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*Anne Herva*

DEPRESSION IN ASSOCIATION  
WITH BIRTH WEIGHT, AGE  
AT MENARCHE, OBESITY AND  
METABOLIC SYNDROME  
IN YOUNG ADULTS

THE NORTHERN FINLAND 1966 BIRTH  
COHORT STUDY

FACULTY OF MEDICINE,  
DEPARTMENT OF PSYCHIATRY,  
DEPARTMENT OF PUBLIC HEALTH SCIENCE AND GENERAL PRACTICE,  
UNIVERSITY OF OULU;  
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UNIVERSITY OF TAMPERE

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*ANNE HERVA*

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The Northern Finland 1966 Birth Cohort Study

Academic dissertation to be presented, with the assent of the Faculty of Medicine of the University of Oulu, for public defence in Auditorium 101 A of the Faculty of Medicine (Aapistie 5 A), on February 23rd, 2007, at 12 noon

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# **Herva, Anne, Depression in association with birth weight, age at menarche, obesity and metabolic syndrome in young adults. The Northern Finland 1966 Birth Cohort Study**

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## ***Abstract***

Depression is a common mental disorder in the Finnish population. There are several biological, psychological and social factors in the background of depression. The aim of this study was to investigate depression in association with birth weight, age at menarche, obesity and metabolic syndrome using data from the Northern Finland 1966 Birth Cohort.

A large, prospectively collected general population-based birth cohort of originally 12058 liveborn children was used as study population. The database provided information on birth characteristics and features of the primary family. The follow-up studies were performed at the age of 14 years by postal inquiry, and at the age of 31 years by postal inquiry and clinical examination. Information on age at menarche and weight and height was obtained from the postal questionnaire at 14 and 31 years and clinical examination at 31 years. Data on abdominal obesity and metabolic syndrome were gathered from the clinical examination. Data on depressive symptoms measured by the Hopkins Symptom Checklist-25 (HSCL-25), self-reported physician-diagnosed lifetime depression and the use of antidepressants were gathered from the postal questionnaire at 31 years.

Females with high birth weight and high ponderal index (index of the birth measures, kg/m<sup>3</sup>) had a higher risk of depressive symptoms at 31 years measured by the HSCL-25 compared with females with normal birth weight and ponderal index. Males with ponderal index belonging to the lowest 5 percentile had an increased risk for physician-diagnosed depression at 31 years. Females with late menarche ( $\geq 16$  years) had an elevated risk of depression measured by the HSCL-25, the use of antidepressants and self-reported physician-diagnosed depression compared with females with menarche at 12–15 years. Obesity measured by BMI at 14 years increased the risk of depressive symptoms measured by the HSCL-25 at 31 years among both males and females. Females who were obese both at baseline and at follow-up had an increased risk of depressive symptoms, and the proportion of those who used antidepressants was higher among females who had gained weight compared to females who had stayed normal-weighted. Males with abdominal obesity measured by waist-to-hip ratio had an increased risk of depressive symptoms and physician-diagnosed depression, and the proportion of those who used antidepressants was higher compared with subjects without abdominal obesity. Abdominal obesity did not associate with depression in females. Metabolic syndrome did not associate with depression.

The results indicate an increased risk of depression at 31 years in females with high birth weight, late menarche, adolescent obesity and weight gain and in males with adolescent obesity and abdominal obesity.

***Keywords:*** birth weight, body mass index, cohort study, depression, follow-up, HSCL, longitudinal study, menarche, metabolic syndrome, waist-to-hip ratio



# **Herva, Anne, Syntymäpainon, menarkeiän, lihavuuden ja metabolisen oireyhtymän yhteys depression nuorilla aikuisilla. Tutkimus Pohjois-Suomen vuoden 1966 syntymäkohortista**

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## ***Tiivistelmä***

Depressio on yleinen mielenterveyden häiriö suomalaisväestössä. Depression taustalla on monia biologisia, psykologisia ja sosiaalisia tekijöitä. Tämän tutkimuksen tavoitteena oli tutkia depressiona selvittäen, onko syntymäpainolla, menarkeiällä, lihavuudella ja metabolisella oireyhtymällä yhteyttä depression Pohjois-Suomen vuoden 1966 syntymäkohorttiaineistossa.

Tutkimusaineistoon kuului alun perin 12058 elävänä syntynyttä lasta. Tietokantaan oli jo aiemmin kerätty aineistoa syntymään ja primaariperheeseen liittyen. Kohortin jäsenten ollessa 14-vuotiaita tehtiin seurantatutkimus postikyselynä ja 31-vuotiaana tehtiin sekä postikysely että kliininen tutkimus. Tiedot menarkeiästä kerättiin 31-vuotispostikyselystä, paino- ja pituustiedot sekä 14- ja 31-vuotispostikyselyistä että kliinisen tutkimuksen tiedoista. Kliininen tutkimus sisälsi tiedot myös keskivartalolihavuuden ja metabolisen oireyhtymän määrittämiseksi. 31-vuotispostikyselyssä depressio-oireita kysyttiin HSCL-25 -oirekyselyllä; lisäksi kysyttiin, oliko lääkäri todennut aiemmin masennusta sekä oliko tutkittavilla käytössä masennuslääkkeitä.

