistance to the anti-inflammatory effects of insulin may cause increased cytokine levels (Esposito and Giuliani 2004). Furthermore, metabolically healthy obese older persons were found to have a more favourable fat distribution and inflammatory profile compared with their metabolically unhealthy obese counterparts (Koster et al. 2010). In addition, non-obese and obese individuals who develop an intense pro-inflammatory state may be more prone to developing the MetS than those with lower levels of inflammation (Stenholm et al. 2010).

2.2.2.4 Proinflammation, diet and the role of white adipose tissue (WAT)

Dietary excess may promote a general proinflammatory state, which could contribute to metabolic disturbances and diseases such as dyslipidemias, cardiovascular disease, and type 2 diabetes (Shelton and Miller 2010, Shelton and Miller 2011, Shoelson et al. 2007, Bays et al. 2008, Gustafson 2010).

Diet may also contribute to metabolic dysregulatios, since a high intake of fructose contributes to problems with obesity and metabolic diseases such as cardiovascular disease, dyslipidemia and type 2 diabetes (Tappy and Le 2010, Angelopoulos et al. 2009). High fructose loading in the liver leads to the synthesis of triglycerides, which may cause the accumulation of liver and abdominal fat (Stanhope et al. 2008). The so-called white adipose tissue (WAT) is the main location for long-term fat storage in the human body, and may have a role in metabolic disturbances (Mathieu et al. 2009). WAT, particularly in the abdomen, is the main contributor to metabolic diseases (Calabro and Yeh 2008, Despres et al. 2008). The adipocytes in WAT are capable of secreting cytokines and chemokines (Carr et al. 1994, Xu et al. 1996, Tilg and Moschen 2006). Thus, WAT may contribute to widespread immune activation, potentially causing or exacerbating diseases linked with inflammation such as type 2 diabetes, cardiovascular diseases, cancer, and depression (Tilg and Moschen 2006).

Elevated homocysteine levels, mainly caused by a deficiency in folate or vitamin B_{12} levels, may have associations with inflammatory parameters (Gori et al. 2005, Mabrouka et al. 2010).

2.4 Diet and depression

2.4.1 Quality of diet and depression

Most research on the association between the diet and depression or DS has focused on different type of diets, and the main interest has been in the impact of fish oils, dietary fish, omega- 3 fatty acids, folate, vitamin B_{12} and obesity.

The so-called Mediterranean Diet Pattern (MDP) has been reported to associate with a reduced risk of depression (Tortosa et al. 2007, Sanchez-Villegas et al. 2009). Due to the current epidemic of obesity, so-called very low carbohydrate (LC) diets that are typically high in protein and fat (particularly saturated fat) have been introduced, and they can be an effective alternative dietary approach for those intending to lose weight (Astrup et al. 2004, Stern et al. 2004, Dansinger et al. 2005). No clear effect on mood has been found in short-term studies with a very low carbohydrate (LC) or a low fat, high carbohydrate diet (LF) when they have been compared with each other (Kogon et al. 1994, Rosen et al. 1982, D'Anci et al. 2009). On the other hand, one study has reported similar improvements in the mood state in overweight obese women with both LC and LF diets (Halyburton et al. 2007). The long-term effects of an LC diet on mood have been poorly studied. Only one randomized, controlled study has compared the effects a moderate energy-restricted LC diet with those of a conventional isocaloric LF diet over a one-year period. Both diets had positive effects on weight loss, but the LF diet had a more favourable effect on the mood state compared with the LC diet (Grinkworth et al. 2009). The sustained improvement in the LF group is consistent with the findings of epidemiological studies showing that diets high in carbohydrates and low in fat and protein are associated with lower levels of anxiety and depression and have beneficial effects psychological well being (Pellegrin et al. 1998, Munoz et al. 2009).

2.4.2 Sources and deficiency of folate and vitamin B_{12}

Folate is a group of water-soluble naturally occurring compounds mostly found in green vegetables, peanuts, legumes and wholegrain bread, but also in milk products and fruits (Chanarin 1979, The National Nutrition Council 2005). In Finland and in the USA, the recommended daily allowance for folate is 300 μg/day and 400μg/day, respectively (The National Nutrition Council 2005, Food and Nutrition Board, Institute of Medicine 1998). The prevalence of a low plasma folate concentration was 10% among the Finnish population aged 25–74 years, and in Eastern Finland only 25% of middle-aged men had the recommended daily allowance for folate (Alfthan et al. 2002, Tolmunen et al. 2003). There has been a large reduction in the prevalence of folate deficiency in the general population due to folic acid fortification of the food supply in Canada (De Wals et al. 2007). On the other hand, among persons aged 65–74 and ≥75 years, approximately 10% and 20%, respectively, were at high risk of folate deficiency in Great Britain (Clarke et al. 2003).

Folate deficiency causes macrocytic anemia and congenital neural tube deficits, as well as neuropsychiatric symptoms similar to vitamin B_{12} deficiency (Lindenbaum and Allen 1995, Reynolds 2006).

Vitamin B_{12} is only synthesized by bacteria, for which reason its only source is food of animal origin, e.g. meat, fish, eggs and milk products (Allen and Dror 2011). The prevalence of vitamin B_{12} deficiency was reported to be 12% in the Finnish population (aged 65–100 years), whereas 5% of Canadians (aged 6–79 years) were vitamin B_{12} deficient (Loikas et al. 2007, Mac Farlane et al. 2011). Lifestyle factors such as smoking, alcohol consumption and a vegetarian diet have been linked with an increased risk of vitamin B_{12} deficiency in younger adults (Herrmann and Geisel 2002, Wolters et al. 2004), but no such association was recorded in an aged Finnish population (Loikas et al. 2007). No specific risk group for lower vitamin B_{12} levels could be defined among the aged, but aging itself increases the probability of vitamin B_{12} deficiency (Loikas et al. 2007). The clinical presentation of vitamin B_{12} deficiency varies considerably and rarely includes all the classic features, such as macrocytic anaemia, peripheral neuropathy, and subacute combined degeneration of the spinal cord. More typically, vitamin B_{12} deficiency presents as nonspecific symptoms of fatigue, lassitude, vertigo and cognitive impairment that could be attributed to old age (Stabler 2000).

Furthermore, an association between depression and low folate or vitamin B_{12} levels has even been reported in the normal range of these vitamins (Coppen and Bailey 2000, Hintikka et al. 2003).

2.4.3 Evaluation of folate intake

The food frequency questionnaire (FFQ) is currently the main method for estimating the role of the diet in the aetiology of chronic diseases. The popularity of the FFQ is based on its feasibility and low cost compared to other methods, and it describes the habitual diet, which is often more relevant to the study hypothesis than the current, short-term diet (Willett 1990). The FFQ includes 132 food items, which are recorded by applying nine possible frequency categories. The collected food data are subsequently converted into nutrients by specific computer software. It is also a well-validated method for estimating the dietary folate intake (Männistö et al. 1996, Paalanen et al. 2006, Kaartinen et al. 2011).

2.4.4 Association between folate intake and depression

Most studies examining the association between folate and depressive symptoms (DS) have been based upon serum folate levels. Many cross-sectional studies have demonstrated that low levels of folate are associated with the risk of depression or elevated depressive symptoms in adults (Lee et al. 1998, Tiemeier et al. 2002, Sanchez-Villegas et al. 2009, Beydoun et al. 2010, a, b), which has been supported in a longitudinal study in an older Korean population (Kim et al. 2008). However, the findings have not been consistent, since no association between folate levels and DS was detected in a longitudinal study among young women registered in general practices in England (Kendrick et al. 2008). In addition, the associations between depressive symptoms or depression and folate levels may be confounded by different subtypes of DS, as in a clinical study in which subjects with low folate levels were more likely to have melancholic depression (Fava et al. 1997).

Research data on the relationship between folate intake and depression are scarce, since only a few cross-sectional studies have reported an association between folate intake and DS or depression (Tolmunen et al. 2003, Sanchez-Villegas et al. 2009, Murakami et al. 2010).

Of the three published prospective studies, two reported an increased risk of depression or recurrent depression in men with a low folate intake (Tolmunen et al. 2004, Astorg et al. 2008). Contradictory results exist, as a recent U.S. population-based study reported that the intake of folate was not associated with DS (Skarupski et al. 2010).

2.4.5 Evaluation of vitamin B_{12} levels

Vitamin B_{12} was technically difficult to measure until the introduction automated, reliable assays (Carmel 2002, Robinson et al. 2010). Despite the advance in assay techniques, relying on vitamin B_{12} measurement alone remains problematic, since most measured vitamin B_{12} is bound to transporter proteins and is not bioavailable. Moreover, the clinical severity of vitamin B_{12} deficiency is unrelated to vitamin B_{12} concentrations (Carmel 2000, Stabler 2000). Only that portion bound to the delivery protein holotranscobalamin, i.e. 20%, is available to end tissues (Carmel 2002). Measurement of this protein is considered a more accurate tool of recent vitamin B_{12} absorption, and a better approximation of end-tissue B_{12} repletion (Bor et al. 2004).

2.4.6 Association between vitamin B_{12} levels and depression

In clinical studies, lower vitamin B_{12} levels have been found to be associated with severe depression (Bell et al. 2001, Mischoulon et al. 2000) or with DS (Robinson et al. 2011). On the other hand, high vitamin B_{12} levels were associated with a good treatment outcome in patients with major depressive disorders in a clinical setting (Hintikka et al. 2003). However, a small randomized trial found no improvement in depression after the administration of vitamin B_{12} as an adjuvant (Hvas et al. 2004). A recent study reported no

clear potentiation of the effect of antidepressant medication on DS by folate and vitamin B_{12} supplementation (Christensen et al. 2011).