Naisilla, joiden syntymäpaino ja ponderaali-indeksi (syntymäpainon ja pituuden suhdetta kuvaava indeksi,  $\text{kg/m}^3$ ) oli korkea, depressio-oireiden riski 31-vuotiaana mitattuna HSCL-25:lla oli suurentunut verrattuna naisiin, joilla oli normaali syntymäpaino ja ponderaali-indeksi. Miehillä, joilla oli hyvin alhainen ponderaali-indeksi kuuluu alimpaan 5 % ryhmään, riski lääkärin toteamaan masennukseen oli suurentunut. Naisilla, joiden menarkeikä oli 16-vuotta tai myöhemmin, riski depressio-oireiden esiintyvyyteen, depressiolääkkeiden käyttöön ja lääkärin toteaman depression esiintyvyyteen oli suurentunut verrattuna naisiin, joiden menarkeikä oli 12–15-vuotta. Lihavuus 14-vuotiaana lisäsi masennusoireiden riskiä mitattuna HSCL-25:lla sekä 31-vuotiailla miehillä että naisilla. Naisilla, jotka olivat lihavia sekä 14- että 31-vuotiaana, masennusoireiden riski oli suurentunut. Naisilla, joiden paino oli noussut, masennuslääkkeiden käyttö oli yleisempää verrattuna naisiin, joilla paino oli pysynyt normaalina. Keskivartalolihavuus oli miehillä yhteydessä suurentuneeseen depressio-oireiden ja lääkärin toteaman masennuksen riskiin, ja he käyttivät yleisemmin masennuslääkkeitä verrattuna miehiin ilman keskivartalolihavuutta. Naisilla keskivartalolihavuus ei ollut yhteydessä masennukseen. Metabolinen oireyhtymä ei ollut yhteydessä masennukseen.

Tulokset osoittavat korkean syntymäpainon, myöhäisen menarkeiän ja nuoruusiän lihavuuden sekä painon nousun lisäävän masennusriskiä 31-vuotiailla naisilla, 31-vuotiailla miehillä nuoruusiän lihavuus sekä keskivartalolihavuus olivat yhteydessä suurentuneeseen masennusriskiin.

*Asiasanat:* depressio, HSCL, kohorttitutkimus, menarkeikä, metabolinen oireyhtymä, painoindeksi, pitkittäistutkimus, seuranta, syntymäpaino, vyötärö-lantio-suhde



*To my family*



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Oulu, December 2006

Anne Herva

## Abbreviations

ACTH	Adrenocorticotrophic hormone
APA	American Psychiatric Association
ATP III	Adult Treatment Panel III
BDI	Beck Depression Inventory
BMI	Body Mass Index
BW-GA	Birth weight relative to gestational age
CI	Confidence interval
CIDI	Composite International Diagnostic Interview
CNS	Central Nervous System
CRF	Corticotropin releasing factor
CRP	C-reactive protein
CSF	Cerebrospinal fluid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECA	Epidemiologic Catchment Area
EEG	Electroencephalogram
HDL	High density lipoprotein
5HIAA	5-hydroxyindoleacetic acid
HPA	Hypothalamic pituitary-adrenocortical
HSCL-25	Hopkins Symptom Checklist-25
5HT	5-hydroxytryptamine
ICD-10	Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death, Tenth Revision
IDF	International Diabetes Federation
NCS	National Comorbidity Survey
NCS-R	National Comorbidity Survey Replication
OR	Odds ratio
REM	Rapid eye movements
SDS	Zung self-rating Depression Scale
SSRI	Selective serotonin reuptake inhibitor
TNF- $\alpha$	Tumour necrosis factor alfa
TRH	Thyrotropin-releasing hormone

WHO World Health Organization  
WHR Waist-to-hip ratio

## **List of original publications**

This thesis is based on the following original publications, which are referred to in the text by the Roman numerals I-IV.

- I Herva A, Pouta A, Hakko H, Läksy K, Joukamaa M & Veijola J. Birth weight and depression at 31 years age: the Northern Finland 1966 Birth Cohort Study. Manuscript.
- II Herva A, Jokelainen J, Pouta A, Veijola J, Timonen M, Karvonen JT & Joukamaa M (2004) Age at menarche and depression at the age of 31 years: findings from the Northern Finland 1966 birth cohort study. *J Psychosom Res* 57: 359-362.
- III Herva A, Laitinen J, Miettunen J, Veijola J, Karvonen JT, Läksy K & Joukamaa M (2006) Obesity and depression: results from the longitudinal Northern Finland 1966 Birth Cohort Study. *Int J Obes* 30: 520-527.
- IV Herva A, Räsänen P, Miettunen J, Timonen M, Läksy K, Veijola J, Laitinen J, Ruukonen A & Joukamaa M (2006) Co-occurrence of metabolic syndrome with depression and anxiety in young adults: the Northern Finland 1966 Birth Cohort Study. *Psychosom Med* 68: 213-216.