Three cross-sectional studies have reported an association between vitamin B_{12} levels and depressive disorders (Penninx et al. 2000, Tiemeier et al. 2002, Ng et al. 2009). The only existing community-based prospective study reported that lower levels of vitamin B_{12} at baseline were associated with a higher risk of incident depression on 2- to 3-year follow-up among older Korean people (Kim et al. 2008). However, previous results have been somewhat inconsistent, since some studies have found no association between vitamin B_{12} levels and DS or depressive disorders (Lindeman R et al. 2000, Morris et al. 2003, Bjelland et al. 2003, Sachdev et al. 2004, Beydoun et al. 2010).

2.4.7. Proposed mediating pathways between folate, vitamin B_{12} and depression

A wide array of aetiological hypotheses has been suggested to explain depression. Of the biological hypotheses, the monoamine hypothesis proposes an important aetiological role for serotoninergic or noradrenergic dysfunction in depression (Stahl 2008). Folate and vitamin B_{12} are involved in single-carbon transfer reactions needed for the production of serotonin and other monoamine neurotransmitters (Coppen et al. 1989). Folate and vitamin B_{12} deficiency may also result in the accumulation of homocysteine, which has been suggested to lead to exitotoxic reactions and may enhance depression (Stabler et al. 1990, Parnetti et al. 1997). Homocysteine can be remethylated to methionine, which requires vitamin B_{12} (Bottiglieri 2005). Methionine is the immediate precursor of S-adenosylmethionine (SAM), the methyl donor of numerous methylation reactions in the brain, many of which are directly involved in the synthesis and metabolism of dopamine, norepinephrine and serotonin (Bottiglieri et al. 2000, Coppen and Bolander-Gouaille 2005). It has even been suggested that a specific subtype of depression may exist with high total plasma homocysteine levels due to low methylation in the central nervous system caused by folate deficiency (Bottiglieri 2000). On the other hand, alternative views of homocysteine include its role as a chemoattractant in tissue damage and inflammation (Dudman 1999). Methyl donation is required for subsequent monoamine neurotransmitter formation: while some empirical evidence for this exists, it is of poor quality (Williams et al. 2005). These findings form a plausible link between folate, vitamin B_{12} and mood, and may also indicate that the association between depression and folate or vitamin B_{12} could be mediated through monoamine synthesis.

In addition to its role in the one-carbon cycle, vitamin B_{12} could play a role in the methylmalonic acid pathway, and its deficiency leads to a rise in the levels of methylmalonic acid. Depressed subjects have been reported to have higher methylmalonic acid levels (Penninx et al. 2000).

Vascular depression is also a possible mediating pathway between folate, vitamin B_{12} and depression or DS. Alexopoulos proposed an operational description of "vascular depression" in 1997, and radiological findings of subcortical ischemic depression were reported in the same year (Alexopoulos et al. 1997, Krishnan et al. 1997). Although some evidence does not support an association between the cortical vascular disease burden and depressive symptoms, the concept is considered reasonably robust (Baldwin 2005). It is also posited that a deficiency of folate or vitamin B_{12} could cause elevated homocysteine levels, thereby increasing atherosclerosis, hence causing vascular depression (Folstein et al. 2007). Moreover, vitamin B_{12} deficiency has been associated with a greater burden of vascular lesions on neuroimaging (De Lau et al. 2009).

3 AIMS OF THE STUDY

This study was undertaken to investigate the association between predominantly melancholic or non-melancholic DS, measured by the BDI, and the MetS, folate intake and serum vitamin B_{12} levels in a population-based study.

The specific aims were:

1. To evaluate the value of the BDI as a screening instrument for depression and the depressive symptom profile using the clinical DSM-IV-based Mini-International Psychiatric Interview (MINI) as a validating measure among middle-aged and elderly subjects living in different geographical regions.

2. To examine the prevalence of the MetS and its components in groups with predominantly melancholic or non-melancholic DS.

3. To study the association between folate intake and DS in groups with predominantly melancholic or non-melancholic characteristics.

4. To assess the correlation between vitamin B_{12} levels and DS in groups with melancholic or non-melancholic features divided according to the BDI.

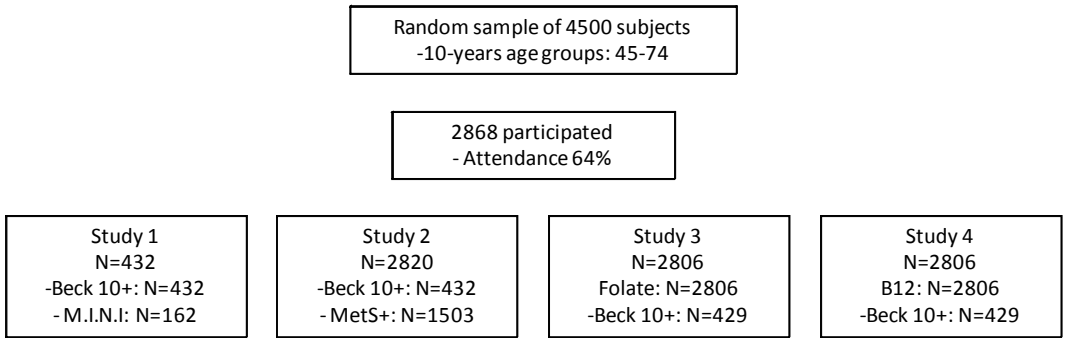
4 SUBJECTS AND METHODS

4.1 Subjects

The study population was enrolled as a part of the national type 2 diabetes prevention programme (FIN-D2D), as a project of the Finnish community-based type 2 diabetes prevention programme, aimed at exploring the ways to implement these preventive methods for type 2 diabetes on a national level. Three hospital districts of Finland, namely Pirkanmaa, Southern Ostrobothnia and Central Finland, were selected for the efficacy survey, which was carried out between October and December 2007 (Saaristo et al. 2007). A representative random sample of 4500 subjects aged 45–74 years, stratified according to gender, 10-year age groups (45–54, 55–64 and 65–74 years) and the three geographical areas, was selected from the National Population Register in August 2007. Of the 4500 persons who were invited by mail to the health examination, 2868 participated (attendance 64%). The participants (N = 2868) and the nonparticipants (N = 1632) did not differ with regard to gender or age.

The Ethics Committee of the Hospital District of Helsinki and Uusimaa granted ethical permission for the study. All participants provided written informed consent prior to participation in the study.

Figure 1 presents a flow chart of studies I–IV. In study I, 432 subjects had a BDI score of 10 points or more, and the MINI was performed on 162 participants out of 432. Of the original population (N = 2868), 48 participants were excluded from the analyses because of incomplete data for the MetS (study II). Similarly, 62 subjects with missing data for folate intake (study III) and the same number of participants without vitamin B_{12} levels were exluded (study IV).



MetS = metabolic syndrome
MINI = The Mini-International Neuropsychiatric Interview
Figure 1. Flow chart of studies I–IV.

4.2 Measurements of depression

The Beck Depression Inventory (BDI) was applied to assess DS. Subjects were asked to rate 21 items from 0 to 3 according to how they felt at that time. The items were summed as a total score with a range from 0 to 63 (Beck et al. 1961, Beck and Beamesderfer 1974). Subjects were categorized to have DS when they scored ≥10 points in the BDI. The cut-off point of 10 in the BDI has been shown to be a useful instrument for detecting depressive symptoms in various adult populations (Beck et al. 1988, Timonen et al. 2006, Räikkönen et al. 2007, Vanhala et al. 2009, Koponen et al. 2010, Korniloff et al. 2010, Mäntyselkä et al. 2011).

Furthermore, to determine the subtype of DS, a summary score of melancholic symptoms in the BDI was calculated based on the DSM-IV-defined criteria (sadness, past failure, loss of pleasure, guilty feelings, punishment feelings, loss of interest, irritability, change in

sleeping and appetite). The subjects were defined to have DS with melancholic characteristics when the number of melancholic symptoms exceeded the number of non-melancholic symptoms (Sheehan et al. 1994, Steer et al. 1999, Ovaskainen et al. 2009, Vanhala et al. 2009).

Furthermore, those cases with DS (BDI score ≥ 10) were examined by an attending psychiatrist, who carried out a normal psychiatric interview. In addition, board-certified psychiatrists who were blind to the actual BDI score performed the Finnish version of the MINI to establish the diagnosis of depression among participants with elevated DS.

4.3. Measurement of the MetS

The MetS was defined according to the modified National Cholesterol Education Program (NCEP-ATPIII) criteria with a cut-off point of 100 mg/dL blood glucose (i.e. 5.6 mmol/l) (Grundy et al. 2005). The use of lipid lowering, antihypertensive, antihyperglycemic, and antidepressive medications was also recorded.

4.4 Assessment of dietary and folate intake

The Food Frequency Questionnaire (FFQ) was used to evaluate the diet over the previous year (Männistö et al. 2006, Kaartinen et al. 2011). It is a well-validated method for estimating dietary folate intake, and also the main method for estimating the role of diet in the aetiology of chronic diseases (Kaartinen et al. 2011, Männistö et al. 1996). Nine possible frequency categories that ranged from never or seldom to at least six times per day were used to evaluate the consumption of 132 food items. Participants were also asked to record those items not listed in the FFQ if they were frequently consumed. The size of the portion was standardized for each food item (e.g., slice and glass). The FFQ was completed by the subjects at the study centre under the surveillance of a trained study nurse. The nurse also carefully checked the data. The software and National Food Composition Database of the National Institute for Health and Welfare were used to derive the nutrient intakes from the food information provided by the participants. The residual method was applied to adjust the folate intake for the dietary energy intake (Willet and Stampfer 1998). Energy adjustment is based on the assumption that a larger, more physically active person needs a greater energy intake, which is associated with a greater absolute intake of all other nutritients. Tertiles of gender-specific folate intake were used, because the mean energy-adjusted folate intake was significantly lower in men than in women.