# Contents

Abstract	
Tiivistelmä	
Acknowledgements	
Abbreviations	
List of original publications	
Contents	
1 Introduction .....	19
2 Review of the literature .....	21
2.1 Definition of depression .....	21
2.2 Prevalence of depression .....	22
2.3 Etiological aspects of depression.....	23
2.3.1 Biological factors in the etiology of depression .....	24
2.3.1.1 Biogenic amines .....	24
2.3.1.2 Hypothalamic pituitary-adrenocortical-axis .....	25
2.3.1.3 Other biological factors related to depression.....	25
2.3.2 Somatic diseases and depression .....	26
2.3.2.1 Cardiovascular diseases and depression .....	26
2.3.2.2 Diabetes mellitus and depression.....	27
2.3.2.3 Other somatic diseases and depression .....	28
2.3.2.4 Depression and physical health in young adults .....	29
2.4 Birth measures and depression .....	29
2.5 Menarche .....	30
2.5.1 Definition and the onset of menarche.....	30
2.5.2 Menarche and depression .....	30
2.6 Overweight and obesity .....	31
2.6.1 Definition and epidemiology of overweight and obesity.....	31
2.6.2 Obesity, overweight and depression .....	32
2.7 The metabolic syndrome.....	33
2.7.1 Definition and epidemiology of the metabolic syndrome .....	33
2.7.2 Pathogenesis of the metabolic syndrome.....	34
2.7.3 Metabolic syndrome, depression and anxiety.....	35

2.8 Summary of the reviewed literature.....	35
3 Aims of the study.....	37
4 Material and methods.....	38
4.1 Study population and data collection.....	38
4.2 Variables.....	40
4.2.1 Outcome variables.....	40
4.2.1.1 Current depression (HSCL-25) (I-IV).....	40
4.2.1.2 Self-reported physician-diagnosed lifetime depression (I-III).....	40
4.2.1.3 Current use of antidepressants (II, III).....	41
4.2.1.4 Current anxiety (IV).....	41
4.2.2 Exposure variables.....	41
4.2.2.1 Birth measures (I).....	41
4.2.2.2 Age at menarche (II).....	42
4.2.2.3 Overweight and obesity (III).....	42
4.2.2.4 Metabolic syndrome (IV).....	43
4.2.3 Confounding variables.....	43
4.2.3.1 Social class in 1966 and 1980.....	44
4.2.3.2 Tobacco exposure variables.....	44
4.2.3.3 Mother's depression during pregnancy.....	45
4.2.3.4 Mother's age at delivery and parity in 1966.....	45
4.2.3.5 Gestational age in 1966.....	45
4.2.3.6 Family type and marital status.....	46
4.2.3.7 Body mass index in 1980.....	46
4.2.3.8 Dwelling place in 1980.....	46
4.2.3.9 Chronic somatic diseases at the age of 14 and 31 years.....	46
4.2.3.10 Use of alcohol at the age of 14 and 31 years.....	46
4.2.3.11 Level of education.....	47
4.2.3.12 Physical activity.....	47
4.2.3.13 Dietary habits.....	47
4.3 Statistical methods.....	47
4.4 Ethical considerations and personal involvement.....	48
5 Results.....	49
5.1 Birth measures and depression.....	49
5.1.1 Birth measures and current depression at age 31.....	49
5.1.2 Birth measures and physician-diagnosed depression at age 31.....	54
5.2 Age at menarche and depression at the age of 31 years.....	54
5.3 Obesity and depression.....	56
5.3.1 BMI at 14 years and depression at 31 years.....	56
5.3.2 BMI at 31 years and depression at 31 years.....	58
5.3.3 Abdominal obesity at 31 years and depression at 31 years.....	60
5.3.4 Weight change and depression at 31 years.....	60
5.4 Metabolic syndrome, depression and anxiety.....	63
6 Discussion.....	65
6.1 Main findings.....	65
6.2 Discussion of the results.....	65
6.2.1 Birth weight and depression (I).....	65

6.2.2 Age at menarche and depression (II) .....	67
6.2.3 Obesity and depression (III) .....	68
6.2.4 Metabolic syndrome and depression (IV).....	70
6.3 Methodological considerations .....	71
6.3.1 Study participants .....	71
6.3.2 Strengths of the study .....	72
6.3.3 Limitations of the study.....	72
7 Conclusions .....	74
7.1 Main conclusions of the results .....	74
7.2 Clinical implications.....	74
7.3 Research implications.....	75
References	
Original publications	



# 1 Introduction

Depression is an illness of major public health concern, as it is one of the most prevalent psychiatric disorders in adults (Boyd & Weissman 1982, Kessler *et al.* 1994, 2003, Ayuso-Mateos *et al.* 2001), and a remarkable cause of working disability (Salminen *et al.* 1997, Mykletun *et al.* 2006). In the Health 2000 Study the 12-month prevalence of major depression in Finland was 6.3% among females and 4.9% among males (Pirkola *et al.* 2005b). The psychosocial and medical burden of depression is considerable, as it is often unrecognized and untreated (Paykel & Priest 1992, Kessler *et al.* 2003). The etiology of depression is multifactorial; depression is a syndrome with biopsychosocial character (O'Keane 2000, Kendler *et al.* 2002, 2006). Depression has various risk factors, from early life events to contemporary life stressors (Boyd & Weissman 1982, Kaplan *et al.* 1987, Kendler *et al.* 2001, 2002, 2006, Korkeila *et al.* 2005, Pirkola *et al.* 2005a).

Depression has been shown to be associated with many somatic diseases such as cardiovascular diseases and diabetes mellitus (Evans *et al.* 2005). Depression increases mortality and morbidity in cardiovascular diseases (Barefoot & Schroll 1996, Musselmann *et al.* 1998, Lett *et al.* 2004), and worsens the course and recovery from physical illness (Evans & Charney 2003).

Obesity is also a problem of public health concern, as it has been increasing among both adults and children in western countries (Kuczmarski *et al.* 1994, Seidell 1995, Mokdad *et al.* 1999). Obesity is a risk factor for many physical diseases (Pi-Sunyer 1994, Brancati *et al.* 1999), and can lead to premature death (Calle *et al.* 1999). Abdominal obesity is particularly harmful due to its association with somatic diseases (Lakka *et al.* 2002b, Goodpaster *et al.* 2003). Abdominal obesity is closely related to insulin resistance (Eckel *et al.* 2005). According to the newest International Diabetes Federation criteria abdominal obesity is the most important criteria of the metabolic syndrome, the combination of metabolic disturbances which are all risk factors for cardiovascular diseases (Eckel *et al.* 2005, Alberti *et al.* 2006).

The risk and etiological factors of depression have been widely studied. Studies on early life factors such as birth measures and depression have reported contradictory findings (Thompson *et al.* 2001, Gale & Martyn 2004, Osler *et al.* 2005), as have studies on obesity and depression (Friedman *et al.* 1996). There are only a few studies on

metabolic syndrome and depression, and some studies focusing on the single component of the metabolic syndrome.

Professor (emerita) Paula Rantakallio started the prospective Northern Finland 1966 Birth Cohort, called nowadays the Northern Finland Health and Well-being Study. Originally, the purpose was to describe and analyse the risk factors for perinatal deaths and low birth weight (Rantakallio 1969, 1988). This thesis is part of the psychiatric follow-up project of the ongoing Northern Finland Health and Well-being Study. This population-based prospective database made it possible to investigate depression in 31-year-old young adults with special attention on birth weight, age at menarche, obesity and metabolic syndrome using both a longitudinal and a cross-sectional study design.

## **2 Review of the literature**

### **2.1 Definition of depression**

The word "depression" means generally a lowered state of mind, the severity of which may be of different grades. As an affect, depression is familiar to everyone as a reaction to losses and disappointments, and can be seen as a normal emotional reaction (Boyd & Weissman 1982, Paykel & Priest 1992, Lehtinen & Joukamaa 1994). Depression may also manifest itself as a symptom as part of a syndrome in different mental or somatic disorders (Boyd & Weissman 1982). Some patients, particularly in general practice, suffer from depression-related somatic symptoms and cannot describe the lowering of their mood or want to hide it from their doctor (Paykel & Priest 1992).

In clinical depression, depression as an illness, depressive mood usually lasts several weeks or months, even years, and there are several co-occurring symptoms for a defined period of time (World Health Organization, WHO 1992, American Psychiatric Association, APA 1994). Clinical depression may exist at different grades, from a disorder when the patient has the ability to work to a difficult illness in which working ability has been lost. Patients may also suffer from delusions and have suicidal thoughts.

Today, the classification of depressive disorders is usually based on the diagnostic criteria of ICD-10 (International Classification of Disorders) (WHO 1992) or DSM-IV (the fourth edition of Diagnostic and Statistical Manual of Mental Disorders) (APA 1994). According to DSM-IV, unipolar forms of mood disorders are divided into three groups: major depressive disorder, dysthymic disorder and depression not otherwise specified (APA 1994). The diagnosis of major depression requires a two-week period of depressed mood or loss of interest or pleasure, together with at least four other symptoms such as fatigue or loss of energy, hopelessness, changes in appetite and weight, psychomotor retardation and agitation, inappropriate guilt, impaired concentration, insomnia or hypersomnia and suicidal thoughts (WHO 1992, APA 1994). The symptoms must not be related merely to substance use, bereavement or medical illness. In DSM-IV the severity of major depression is also categorized by the number of symptoms: mild, moderate or severe (with or without psychotic symptoms). The diagnosis of major depression is basically the same in DSM-IV and ICD-10, although ICD-10 requires one

symptom less than DSM-IV and includes fatigue or loss of energy in the core symptoms (WHO 1992, APA 1994). Dysthymic disorder is a chronic disturbance of mood in which depressed mood occurs most of the day for at least two years (APA 1994). Depressive disorder not otherwise specified includes disorders with depressive features that do not fulfil the criteria for major depressive disorder, dysthymic disorder, adjustment disorder with depressed mood, or adjustment disorder with mixed adjustment and depressed mood (APA 1994). The diagnosis "adjustment disorder with depressed mood" is used when clinically significant depressive symptoms occur as a psychological response to a recognizable stressor during a time period of three months after the onset of the stressor, and the disturbance does not meet the criteria for another specific Axis I disorder or is not part of a preexisting Axis I or Axis II disorder (APA 1994).

The diagnosis of major depression usually requires interviewing the patient, while depressive symptoms can also be ascertained by several self-report questionnaires such as Beck's depression inventory (BDI) (Beck *et al.* 1961), Zung self-rating Depression Scale (SDS) (Zung 1965) or Hopkins Symptom Checklist -25 (HSCL-25) (Derogatis *et al.* 1973).