4.5 Laboratory analysis

The study laboratory sampling was conducted in accordance with the World Health Organization MONICA protocol (World Health Organization 1988). Blood samples were drawn for measurement of fasting plasma (fP) glucose, fS triglycerides, fS HDL, LDL cholesterol concentrations, and serum vitamin B_{12} following an overnight fast. Centrifugation was carried out within 1 h at room temperature to separate the serum and plasma. The samples were then aliquoted into storage tubes and stored frozen at a minimum of −20 °C before transportation frozen to the National Institute for Health and Welfare. The samples were stored at −70 °C in the National Institute for Health and Welfare until they were analyzed in the same laboratory. Participants were advised to contact their own physician in the case of any abnormality in the laboratory results. The Laboratory of Analytical Biochemistry at the National Public Health Institute, Helsinki, performed all assays using a ci82000 analyzer (Abbott Laboratories, Abbott Park, IL).

The Chemiluminescent Microparticle Immuno Assay (CMIA) was used to measure serum vitamin B_{12} with a reference range of 138–652 pmol/L for the normal serum vitamin B_{12} level. The interassay coefficients of variation (CV) of B_{12} vitamin were 6.2% and 5.0% at the levels of 150 pmol/L and 380 pmol/L, respectively.

A hexokinase method (Abbott Laboratories, Abbott Park, IL) was used to determine plasma glucose, and serum HDL cholesterol and triglyceride concentrations were

measured with enzymatic kits from Abbott Laboratories (Abbott Park, IL). The concentrations of LDL cholesterol were calculated using the Friedewald formula (Friedewald et al. 1972).

4.6 Other measurements

Height (in cm) was measured to the nearest 0.1 cm, and weight (in kg) was measured in light clothing and without shoes to the nearest 0.1 kg. The body mass index (BMI) was calculated as weight in kilograms (kg) divided by the square of height in metres (m). Waist circumference (in cm) was measured midway between the lowest rib margin and the iliac crest. Blood pressure was measured twice in a sitting position after a minimum of 15 minutes of acclimization and before blood sampling using a mercury sphygmomanometer. Education was assessed according to years of education. The participants were categorized as married, single, separated or widowed according to information provided. Employment status was asked, and the number of employed participants was counted. Self-administered questionnaires were used to evaluate current smoking and alcohol consumption, which were then dichotomized (no or yes).

The participants reported their leisure-time physical activity (LTPA) according to three categories: 1) low: almost completely inactive (e.g., reading, watching television, or doing some minor physical activity); 2) moderate: some physical activity more than 4 h per week (e.g., walking, cycling, light gardening, fishing, or hunting); and 3) high: vigorous physical activity more than 3 h per week or regular exercise or competitive sports several times a week (e.g., running, jogging, skiing, ball games or heavy gardening). LTPA was assessed with the question: "How much physical activity do you practice during leisure time?" (Korniloff et al. 2010).

To establish a chronic diseases sum index, the participants were asked the question "Have you had any of the following diseases that have been diagnosed or treated by a doctor in the last 12 months." Elevated blood pressure, heart failure, angina pectoris/other cardiovascular event, diabetes, cancer, bronchial asthma/emphysema and rheumatoid arthritis/other arthropathy/spinal diseases were included in the chronic diseases sum index, which ranged from 0 to 7 (Mäntyselkä et al. 2011).

4.6 Statistical analysis

4.6.1 Study I

Differences between genders in characteristics were tested by t-tests and chi-squared tests. Receiver operating characteristic (ROC) curves were constructed to determine the cut-off point of BDI that corresponds to the MINI criteria, with bias-corrected bootstrap confidence intervals (CIs). Sensitivity, specificity, positive and negative predictive values, the likelihood ratio, and their 95% CI values were calculated. The difference between genders in the area under the receiver operating characteristic curve (AUC) was evaluated by using an algorithm suggested by DeLong with permutation (DeLong et al. 1988). The level of statistical significance was set at 0.05

4.6.2 Study II

The results are expressed as means with SDs and 95% confidence intervals (CIs). The groups were statistically compared using chi-squared tests or analysis of variance (ANOVA). Logistic regression was used to model the prevalence of the MetS using appropriate covariates. +

4.6.3 Study III

The data are presented as means with standard deviations (SD) and counts with percentages. Statistical comparison between the groups was conducted using the chi-squared test and t-test. Univariate and multivariate logistic regression analyses were

performed to identify the appropriate predictors of depressive symptoms with linearity contrast.

4.6.4 Study IV

The data are presented as means with standard deviations or counts with percentages. Groups were statistically compared using the t-test, permutation test or chi-squared test, as appropriate.

Multivariate logistic regression was used to analyse the relative risk ratios (RRR) and their 95% confidence intervals (95% CI) for the presence of non-melancholic and melancholic DS with appropriate contrasts. The multinomial (polytomous) logistic regression model is an extension of the binomial logistic regression model and is used when the dependent variable has more than two nominal (unordered) categories.

5 RESULTS

5.1 Beck depression inventory (BDI) as a screening tool for depression (study I)

The distribution of baseline characteristics of the entire study population (n = 2840) according to gender is presented in Table 8.

Table 8. Distribution of baseline characteristics of the entire study population (n = 2840) according to gender.

Variables	Male N = 1352	Female N = 1488
Demographics		
Age groups, n (%)		
45–54	392 (29)	485 (33)
55–64	454 (34)	514 (35)
65–74	506 (37)	489 (33)
Marriage or common law marriage, n (%)	1092 (81)	1058 (71)
Educational status, n (%)		
Basic education only	537 (40)	547 (37)
Vocational education	397 (29)	346 (23)
Upper secondary school	297 (22)	448 (30)
Higher education	108 (8)	139 (9)
Employed, n (%)	609 (45)	705 (47)
Clinical		
Body mass index, kg/m^2, mean (SD)	27.5 (4.2)	27.6 (5.3)
Waist, cm, mean (SD)	100 (12)	90 (13)
Blood pressure, mm/Hg, mean (SD)		
Systolic	138 (19)	135 (19)
Diastolic	83 (10)	80 (9)
HDL cholesterol, mmol/l, mean (SD)	1.32 (0.32)	1.55 (0.34)
Total triglycerides, mmol/l, mean (SD)	1.49 (0.99)	1.28 (0.61)
Fasting plasma glucose, mmol/l, mean (SD)	6.43 (1.26)	6.03 (1.06)

Metabolic syndrome, modified NCEP-ATPIII criteria, n (%)	755 (56)	757 (51)
Use of antidepressive medication, n (%)	52 (4)	98 (7)
Lifestyle factors		./..
Current smoker, n (%)	336 (25)	289 (19)
Current use of alcohol, n (%)	970 (72)	729 (49)
Leisure time physical activity, n (%)		
Low	254 (19)	265 (18)
Moderate	750 (55)	865 (58)
High	297 (22)	314 (21)

HDL = high-density lipoprotein
NCEP = National Cholesterol Education Program

Figure 2 illustrates the distribution of the BDI scores according to gender in the entire study population (n = 2840).

The mean BDI score was 13.6 in males and 14.1 in females (p= 0.55).
To validate the diagnosis of depression, the MINI was performed for 162 out of 432 participants (57 males and 105 females) scoring ≥10 in the BDI.
The characteristics of MINI-based depression in the present sample are presented in Table 9.
Leisure-time physical activity was more common among those without depression compared to subjects with depression, while depressed subjects smoked more often than their non-depressed counterparts. The 162 study participants did not differ from cases not attending the MINI (112 males and 158 females) with regard to socio-demographic variables.

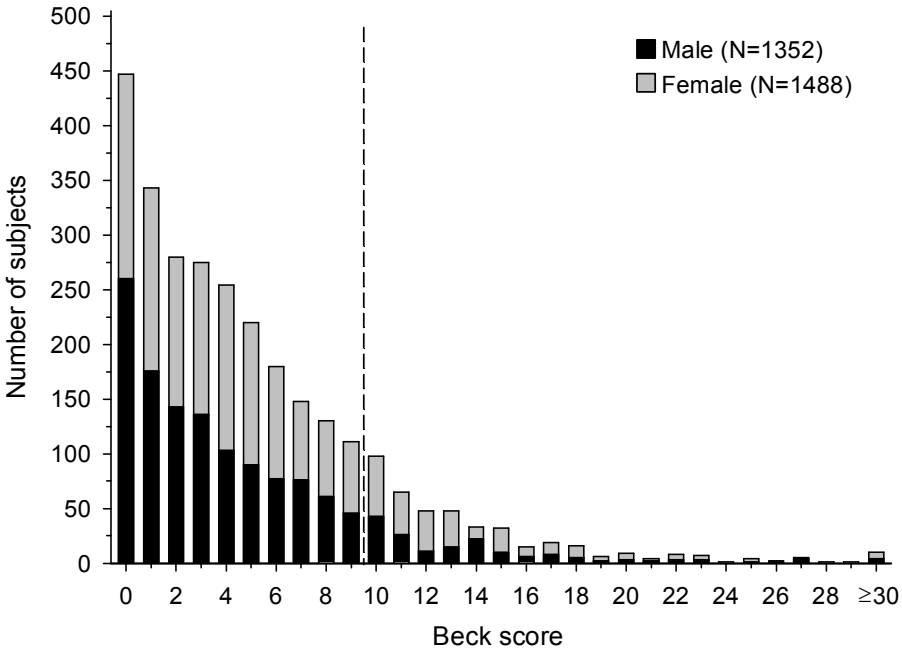


Figure 2. Distribution of BDI scores according to gender in the entire study population (n = 2840).

Table 9. Characteristics of the study population according to the depression status (study I).

	MINI-based depression		
Variable	Not present N = 117	Present N = 45	P-value
Number of female, n (%)	76 (65)	29 (64)	0.95
Age, years, mean (SD)	62 (8)	59 (8)	0.091
Marriage or common law marriage, n (%)	80 (68)	32 (71)	0.74
Employment status, n (%)			0.095
Employed	36 (31)	13 (29)	
Unemployed	3 (3)	5 (11)	
Retired	78 (66)	(27 (60)	
Educational status, n (%)			0.89
Basic education only	42 (36)	19 (42)	
Vocational education	24 (21)	9 (20)	
Upper secondary school	38 (32)	13 (29)	
Higher education	13 (1)11	4 (9)	
Leisure-time physical activity, n (%)			0.003
Low	29 (25)	22 (49)	
Moderate	60 (51)	20 (44)	

High	28 (24)	3 (7)	
Current smoker, n (%)	20 (17)	14 (31)	0.05
Current use of alcohol, n (%)	97 (83)	37 (82)	0.92

The sensitivity and specificity curves of the BDI are presented in Figure 3. A score of 15 simultaneously maximized the sensitivity (0.56 (95% CI: 0.40 to 0.70)) and specificity (0.77 (95% CI: 0.68 to 0.84)). The PPV (positive predictive value) of 0.48 (95%CI: 0.34 to 0.62) and the NPV (negative predictive value) of 0.82 (95%CI: 0.73 to 0.89) were favourable for the cut-off score of 15 points as well as the LR+ (likelihood ratio for positive result) of 2.41 (95%CI: 1.58 to 3.67) as compared to other cut-off levels.

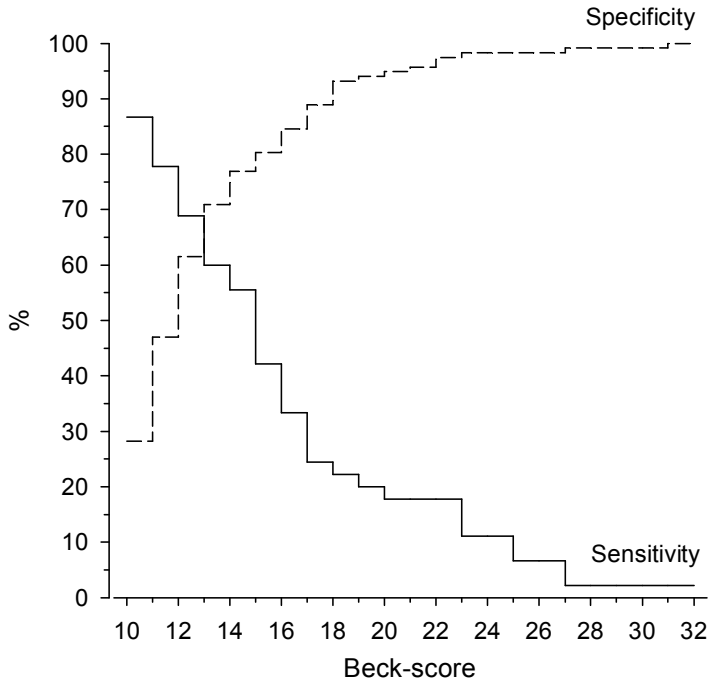
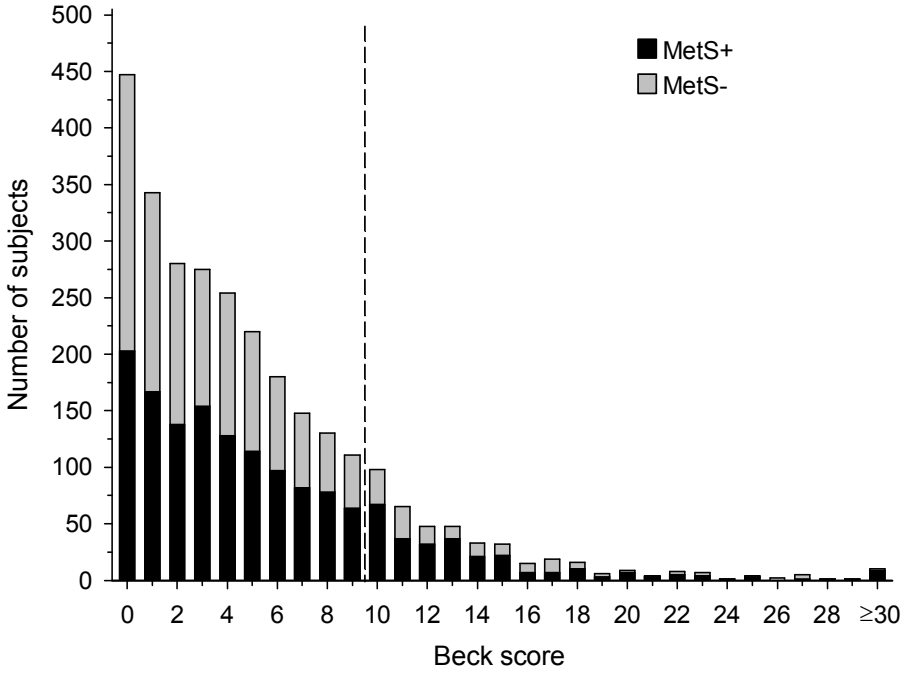


Figure 3. Sensitivity and specificity curves of the depression diagnosis on the basis of the BDI. The reference test is the MINI (study I).

5.2 Prevalence of metabolic syndrome (MetS) in subjects with melancholic and non-melancholic depressive symptoms (study II)

The number of subjects with the MetS in the entire study population according to the BDI scores is presented in Figure 4.



MetS = the metabolic syndrome

Figure 4. Number of subjects with the MetS in the entire study population according to scores in the Beck Depression Inventory (BDI) (study II).

The study population (N = 2820) included 432 subjects scoring ≥10 on the BDI, who were further divided into groups with predominantly non-melancholic DS (N = 293) and melancholic DS (N = 139). The groups with non-melancholic and melancholic DS and those without DS differed significantly from each other in several demographic and biochemical variables (Table 10). The BMI, as well as the fasting plasma glucose and triglyceride concentrations were highest in the group with non-melancholic DS (Table 10). Differences were also seen in smoking and LTPA. Smoking was most common in subjects with melancholic DS compared to those with non-melancholic DS or to subjects without DS. A high level of physical activity was least common among those with non-melancholic DS (Table 10), while those with melancholic DS or without DS formed the reference population. LTPA was lower among the two depressed groups than in non-depressed population. The use of antidepressive medication was not higher in the group with melancholic DS compared to those with non-melancholic characteristics (p = 0.10, age and sex adjusted).

Table 10. Demographic, biochemical and lifestyle variables and use of antidepressive medication by those in the identified depressive symptom groups (study II).

Variables	Depressive symptoms			P value*
	A N = 293	B N = 139	No N = 2388	
Age, years, (SD)	61 (8)	61 (9)	59 (8)	<0.001
Female, n (%)	180 (61)	83 (60)	1220 (51)	0.001
Body mass index, kg/m^2	29.0 (6.1)	27.7 (4.3)	27.3 (4.7)	<0.001
Waist, cm, (SD)				
Male	104 (14)	104 (14)	100 (11)	<0.001
Female	95 (16)	91 (11)	90 (13)	<0.001
Blood pressure, mmHg, (SD):				
Systolic (SD)	137 (19)	135 (18)	137 (19)	0.067
Diastolic (SD)	81 (10)	80 (9)	82 (10)	0.44
HDL cholesterol, mg/dL, (SD):				
Male	49.5 (11.2)	48.3 (12.4)	51.0 (12.4)	0.13
Female	58.4 (12.4)	58.4 (12.0)	60.3 (13.1)	0.16
Total triglycerides, mg/dL, (SD):	132.0 (71.7)	124.0 (56.7	120.5 (73.5))	0.015
Fasting plasma glucose, mg/dL, (SD):	114.6 (25.1)	110.1 (18.2)	111.9 (20.7)	0.048
Smoking, n (%)	72 (25)	41 (30)	510 (21)	0.001
Using alcohol, n (%)	156 (53)	72 (52)	1471 (62)	0.20
LTPA, n (%)				<0.001
Low	97 (33)	46 (33)	376 (16)	
Moderate	153 (52)	66 (47)	1396 (60)	
High	24 (8)	22 (16)	565 (24)	
Antidepressive medication, N (%)	47 (16)	32 (23)	71(3)	<0.001

* Adjusted for age and sex.
A = non-melancholic depressive symptoms
B = melancholic depressive symptoms
LTPA = leisure time physical activity
HDL = high-density lipoprotein

The prevalence of the MetS according to the depressive symptom status in males and females is presented in Table 11.
The highest prevalence of the MetS (69%) was found in both males (95% CI 60 to 77) and females (95% CI 62 to 76) in the subgroup of non-melancholic DS compared to those with melancholic DS (61%; 95% CI 47 to 74 vs. 51%; 95% CI 39 to 62) or to those without DS (54%; 95% CI 52 to 57 vs. 48%; 95% CI 45 to 51) (Table 11). No interaction between sex and depressive symptom status was found in the groups with DS. Except for the glucose criterion in males, the highest prevalence for each criterion was found among the persons with non-melancholic DS (see article II, Figure 2).

Table 11. Prevalence of metabolic syndrome according to depressive symptom status in males and females (study II).