## 2.2 Prevalence of depression

Depression is a common public health problem causing a remarkable amount of individual suffering, functional disability and self-destructive behaviour (Isometsä *et al.* 1994, Paykel & Priest 1994, Kessler *et al.* 1994, 2003). During lifetime, approximately one fifth of the population suffers from major depression (Kessler *et al.* 1994, 2003). According to population surveys, the prevalence of clinically significant depression varies from 2.6% to 5.5% in men and from 6.0% to 11.8% in women (Lehtinen & Joukamaa 1994). The prevalence of depressive symptoms is much higher, varying from 10% to 19% among men and from 18% to 34% among women (Lehtinen & Joukamaa 1994). It is estimated that only one third of the patients suffering from major depression in Finland receive treatment (Lehtinen & Joukamaa 1994, Hämäläinen *et al.* 2004).

In the National Comorbidity Survey (NCS) conducted in 1990-1992, the lifetime prevalence of major depression among US adults was 17.1%, and the 12-month prevalence was 10.3% (Kessler *et al.* 1994). The National Comorbidity Survey Replication (NCS-R), conducted in 2001-2002, found a lifetime prevalence of major depression among US adults of 16.2%, and a 12-month prevalence of 6.6% (Kessler *et al.* 2003). In a study conducted by Jacobi *et al.* 2004, the lifetime prevalence of any unipolar depression in the German population was reported to be 17.1%, and the 12-month prevalence 10.7%.

There exist several epidemiological studies in which the epidemiology of depression has been studied in Finland. In the cross-sectional Mini-Finland Health Survey the point prevalence of neurotic depression of individuals aged 30 or over was 4.6%, being 3.9% among males and 6.0% among females (Lehtinen *et al.* 1990). In the longitudinal UKKI Study the prevalence of depression among 31- to 89-year-old adults was 5.3%, being 3.2% among men and 7.3% among women (Lehtinen *et al.* 1993). Isometsä *et al.* (1997) reported in a study of 2293 subjects aged 25-79 years interviewed by telephone a 6-

month prevalence of 4.1% for major depressive episode. In another study by Lindeman *et al.* (2000) the total population prevalence of major depressive episode was 9.3%; 7.2% among males and 10.9% among females.

The most recent results regarding the prevalence of depression in Finland are from the ODIN study (Ayuso-Mateos *et al.* 2001) and from the Health 2000 Study (Pirkola *et al.* 2005b). In the ODIN study the prevalence of major depressive disorder was 4.7% among urban subjects (2.7% among men and 6.6% among women), and 4.1% among rural subjects (4.3% among men and 3.8% among women) (Ayuso-Mateos *et al.* 2001). In the Finnish Health 2000 Study the prevalence of major depression during the past 12 months measured by the CIDI-interview (Composite International Diagnostic Interview) among subjects 30 years or more was 3.4% among men and 6.3% among women (Pirkola *et al.* 2005b). With regard to young adults, in the Finnish Health Care Survey of 433 young adults the 12-month prevalence of major depression was 9.4%; 8.1% among males and 10.7% among females (Haarasilta *et al.* 2001). In a study of 245 Finnish subjects aged 20-24 years the one-month prevalence of major depression was found to be 6.9%; 5.4% among males and 7.8% among females (Aalto-Setälä *et al.* 2001).

### 2.3 Etiological aspects of depression

Depression is a biopsychosocial disease; there are several biological, psychological and social factors behind depressive disorders (Blazer 2000, O'Keane 2000, Kendler *et al.* 2002, 2006). Major depression is suggested to be a familial disorder (Sullivan *et al.* 2000, Kendler *et al.* 2001, Kendler & Aggen 2001). The familiarity results partly from genetic influences, although environmental factors specific to an individual are also etiologically important (Sullivan *et al.* 2000, Kendler *et al.* 2001, 2002, 2006). It is known that the risk of depression is higher among first-degree relatives of individuals suffering from unipolar depression (Sullivan *et al.* 2000). The familiarity of depression has also been shown in twin-studies, where markedly higher rates of depression have been found among twins than in the general population, as well as significantly higher monozygotic than dizygotic concordance (McGuffin *et al.* 1991). Major depression is suggested to be equally heritable in men and women (Kendler & Prescott 1999). In addition, early adverse life experiences influence the risk of later depression (Aro 1994, Kendler *et al.* 2002, 2006, Korkeila *et al.* 2005, Pirkola *et al.* 2005a), and many psychosocial factors such as physical disability, social isolation and economical problems may predict depression. (Kaplan *et al.* 1987, Aro 1994, Kendler *et al.* 2002, 2006). In major depression there are often generating factors which may be current negative life events or losses; together with genetic and personality factors they may result in depression (Kendler *et al.* 2001). It can be stated that depression is a complex disorder that does not result from either genetic or environmental influences alone, but rather from the interaction of both these factors (Sullivan *et al.* 2000, Kendler *et al.* 2002, 2006).

In this chapter the etiology of depression is reviewed in more detail with regard to biological factors.