	Male % (95% CI)	Female % (95% CI)	RR (95% CI)
BDI < 10	54 (52 to 57)	48 (45 to 51)	1.13 (1.04 to 1.22)
Depressive symptoms:			
non-melancholic	69 (60 to 77)	69 (62 to 76)	1.00 (0.86 to 1.17)
melancholic	61 (47 to 74)	51 (39 to 62)	1.20 (0.89 to 1.62)

RR = relative risk

Subjects with non-melancholic DS had two-fold higher odds (2.10; 95% CI 1.62 to 2.73, $p < 0.001$) for the MetS in the logistic regression analyses adjusted for age and sex, whereas melancholic DS were not associated with the MetS (OR 1.15; 95% CI 0.81 to 1.61, $p = 0.44$) when subjects without DS formed the reference group. Non-melancholic DS were associated with the MetS (OR 1.84; 95% CI 1.20 to 2.80, $p = 0.005$) when compared to the melancholic group (see article II, Table 2).
Non-melancholic DS were associated with the MetS (OR 1.68; 95% CI 1.16 to 2.22, $p < 0.001$), whereas melancholic DS did not associate with the MetS (OR 0.92; 95% CI 0.64 to 1.13, $p = 0.67$) when multivariate logistic regression analysis adjusted for sex, age, smoking, alcohol use and LTPA was applied. Non-melancholic DS were also associated with the MetS (OR 1.87; 95% CI 1.19 to 2.93, $p = 0.006$) when compared to the melancholic group (see article II, Table 2).

5.3 Association between folate intake and melancholic depressive symptoms (study III)

The study population (N = 2806) included 429 subjects with a BDI score ≥10. The general characteristics of the two subgroups with BDI scores <10 or ≥10 are presented in Table 12. Participants with elevated DS were less educated, more likely to be older or female. They also had a higher BMI, were unmarried or unemployed, and their level of physical activity was lower. Subjects with DS used less alcohol than their non-depressed counterparts (Table 12).

The population with BDI ≥10 was further divided into groups with predominantly melancholic (N = 138) and non-melancholic DS (N = 291).

Table 12. Distribution of baseline factors according to depressive symptom status (study III).

	Depressive symptoms status		P-value
	BDI score ≥10 N = 429	BDI score <10 N = 2377	
Female, n (%)	263 (61)	1215 (51)	<0.001
Age, years, mean (SD)	61 (9)	59 (8)	<0.001
Body Mass Index (kg/m^2), mean (SD)	28.6 (5.6)	27.3 (4.7)	<0.001
Education years, mean (SD)	10 (8.13)	11 (8.14)	<0.001
Marital status, n (%)			<0.001
Married	286 (67)	1842 (78)	
Single	47 (11)	181 (8)	
Separated	61 (14)	215 (9)	
Widowed	33 (8)	130 (5)	
Employed, n (%)	113 (26)	1229 (52)	<0.001
Current smoker, n (%)	111 (26)	508 (21)	0.038
Using alcohol, n (%)	225 (52)	1465 (62)	<0.001
Leisure time physical activity, n (%)			<0.001
Low	141 (35)	375 (16)	
Moderate	218 (54)	1391 (60)	
High	46 (11)	561 (24)	
Chronic diseases sum index (0–7), mean (SD)	1.12 (1.30)	0.60 (1.06)	<0.001
Use of antidepressive medication, n (%)	77 (18)	71 (3)	<0.001

The mean energy-adjusted folate intake was 434 ± 93 μg/day among those without DS (BDI < 10) and 421 ± 103 μg/day in subjects with DS (BDI ≥ 10) (p = 0.007) (Figure 5).

Furthermore, subjects with melancholic DS had a lower mean energy-adjusted folate intake as compared to subjects with non-melancholic DS (408 ± 84 μg/day vs. 427 ± 110 μg/day, p = 0.007).
Men had a lower mean energy-adjusted folate intake than women (406 ± 83 μg/day vs. 455 ± 98 μg/day, p < 0.001).

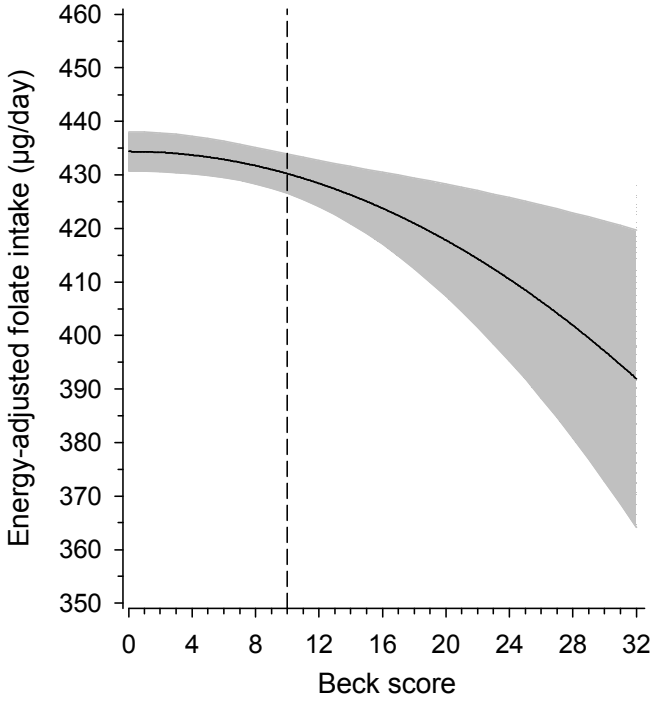


Figure 5. Estimated energy-adjusted folate intake of the subjects according to the Beck Depression Inventory score. The curve with 95% confidence band was derived from a quadratic model (study III).

Melancholic DS were linearly and inversely associated with gender-specific tertiles of the folate intake (p for linearity = 0.005), while non-melancholic DS were not (p for linearity = 0.12). A linear association was also found between DS and gender-specific tertiles of folate intake (p for linearity = 0.003) (Figure 6).

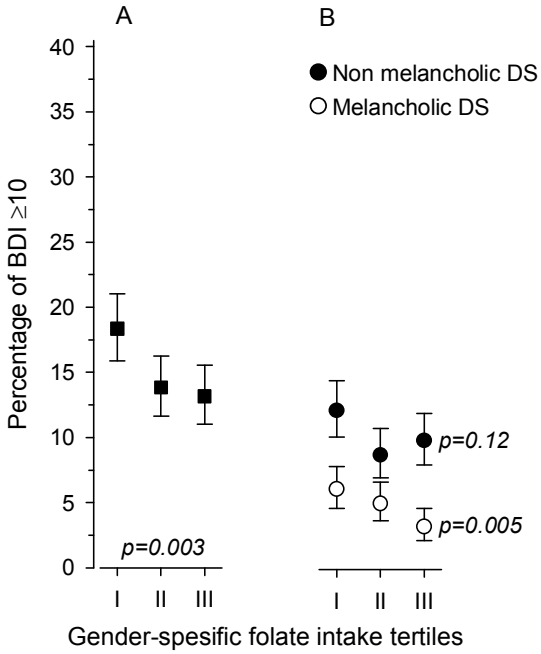


Figure 6. Panel A: Prevalence of DS (depressive symptoms, Beck ≥10) with 95%CIs according to gender-specific folate intake tertiles

Panel B: Prevalence of DS with melancholic and non-melancholic characteristics with 95%CIs according to gender-specific folate intake tertiles
P-values introducing non-adjusted linearity (study III).

The OR for melancholic DS was 0.52 (95% CI 0.33 to 0.82) for the high folate intake tertile versus the low tertile (p for linearity = 0.005) in the unadjusted model, while the unadjusted ORs for non-melancholic DS remained nonsignificant. After several adjustments, the OR for melancholic DS was still 0.55 (95% CI 0.34 to 0.90) for the high folate intake tertile versus the low tertile (p for linearity = 0.018). The multivariate ORs for non-melancholic DS were nonsignificant (Table13).

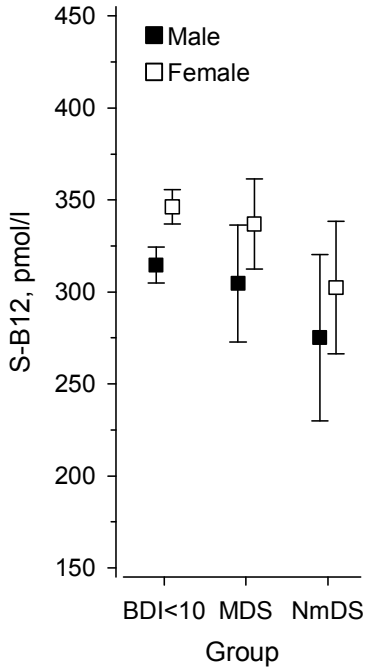
Table 13. Association between different dietary folate intake tertiles (I = low, II = medium and III = high) and both non-melancholic and melancholic depressive symptoms (DS) (study III).

	BDI ≥10				
	Non-melancholic DS			Melancholic DS	
	OR (95% CI)	P-value For linearity		OR (95% CI)	P-value for linearity
Model 1					
I	1 (Reference)	0.12		1 (Reference)	0.005
II	0.69 (0.51 to 0.94)			0.81 (0.54 to 1.21)	
III	0.79 (0.59 to 1.06)			0.52 (0.33 to 0.82)	
Model 2					
I	1 (Reference)	0.08		1 (Reference)	0.006
II	0.68 (0.50 to 0.93)			0.83 (0.55 to 1.26)	
III	0.76 (0.56 to 1.03)			0.53 (0.33 to 0.83)	
Model 3					
I	1 (Reference)	0.47		1 (Reference)	0.024
II	0.76 (0.55 to 1.05)			0.96 (0.63 to 1.48)	
III	0.89 (0.64 to 1.23)			0.57 (0.35 to 0.92)	
Model 4					
I	1 (Reference)	0.24		1 (Reference)	0.018
II	0.73 (0.52 to 1.01)			0.95 (0.62 to 1.46)	
III	0.82 (0.59 to 1.14)			0.55 (0.34 to 0.90)	

Model 1: unadjusted
Model 2: adjusted for age and antidepressive medication
Model 3: adjusted for age, antidepressive medication, BMI, leisure-time physical activity, alcohol, smoking, marital status, and years of education
Model 4: adjusted for age, BMI, leisure-time physical activity, alcohol, smoking, marital status, years of education and chronic diseases

5.4 Association between vitamin B_{12} levels and melancholic depressive symptoms (study IV)

The study population was the same as in study III (Table 12).
A difference between males and females was found in vitamin B_{12} levels (312 ± 171 pmol/L vs. 343 ± 168 pmol/L, $p < 0.001$). Figure 7 illustrates the distribution of S-B_{12} levels among men and women according to depressive symptom status.