### **2.3.1 Biological factors in the etiology of depression**

#### **2.3.1.1 Biogenic amines**

Neurochemical changes play an important role in the etiology of depression (Hindmarch 2002, Malhi *et al.* 2005). The monoamine hypothesis was presented in the 1960s, suggesting that an important mechanism behind depression is dysregulation in the neuronal monoamines, noradrenalin, serotonin and dopamine (Schildkraut 1965, Stahl 1998, Hindmarch 2002, Malhi *et al.* 2005). As reviewed by Hindmarch (2002), the monoamine hypothesis is based on pharmacological observations that antidepressive medication raises the functional capacity of the biogenic amines in the brain. Although the monoamine concentrations increase in a few hours, clinical response to the antidepressive treatment comes later, usually in one to four weeks (Malhi *et al.* 2005). Thus, it seems that much more complex dysregulation exists behind depression (Syvälahti 1994). Lately, the focus has moved away from single neurotransmitters to such areas as neurobehavioural systems, neural circuits and signal transduction (Thase 2000).

Noradrenergic neurons have their origins in the locus ceruleus and they project to the cerebral cortex, limbic system, basal ganglia, hypothalamus and thalamus (Malhi *et al.* 2005). As reviewed by Malhi *et al.* (2005), there are both excitatory ( $\alpha_1$ ,  $\beta$ ) and inhibitory ( $\alpha_2$ ) adrenergic receptors in the central nervous system (CNS). In depression there seems to be hypersensitivity of the  $\alpha_2$ -receptors, which leads to diminished noradrenergic activity. This lowered activity may be reversed by antidepressive treatment.

Reduced serotonergic function has been suggested to be one pathophysiological mechanism in depression (Mann 1999, Malhi *et al.* 2005). Serotonin (5-hydroxytryptamine, 5HT) is produced from enzymes after the amino acid tryptophan is transported into the serotonin neuron, where it is converted into 5-hydroxytryptophan by the enzyme tryptophan hydroxylase. 5-hydroxytryptophan is then converted into serotonin by the enzyme aromatic amino acid decarboxylase and stored in synapse vesicles (Stahl 2001). Serotonergic neurons project from the brainstem dorsal raphe nuclei to the cerebral cortex, hypothalamus, thalamus, basal ganglia, septum and hippocampus, and have both inhibitory and facilitatory functions in the brain (Thase 2000). As reviewed by Mann (1999), several serotonin receptor subtypes exist in the serotonergic system, of which especially 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors play an important role in depression. Increased numbers of 5-HT<sub>2A</sub> receptors have been found among individuals committing suicide (Mann 1999). In addition, lowered concentration of the metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA) has been found in the cerebrospinal fluid of depressed patients (Mann & Malone 1997). In the pharmacotherapy of depression selective serotonin re-uptake inhibitors (SSRIs) have been shown to be effective and are nowadays the most popular class of antidepressive drugs (Lucki 1998).

The dopaminergic system is also involved in the pathogenesis of depression (Malhi *et al.* 2005, Nutt 2006). Dopamine is produced in dopaminergic neurons from tyrosine (Stahl 2001). There are four dopamine pathways in the brain (Thase 2000). Reflecting dysregulation of the dopaminergic system, lower cerebrospinal fluid levels of homovanillic acid, the metabolite of dopamine, have been found in depressed suicide

attempters (Sher *et al.* 2006). Psychotic symptoms in depression may be a consequence of reduced dopaminergic function (Malhi *et al.* 2005). In recent years, brain imaging studies have also revealed evidence of reduced synaptic dopamine levels (Nutt 2006).

### *2.3.1.2 Hypothalamic pituitary-adrenocortical-axis*

Many hormonal abnormalities are related to depression. One of the most important biological factors in the pathogenesis of depression is dysregulation in the hypothalamic pituitary-adrenal (HPA) axis (Barden 2004). As reviewed by Barden (2004), the secretion of glucocorticoids from the adrenal glands increases in reaction to stress. The secretion of glucocorticoids is regulated by corticotrophin (ACTH) via stimulation of the corticotrophin releasing factor (CRF), which is secreted from the hypothalamus (Barden 2004).

In depression there is hyperactivity of the HPA axis caused by hypersecretion of CRF (Arborelius *et al.* 1999). Increased plasma corticotrophin release factor concentrations have been found among depressed individuals (Catalan *et al.* 1998, Galard *et al.* 2002). Elevated CRF concentrations have also been found in the locus ceruleus of depressed subjects (Bissette *et al.* 2003). High cortisol concentrations may cause cortical atrophy in the brain and thus damage the negative feedback to the hypothalamus (Thase 2000). However, hyperactivity of the HPA axis is normalized by sufficient pharmacological treatment of depression (Arborelius *et al.* 1999).

As reviewed by Brown *et al.* (2004), depression may be associated with many medical conditions influenced by dysregulation of the HPA axis. One of the disorders is metabolic syndrome, in which HPA axis abnormalities have been reported concurrently with other etiological factors (Brunner *et al.* 2002). Hypersensitivity of the HPA axis seems to associate especially with abdominal obesity, (Björntorp 1997, Björntorp & Rosmond 2000), and an association also exists between intra-abdominal fat and depression (Thakore *et al.* 1997, Stunkard *et al.* 2003). In addition, the HPA axis is involved in the associations between depression and cardiovascular diseases (Joynt *et al.* 2003) and depression and diabetes mellitus (Musselmann *et al.* 2003).