BDI = Beck Depression Inventory
MDS = melancholic depressive symptoms
NmDS = non-melancholic depressive symptoms
Figure 7. Distribution of S-B_{12} levels among men and women according to depressive symptom status (study IV).

Subjects with depressive symptoms were subdivided into groups with predominantly melancholic (N = 138) and non-melancholic DS (N = 291) to further examine the vitamin B_{12} levels. An independent linearly inverse association between the B_{12} level tertiles and melancholic depressive symptoms was found in the multinomial regression analysis: the relative risk ratio (RRR) was 2.75 (95% CI 1.66 to 4.56, p for linearity <0.001) in the lowest vitamin B_{12} level tertile as compared to the highest (Table14). No association between B_{12} vitamin tertiles and non-melancholic DS was detected, since the RRR for the lowest vitamin B_{12} level tertile versus the highest was 1.20 (95%CI 0.86 to 1.66, p for linearity 0.28) (Table 14).

Table 14. Relative risk ratios for having non-melancholic or melancholic depressive symptoms and their 95% confidence intervals (95% CI) from multinomial regression analysis (study IV).

Variables	NmDS versus BDI < 10 RRR (95% CI)	P-value	MDS versus BDI < 10 RRR (95 % CI)	P-value
Vitamin B_{12} tertiles*				
I	1 (reference)	0.28#	1 (reference)	<0.001#
II	1.01 (0.72 to 1.41)		1.90 (1.21 to 3.22)	
III	1.20 (0.86 to 1.66)		2.75 (1.66 to 4.56)	
Male sex	0.59 (0.44 to 0.79)	<0.001	0.82 (0.54 to 1.23)	0.34
Age	1.02 (1.00 to 1.04)	0.041	1.02 (1.00 to 1.05)	0.091
BMI	1.02 (1.00 to 1.05)	0.11	0.98 (0.94 to 1.02)	0.32
Smoking	1.23 (0.88 to 1.71)	0.23	1.41 (0.91 to 2.20)	0.13
Using alcohol	1.09 (0.81 to 1.45)	0.59	0.84 (0.56 to 1.26)	0.39
LTPA		<0.001#		0.006#
I	1 (reference)		1 (reference)	
II	0.50 (0.37 to 0.68)		0.42 (0.27 to 0.64)	
III	0.24 (0.15 to 0.39)		0.43 (0.24 to 0.76)	
Years of education	0.98 (0.94 to 1.02)	0.24	1.00 (0.95 to 1.06)	0.99
Living alone	1.29 (0.95 to 1.75)	0.10	1.93 (1.30 to 2.88)	0.001
Energy intake	1.00 (1.00 to 1.00)	0.90	1.00 (1.00 to 1.00)	0.74
Use of antidepressive medication	5.51 (3.55 to 8.54)	<0.001	9.45 (5.63 to 15.86)	<0.001
Chronic diseases sum index	1.41 (1.26 to 1.59)	<0.001	1.21 (1.02 to 1.45)	0.031

* Gender specific tertiles: Male I > 340 pmol/L, II = 255–340 pmol/L, III < 255 pmol/L; Female I > 380 pmol/L, II = 280–379 pmol/L, III = <280 pmol/L.
# P for linearity.
RRR = relative risk ratio
BDI = Beck Depression Inventory
NmDS = non-melancholic depressive symptoms
MDS = melancholic depressive symptoms
BMI = body mass index
LTPA = leisure-time physical activity

6 DISCUSSION

6.1 Pivotal findings

According to first study, a BDI score of 15 simultaneously maximized the sensitivity and specificity of the BDI in detecting depression compared to other suggested cut-off points of 14 and 18. In addition, the area under the ROC curves did not differ between genders. Thus, these results suggest that the BDI with a cut-off point of 15 is a fairly valid screening instrument for the detection or exclusion of depression in population-based subjects. On the other hand, when taking into account the findings of this study and others, the BDI alone cannot provide an accurate diagnosis of depression or replace clinical diagnostic interviews.

Study II had two novel findings. Firstly, the prevalence of the MetS was higher in subjects with predominantly non-melancholic DS compared to those with melancholic DS. Secondly, study II reported that the subjects with non-melancholic DS also had two-fold higher odds for the MetS, whereas melancholic DS were not associated with the MetS, when those without DS formed the reference group. When compared to the melancholic group, non-melancholic DS were associated with the MetS. Correspondingly, this result remained significant after multivariate logistic regression analysis adjusted for sex, age, smoking, alcohol use and LTPA. The components of the MetS explaining this finding include the elevated fasting glucose and triglyceride levels in the group with non-melancholic DS, and the higher waist circumference in females within the same group. The finding displayed no interaction with sex.

Study III showed that the unadjusted OR for melancholic DS was almost 50% lower for the high folate intake tertile versus the low tertile, while the unadjusted OR for non-melancholic DS remained nonsignificant. The result remained constant even after several adjustments. DS also linearly associated with gender-specific tertiles of folate intake. Furthermore, melancholic DS were linearly inversely associated with gender-specific tertiles of folate intake, while non-melancholic DS were not.

Vitamin B_{12} levels showed an independent linearly inverse association with the risk of melancholic DS. The relative risk ratio (RRR) for melancholic DS was almost three-fold higher in the lowest vitamin B_{12} level tertile as compared to the highest when those with melancholic DS were compared to those without DS. There was no association between B_{12} vitamin tertiles and subjects with non-melancholic DS.

6.2. Study population, methods and design

The study population consisted of middle-aged and elderly Caucasian subjects from three hospital districts of Finland, namely Pirkanmaa, Southern Ostrobothnia and Central Finland. The prevalence of the MetS was also common in both sexes for the same reason (56% for males and 51% for females). The strengths of the study include a large population-based sample from the National Population Register containing middle-aged and elderly subjects with a substantial prevalence of DS. The study population was also geographically representative, covering both urban and rural districts in three study areas. In addition, a WHO-based study methodology was used, and the laboratory analysis was carried out in one series. However, the study group can be considered genetically homogeneous, which limits the possibility to generalize the results to a wider, genetically more heterogeneous sample. The use of clinical DSM-IV-based Mini-International Psychiatric Interview (MINI) as a validation measure for depression is considered as a strength in study I. The FFQ used in study III is also a well-validated method for estimating the dietary folate intake. It describes the habitual diet, which is often more relevant in the aetiological evaluation of chronic diseases than the current, short-term diet.

Some additional limitations of the present study warrant consideration. Firstly, in study I, only those who scored ≥ 10 in the BDI were invited for a further examination, at which

point only 38 % attended the MINI, which has to be considered as a limitation. Moreover, the time difference between BDI scoring and clinical examination was in some cases several weeks. Secondly, in studies II–IV, the detection of DS was based on a self-rating scale, and not on a diagnostic interview for depression. The MINI-based diagnosis was not applied in studies II–IV, because a sufficient number of subjects with DS of either melancholic or non-melancholic characteristics was needed to enhance the comparison of the results of those studies with former reports. Thirdly, as the study population was in advanced middle age, the generalizability of the results to younger age groups may be limited. Fourthly, the FFQ has certain limitations. When using the FFQ, subjects may also tend to overestimate foods that are considered healthy and underestimate those regarded as unhealthy. It mainly collects data on food groups and not on specific food items. Moreover, the presented food list limits flexibility compared to handwritten diet records; for example, information on cooking methods is lost and subjects must make their usual portion sizes conform with those listed on the form. Finally, due to the cross-sectional study design, we cannot make inferences of causality.

6.3 Beck Depression Inventory (BDI) as a screening tool for depression (study I)

According to the present study, a BDI score of 15 simultaneously maximized the sensitivity and specificity compared to the widely used cut-off points of 14 and 18, which are quite close to this cut-off point. With the cut-off of 15, PPV was 0.48, NPV 0.82 and LR+ 2.41.

The diagnostic performance of the BDI was weaker in the present study than in the previous two studies, since the sensitivity and PPV for a cut-off point of 15 in the BDI were 0.56 and 0.48 in the present study, whereas Nuevo et al. (2009) presented 0.63 and 0.60 and Lasa et al. (2000) 1.00 and 0.72. However, the present NPV of 0.82 was similar to that found in the study by Nuevo et al. (0.83), while the specificity was 0.77 compared to 0.81. Likelihood ratios were not presented by Nuevo et al. or Lasa et al. Compared to other epidemiological studies evaluating a screening test, the encountered sensitivity, specificity and PPV were not on a high level. The sensitivity of over 0.70 and specificity of over 0.90 would validate the BDI as a screening test for major depression, while the PPV of 0.71 found here may be poor for clinical practice (Lustman et al. 1997). However, low PPVs of a screening test can be justified if early detection is essential (e.g. to reduce suicidality) (Lustman et al. 1997). In addition, an NPV value of 0.93 has been justified (Lustman et al. 1997), while NPV was 0.82 in the present study for a cut-off point of 15. PPV and NPV are also directly proportional to the prevalence of the condition, namely depression, as PPV tends to be higher and NPV lower when the prevalence increases. The present likelihood ratio of 2.41 means that a cut-off point of 15 in the BDI only results in a small increase in the probability of detecting depression.