### *2.3.1.3 Other biological factors related to depression*

In addition to the above-mentioned mechanisms there are several hormonal and other biological factors that are suggested to be related to the pathophysiology of depression. As the prevalence of depression worldwide is greater among women than among men (Blazer *et al.* 1994, Piccinelli & Wilkinson 2000), it has been suggested that gonadal hormones, especially estrogen, may play an important role in the pathophysiology of depression among women (Halbreich 2000). As reviewed by Rubinow *et al.* (1998), estradiol may regulate serotonergic activity by regulating the number and function of serotonin receptors in the brain. In addition, as reviewed by Epperson *et al.* (1999), estrogen may increase serotonin biosynthesis and affect dopaminergic function by increasing dopamine neurotransmission in the pituitary gland, hypothalamus, nigrostriatal

system and mesolimbic brain regions. Estrogen treatment has been beneficial in treating depression especially in perimenopausal and postpartum depression (Ahokas *et al.* 2001, Rasgon *et al.* 2002). In addition, lowered follicular phase plasma estradiol levels have been found in women with depression (Young *et al.* 2000). On the other hand, the prevalence of depression among women is also high in reproductive age when estrogen levels are high (Halbreich 2000). However, the role of estrogen in depression is not clear and needs much more research (Stahl 1998). With regard to progesterone, as reviewed by Epperson *et al.* (1999), there is no evidence on the effect of progesterone in the treatment of depression. It is, however, suggested that progesterone may also have a role in the pathogenesis of depression (Epperson *et al.* 1999).

Thyroid dysfunction has been found to be associated with depression (Thase 2000). As reviewed by (Musselmann & Nemeroff 1996), alterations in thyroid-stimulating hormone response to thyrotropin-releasing hormone (TRH), an abnormally high rate of antithyroid antibodies and elevated cerebrospinal fluid (CSF) TRH concentrations have been documented in depressed individuals.

Chronobiological disturbances are common in depression, and sleeping problems are one of the most common symptoms of depression. In addition, abnormalities in sleep electroencephalograms (EEG) have been found among depressed individuals. The rapid eye movement (REM sleep) latency has been shown to be shortened and the first REM sleep period lengthened (Berger *et al.* 2003). In addition, a higher consumption of fish has been shown to be associated with a reduced risk of depression suggesting that omega-3 fatty acids may also play a role in the pathophysiology of depression (Tanskanen *et al.* 2001, Timonen *et al.* 2004)

### ***2.3.2 Somatic diseases and depression***

Depression occurs together with many chronic somatic diseases (Evans & Charney 2003, Evans *et al.* 2005). As reviewed by Evans *et al.* (2005), a medical illness may be a risk factor for depression, and depression itself may be a causal factor in many somatic diseases such as ischaemic heart disease and stroke. Depression may hamper recovering from a somatic disease and many patients do not receive appropriate treatment for depression (Evans *et al.* 2005). Depression may be difficult to recognize in patients with somatic symptoms (Paykel & Priest 1992, Evans *et al.* 2005), or patients may be ashamed of depressive symptoms and unwilling to share them with a physician (Paykel & Priest 1992). The somatic diseases presented in this chapter are considered to be the most relevant ones in the context of the present study.

#### ***2.3.2.1 Cardiovascular diseases and depression***

Depression has been shown to be a risk factor for cardiovascular diseases (Glassman & Shapiro 1998, Carney *et al.* 2002, Lett *et al.* 2004). In addition, depression increases the mortality in patients with coronary heart disease (Barefoot & Schroll 1996, Musselmann *et al.* 1998, Lett *et al.* 2004). Aromaa *et al.* (1994) studied the associations between

depression and cardiovascular diseases in the nationally representative Mini-Finland Health Survey. The study was based on 5355 individuals diagnosed at baseline with chronic somatic diseases and mental disorders and followed for 6.6 years. Depression was associated with cardiovascular diseases at the baseline. In the follow-up, the risk of developing and dying of cardiovascular diseases was significantly elevated among depressed individuals, both with and without cardiovascular diseases, at the beginning of the study. In a study conducted by Barefoot and Schroll (1996) 730 individuals born in Glostrup, Denmark, were examined physically and psychologically in 1964 and 1974 and were followed for about 27 years. In the follow-up, subjects with elevated depressive symptoms had a significantly higher risk of developing ischaemic heart disease. As reviewed by Rudisch and Nemeroff (2003), 17% to 27% of patients with coronary artery disease have major depression, and a much more larger proportion have depressive symptoms.