The study population was older (mean age 61 years for males and 62 years for females) than in the study by Nuevo et al. (respective means 42 years and for 43.5 years) and that by Viinamäki et al. (mean age of the sample 44 years) (Nuevo et al. 2009, Viinamäki et al. 2004). In the study by Lasa et al., only the age of the entire screened population was reported, of which nearly a third was between 18 and 29 years and the rest between 30 and 64 years (Lasa et al. 2000). The cut-off point preferred here is similar to that found in the study by Viinamaki et al. (15 vs. 14). However, they conducted a smaller number of interviews compared to the present study, and the material consisted of medical patients. The study by Lasa et al. included a smaller number of cases attended from a rather restricted geographic area, although it was performed among the general population. A lower cut-off point of 12/13 showed 100% sensitivity and 99% specificity. The recent study by Nuevo et al. with a larger number of subjects interviewed in a relatively restricted geographic area in Finland among the general population suggested a higher cut-off point (17/18 on the BDI) than the present study, but the inclusion criterion for the more exact diagnostic interview was higher (BDI 13), favouring a higher cut-off point (Nuevo et al. 2009). In addition to different samples, one possible reason for the variation in cut-off points may lie in the

differing diagnostic evaluation. The present study used the DSM-IV-based clinical Finnish version of the MINI as a validation tool for depression, while Lasa et al. and Nuevo et al. used the SCAN interview based on the ICD-10 criteria (Lasa et al. 2000, Nuevo et al. 2009).

The Beck Depression inventory is focused on symptoms of sadness, pessimism, past failure, loss of appetite, loss of pleasure, self-dislike, self-criticism and suicidal thoughts or wishes, which reflect the DSM-IV criteria for major depressive disorder. However, it is widely agreed that the Beck Depression Inventory alone cannot provide an accurate diagnosis of depression or replace clinical diagnostic interviews (Gilbody et al. 2008). According to the results of the present study, the BDI with a cut of point of 15 is a valid screening instrument for the detection or exclusion of depression.

6.4 Prevalence of the metabolic syndrome (MetS) in subjects with melancholic and non-melancholic depressive symptoms (study II)

This study had two novel findings. Firstly, the prevalence of the MetS was higher in subjects with predominantly non-melancholic DS compared to those with melancholic DS. Secondly, the odds for the MetS were two-fold higher in subjects with predominantly non-melancholic DS, whereas melancholic DS were not associated with the MetS when subjects without DS formed the reference group. Certain components of the MetS explained the finding: the elevated fasting glucose and triglyceride levels in the group with non-melancholic DS, and the higher waist circumference in females within the same group. The result displayed no interaction with sex, and remained statistically significant even after multiple adjustments, suggesting a genuine difference between the non-melancholic and melancholic subgroups. This is partly in line with the finding that perceived depression detected by a BDI score ≥14/15 was associated with elevated blood glucose among men and a large waist circumference among women (Miettola et al. 2008).

No other studies have examined the prevalence of the MetS among populations with non-melancholic or melancholic DS. However, Lamers and co-workers demonstrated in a cross-sectional study based on a clinical sample and healthy controls that the MetS was more common in the severe atypical depressive class compared to the severe melancholic depressive class. The prevalence of abdominal obesity and hypertriglyceridemia was also higher among subjects in the severe atypical depressive class than in the severe melancholic class (Lamers et al. 2010). Interestingly, women with undifferentiated and atypical features of major depressive disorder exhibited a higher BMI, as well as whole body and abdominal fat mass compared to healthy controls (Cizza et al. 2012).

However, the results of this study are not fully comparable with previous studies due to differences in the study settings and subgroup definitions. Nevertheless, the results from both of the previous studies and from the present study suggest differences in lipid metabolism between subtypes of DS. Taking into account the results of this and the studies by Lamers et al. and Cizza et al., DS with non-melancholic characteristics and the severe atypical depressive class may have common features in terms of the higher prevalence of the MetS, or higher BMI, waist circumference and triglyceride levels compared to those with more melancholic features. An alternative explanation for these to some extent congruent results may be the similarity of the non-melancholic group in this study and the atypical depressive population in the other settings.

The only longitudinal study by Vanhala and co-workers reported the highest risk for the MetS among women in the subgroup with more melancholic symptoms, which may at least in part be explained by the more severe DS among women than men, and by the long-term use of antidepressive medications during the seven-year study period (Vanhala et al. 2009). On the other hand, a recent study revealed that the association between DS and MetS could not be explained by antidepressant medication (Pyykkönen et al. 2012).

In the present study population, physical activity was lower in both groups with DS, which is noteworthy, since physical exercise could effectively relieve depressive symptoms (Leppämäki et al. 2002). Moreover, an earlier study based on the same material as the

present one demonstrated that the prevalence of simultaneous MetS and DS was higher in participants with low LTPA compared with participants with high LTPA (Korniloff et al. 2010). It was also observed that smoking was most prevalent in the group with melancholic DS, which is in line with other studies reporting that depressed subjects are more likely to smoke (van Gool et al. 2003, Bonnet et al. 2005). The underlying mechanisms involved may include a shared genetic vulnerability to both nicotine dependence and depression, or the use of smoking as a form of self-medication (Lerman et al. 1998).

The results suggest that the liability to the MetS is particularly associated with non-melancholic DS, which may suggest possible differences between types of DS in the susceptibility to the MetS. The role of a higher waist circumference in females among the subgroup of non-melancholic DS is also interesting, as inflammation and the induction of oxidative and nitrosative stress may be connected with depression, and may provide an explanation for the association between depression and obesity and the MetS (Maes et al. 2011). The results of the present study can be of clinical importance if the subtype of DS should be taken into account in the selection of antidepressive medication as, for instance, tricyclic antidepressant (TCA) users more often gain weight or have the MetS (McElroy 2009, van Reedt et al. 2010b). Mirtazapine may be placed between the selective serotonin reuptake inhibitors (SSRI) and TCAs in terms of the relative risk of weight gain (Fava 2000). In addition, paroxetine may be more likely to cause weight gain than the other SSRIs in the long term (Fava 2000, Gartlehner et al. 2008).

6.5 Association between folate intake and melancholic depressive symptoms (study III)

The novel finding of the present study is that the folate intake was associated with melancholic DS but not with non-melancholic DS after taking into account a large number of potential confounders. This result is in line with the monoamine hypothesis of depressive disorders connecting a low folate intake with diminished serotonin synthesis (Stahl 2008). On the other hand, elevated homocysteine levels, mainly caused by a deficiency in folate or vitamin B_{12} levels, may have associations with inflammatory parameters (Gori et al. 2005, Mabrouka et al. 2010). Therefore, a low folate intake may be associated with depression via homocysteine and inflammation.

Depression itself is accompanied by inflammation (Maes 2011). To our knowledge, no previous studies have evaluated the folate intake in a melancholic or non-melancholic depressive population, but the results of the present study are consistent with a clinical study among adult outpatients with major depressive disorder, in which subjects with low folate levels were more likely to have melancholic depression than those with normal or higher folate levels (Fava et al. 1997).

A linearly inverse association was also detected between DS and gender-specific tertiles of folate intake in the whole study population. These results in relation to the role of a lower folate intake and DS are consistent with previously published population-based studies. However, methodological differences exist regarding the lack of sub-typing of the DS, and evaluation of dietary exposure. For example, Finnish population-based studies on middle-aged and elderly men revealed a protective effect of folate intake on depressive symptoms originally in a cross-sectional setting, and subsequently an effect on depression in a follow-up setting (Tolmunen et al. 2003, Tolmunen et al. 2004). A low folate intake was associated with depression among currently smoking men and men with low anxiety levels in a cross-sectional study among university graduates (Sanchez-Villegas et al. 2009). According to a Japanese cross-sectional study conducted on adolescent boys and girls, a higher folate intake was independently correlated with a lower prevalence of depressive symptoms (Murakami et al. 2010). Contradictory results exist, since an American longitudinal study reported that the intake of folate was not associated with DS over time in community-residing older adults (Skarupski et al. 2010). Therefore, evidence for the relationship between folate intake and depression remains ambiguous and cannot be considered conclusive.

An association between folate intake and depression has been suggested to be most apparent in aging populations (Reynolds 2002). In addition, several factors may influence the absorption and metabolism of folate. Firstly, alcohol can have impact on the absorption and metabolism of folate, leading to a reduction in the potential beneficial effects of folate intake on depression (Koehler et al. 2001, Chiuve et al. 2005). Secondly, cigarette smoking increases folate requirements by interfering with folate utilization and/or metabolism (Bailey 1990, Piyathilake et al. 1994), which may lead to a higher prevalence of folate deficiency among smokers. However, in the present study, the linear association of folate intake tertiles and DS with melancholic characteristics also remained constant in the multivariate model including antidepressive medication.

The results of the present study suggest an association between a low folate intake and DS, which is congruent with some previous findings. In this study, a linear association was observed between folate intake tertiles and DS with melancholic characteristics, but not with non-melancholic characteristics. These findings suggest that folate may play a role in the pathogenesis of DS, which may associate with melancholic characteristics.

6.6 Association between vitamin B_{12} levels and melancholic depressive symptoms (study IV)

The novel finding according to the present population-based study was that vitamin B_{12} levels showed an independent linearly inverse association with the risk of melancholic DS, but not with non-melancholic DS when those without DS formed the reference group. This result is in line with the monoamine hypothesis of depressive disorders connecting a low vitamin B_{12} level with diminished synthesis of serotonin and other monoamines (Stahl 2008). Another link may be via inflammation, as a deficiency of vitamin B_{12} can lead to elevated homocysteine levels which, according to some data, could be associated with inflammatory parameters (Gori et al. 2005, Mabrouka et al. 2010). In this way, depression and vitamin B_{12} levels could be associated with each other. An approximately three-fold higher RRR was observed in the current study for melancholic DS in the lowest vitamin B_{12} tertile compared to those without DS. Thus, the risk is congruent with the results from a recent study in which vitamin B_{12} deficiency appeared to be associated with the occurrence of DS (OR = 2.68) (Ng et al. 2009). In two earlier studies, the risk levels were similar, but somewhat lower (OR 2.05 and 1.64, respectively) (Penninx et al. 2000, Tiemeier et al. 2002).

The association between vitamin B_{12} levels and depression is to some extent controversial, since incongruent results have also been published. All the studies showing positive relationships between vitamin B_{12} levels and DS or depressive disorders have been conducted among older populations (Penninx et al. 2000, Tiemeier et al. 2002, Kim et al. 2008, Ng et al. 2009), while most previous population-based studies showing no association have had younger populations than that of the present study (Bjelland et al. 2003, Morris et al. 2003, Beydoun et al. 2010). Some exceptions exist, since an American and an Australian study failed to detect this association among older populations (Lindeman et al. 2000, Sachdev et al. 2005). With regard to these partly inconsistent results, the age of the study population and the distribution of depression subtypes are important. However, methodological differences in subject selection and in the measurement of depressive symptoms or depression, or in the B_{12} status, may also contribute to differing findings. In Finland, 11–21% of persons were reported to have DS when assessed according to the BDI with the same, rather low cut-off score of 10 points, which is in line with the prevalence of 15% recorded in the present study (Vaananen et al. 2008,Vanhala et al. 2009).

On the basis of previous results, the elderly may be more vulnerable to low vitamin B_{12} levels, because vitamin B_{12} deficiency is more common in the aged. Its prevalence was 12% in the Finnish population (aged 65–100 years) compared to the finding that 5% of Canadians (age 6–79 years) were vitamin B_{12} deficient (Loikas et al. 2007, Mac Farlane et al. 2011). In younger adults, lifestyle factors such as smoking, alcohol consumption and a vegetarian diet are known risk factors for vitamin B_{12} deficiency (Herrmann and Geisel

2002, Wolters et al. 2004). However, no such association was recorded in an aged Finnish population (Loikas et al. 2007). No particular risk group for lower vitamin B_{12} levels could be defined among the aged (Loikas et al. 2007). On the other hand, gastrointestinal diseases, especially atrophic gastritis in the elderly, may increase the risk of vitamin B_{12} deficiency (Loikas et al. 2007). The association with age may have an alternative explanation as well, since the brain effects of low vitamin B_{12} may not manifest until much later in life.

A higher risk of melancholic depressive symptoms was associated with lower vitamin B_{12} levels in the current study. These findings suggest that vitamin B_{12} may contribute to the pathogenesis of DS.

6.7 Implications for clinical practice and research

The results of study I warrant that the routine use of the BDI in the screening of DS among population-based samples should be carefully evaluated, as its ability to detect depression is not very robust. Overall, studies are needed to evaluate the correlation between the BDI and diagnostic interviews in the diagnostic process of depression in population-based samples. Compared to the current study, future studies should include a higher proportion of subjects who attend the diagnostic interview to validate the diagnosis of depression.

According to study II, the possible susceptibility to the MetS among those having DS with non-melancholic characteristics may highlight that the subtype of DS should be taken into account in the selection of antidepressive medication as, for instance, tricyclic antidepressant users more often gain weight or have the MetS. Those administered mirtazapine and paroxetine may also have a higher tendency to suffer from weight problems. In addition, the tendency for the MetS may warrant the screening or follow-up of the MetS and its components in this particular group of DS. From the research point of view, the result supports the contention that depression, as a whole, is not a homogeneous entity. Several subtypes may exist, such as those with non-melancholic or melancholic features. These possible subtypes should be studied more thoroughly with regard to genetic, hormonal and metabolic parameters. Overall, the finding of study II should be verified and replicated in samples with different ages and ethnic groups, and further studies are therefore needed.

The findings of studies III and IV correlate a low folate intake and low vitamin B_{12} levels with the risk of melancholic DS, which may also have practical implications. Clinicians should take into account the patient's folate or vitamin B_{12} status when examining or treating patients with depression, especially with melancholic characteristics. At the same time, it would be adequate to evaluate the dietary patterns of patients with DS. The results of studies II, III and IV support the idea of different depressive subtypes, and also highlight the importance of genetically screening these different depressive subgroups. In addition, the possible role of both folate intake and vitamin B_{12} levels in the pathogenesis of depression warrant research in this field. Nevertheless, further studies are needed to evaluate the possible associations between DS and the intake of folate or vitamin B_{12} levels among populations comprising different ages or various ethnic groups and depressive subtypes.

Finally, due to the cross-sectional design of the study, inferences of causality cannot be made. Therefore, longitudinal, population-based studies with a sufficient number of participants in different age and ethnic groups are warranted to evaluate the prevalence of the MetS, and the role of folate intake or vitamin B_{12} levels among subjects with predominantly melancholic or with non-melancholic characteristics. Their target may be to evaluate whether depression with melancholic or non-melancholic subtypes might have different aetiological roles in terms of proinflammation and the diet.

7 SUMMARY

This study was conducted to evaluate the value of the BDI as a screening instrument for depression using the clinical DSM-IV-based Mini-International Psychiatric Interview (MINI) as a validating measure. It also evaluated the role of the MetS and its components, folate intake, and vitamin B_{12} levels in groups with predominantly melancholic or non-melancholic DS.

The study population was enrolled as a part of the national type 2 diabetes prevention programme (FIN-D2D), as a project of the Finnish community-based type 2 diabetes prevention programme, aimed at exploring the ways to implement preventive methods for type 2 diabetes on a national level. Three hospital districts of Finland, namely Pirkanmaa, Southern Ostrobothnia and Central Finland, were selected for the efficacy survey, which was carried out between October and December 2007. A representative random sample of 4500 subjects aged 45–74 years, stratified according to gender, 10-year age groups (45–54, 55–64, and 65–74 years) and the three geographical areas, was selected from the National Population Register in August 2007. Of the 4500 persons who were invited by mail to the health examination, 2868 participated (attendance 64%).

DS was assessed by using the BDI, and a cut-off point of 10 was applied to capture DS. A summary score of DSM-IV-based criteria of melancholic symptoms in the BDI was used to determine the subtype of DS by dividing the participants with elevated DS into melancholic and non-melancholic depressive symptom subgroups. In the evaluation of the MetS, the modified NCEP-ATPIII criteria with a cut-off point of 100 mg/dL (5.6 mmol/L) blood glucose were applied. The diet over the previous 12 months was assessed using the FFQ. Serum vitamin B_{12} was measured using the CMIA. The study methods followed the World Health Organization MONICA protocol.

The study demonstrated that BDI with a cut-off point of 15 is a valid screening instrument for the detection or exclusion of depression in population-based subjects. However, the BDI alone cannot provide an accurate diagnosis of depression or replace clinical diagnostic interviews.

The prevalence of the MetS was higher in subjects with predominantly non-melancholic DS compared to those with melancholic DS or to those without DS. The odds for the MetS were two-fold higher in subjects with predominantly non-melancholic DS, whereas melancholic DS were not associated with the MetS when subjects without DS formed the reference group. When compared to the melancholic group, non-melancholic DS were associated with the MetS. The components of the MetS explaining the finding include the elevated fasting glucose and triglyceride levels in the group with non-melancholic DS, and the higher waist circumference in females within the same group. These results suggest that the liability to the MetS is particularly associated with non-melancholic DS, which may suggest possible differences among the types of DS in the susceptibility to the MetS.

In this study, the folate intake was associated with melancholic DS but not with non-melancholic DS. The result remained constant even after several adjustments. DS was also linearly inversely associated with gender-specific tertiles of folate intake.

Vitamin B_{12} levels demonstrated an independent linearly inverse association with the risk of melancholic DS. The RRR for the melancholic DS population to belong to the lowest vitamin B_{12} level tertile (compared to the highest) was almost three-fold higher when those with melancholic DS were compared to those without DS. There was no association between B_{12} vitamin tertiles and subjects with non-melancholic DS. The findings of the present study suggest that folate intake and vitamin B_{12} may contribute to the pathogenesis of DS, which may be associated with melancholic characteristics.

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ORIGINAL PUBLICATIONS (I-IV)

I

Beck Depression Inventory (BDI) as a screening tool for depression. A population-based Finnish cross-sectional study

Seppälä J, Vanhala M, Kautiainen H, Eriksson J, Kampman O, Oksa H, Ovaskainen Y, Viikki M, Koponen H

Psych Fennica 41: 42-52, 2010

II

Prevalence of metabolic syndrome in subjects with melancholic and non-melancholic depressive symptoms. A Finnish population-based study

Seppälä J, Vanhala M, Kautiainen H, Eriksson J, Kampman O, Mäntyselkä P, Oksa H, Ovaskainen Y, Viikki M, Koponen H

J Affect Disord 136(3): 543-549, 2011

III

Association between folate intake and melancholic depressive symptoms. A Finnish population-based study

Seppälä J, Koponen H, Kautiainen H, Eriksson J, Kampman O, Männistö S, Mäntyselkä P, Oksa H, Ovaskainen Y, Viikki M, Vanhala M

J Affect Disord 136(3): 543-549, 2012

IV

Association between vitamin B_{12} levels and melancholic depressive symptoms. A Finnish population-based study

Seppälä J, Koponen H, Kautiainen H, Eriksson J, Kampman O, Leiviskä J, Männistö S, Mäntyselkä P, Oksa H, Ovaskainen Y, Viikki M, Vanhala M

Depression and Anxiety. Submitted.

Jussi Seppälä

Depressive Symptoms, Metabolic Syndrome and Diet

The metabolic syndrome, low folate intake or lower vitamin B12 levels may be associated with depression. However, the impact of melancholic or non-melancholic depressive symptoms has not been evaluated.

The results of this study support the use of the Beck Depression Inventory as a screening tool for depressive symptoms. A higher risk of the metabolic syndrome was associated with non-melancholic depressive symptoms. In addition, those with a lower folate intake or lower vitamin B12 levels had a higher risk of melancholic depressive symptoms.

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