The mechanism behind the association between depression and cardiovascular diseases is complex and unclear, although several interaction mechanisms have been proposed (Carney *et al.* 2002). Joynt *et al.* (2003) introduced seven possible mechanisms for the relationship between depression and cardiovascular diseases: non-compliance with cardiac rehabilitation programmes and medical regimens; clustering of risk factors (e.g. obesity, hypertension, smoking, diabetes, hypercholesterolemia); hypothalamic-pituitary-adrenal (HPA) axis hyperactivity and increased cortisol secretion; heart rhythm disturbances; elevated plasma levels of cytokines leading to atherosclerosis; platelet reactivity and psychological stress. As reviewed by Joynt *et al.* (2003), activation of the HPA axis may speed up the development of cardiovascular diseases by elevated cortisol and catecholamines, which have also been found in depression. However, recognizing and treating depression is important among patients with cardiovascular diseases (Evans & Charney 2003). SSRIs appear to be a relatively safe and effective treatment for depression in patients with comorbid coronary heart disease (Roose 2003). Furthermore, as reviewed by Davidson *et al.* 2006, randomized controlled trials should be carried out to determine whether SSRIs, psychotherapy or combined treatment can reduce the risk of cardiovascular events and mortality associated with depression in patients with cardiovascular diseases.

### 2.3.2.2 *Diabetes mellitus and depression*

According to WHO, diabetes mellitus is a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both (WHO 1999). Type 1 diabetes mellitus comprises the majority of cases that are insulin deficient and in which pancreatic islet beta-cell destruction is present while type 2 includes the common major form of diabetes resulting from defect(s) in insulin secretion, almost always with a major contribution from insulin resistance (WHO 1999).

Depression has been shown to be associated with an increased risk of onset of diabetes mellitus (Eaton *et al.* 1996, Musselmann *et al.* 2003). In the Epidemiologic Catchment Area (ECA) Program survey with 3481 adults it was found that major depressive disorder

predicted the onset of diabetes mellitus (Eaton *et al.* 1996). Diabetes is also a risk factor for depression, and according to a meta-analysis by Anderson *et al.* (2001), the presence of diabetes doubles the risk of comorbid depression.

As reviewed by Musselmann *et al.* (2003), depression is associated with biological modifications that may lead to increased sensitivity of depressed individuals to type 2 diabetes. The mechanisms behind the association between depression and diabetes are still unclear. However, depression is associated with such metabolic abnormalities as increased release of catecholamines, glucocorticoids and growth hormone, alterations in glucose transport and increased secretion of cytokines. These can lead to insulin resistance and eventually to diabetes (Musselmann *et al.* 2003). In addition, insulin resistance has been suggested to be associated with depression (Timonen *et al.* 2005, Timonen *et al.* 2006).

### 2.3.2.3 *Other somatic diseases and depression*

Most malignant cancers are experienced as life-threatening, and are thus significant stressors for individuals. As reviewed by Spiegel and Giese-Davis (2003), the prevalence of depression among cancer patients is high. It has been suggested that chronic and severe depression may also increase the risk of cancer, speed cancer progression and increase mortality (Spiegel & Giese-Davis 2003). However, in a recent Finnish cohort study of 10 892 women depression did not increase breast cancer risk during a follow-up of 6 to 9 years (Aro *et al.* 2005).

Patients with chronic pain often have comorbid depression (Campbell *et al.* 2003). The prevalence rates of depression among patients with chronic pain have been found to be as high as from 30% to 54% (Banks & Kerns 1996). Depression may be a consequence of pain, but depression may also be manifested as a pain symptom (Magni 1987). As reviewed by Campbell *et al.* (2003), long-lasting pain may produce several maladjusted coping responses that may in turn have an effect on how the pain is experienced. The same neurochemical transmitters may be involved in both depression and pain, serotonin, noradrenalin, substance P and CRF (Campbell *et al.* 2003).

Depression is common among post-stroke patients: the prevalence of major depression among hospitalized subjects has been found to be as high as 19% (Robinson 2003). Depression may also increase the risk of stroke. Treatment of depression among post-stroke patients is important, as it also enhances recovery from stroke and improves function and cognition (Robinson 2003).

As reviewed by Kanner (2003), epilepsy is the most frequent psychiatric disorder in epilepsy. Lifetime prevalence of depression among epilepsy patients is 6% to 30%, and the risk of dying from suicide has been reported as much as 10 times higher compared to the general population. Depression may be hard to recognize among epileptics as the symptoms are often atypical, which is why it is untreated and causes much suffering (Kanner 2003). In Parkinson disease, about 50% of the patients have depressive symptoms (McDonald *et al.* 2003).

### 2.3.2.4 Depression and physical health in young adults

Huurre and Aro (2002) investigated long-term psychosocial effects of persistent chronic illness in a follow-up study of subjects aged 16-32 years. Adults with persistent chronic illness limiting daily life reported more depression and lower self-esteem than those with non-limiting chronic illness or healthy controls. However, no significant differences in psychosocial well-being were found between adults with any chronic illness and healthy controls (Huurre & Aro 2002). The associations between major depression and characteristics of chronic illness were studied in a general population study of 509 Finnish adolescents and 433 young adults (Haarasilta *et al.* 2005). As a result, chronic illness, respiratory allergies, poor self-rated health and frequent sick-days were associated with depression. The associations were stronger in the younger age group.

Within the Northern Finland 1966 Birth Cohort, atopic disorders have been found to increase the risk of depression about two- to three-fold when compared with subjects without atopic disorders (Timonen *et al.* 2002, Timonen *et al.* 2003). In addition, with regard to risk factors of cardiovascular diseases, depressive symptoms measured by Beck's Depression Inventory during early adulthood have been found to be associated with higher levels of carotid intima-media thickness in men, but not in women (Elovainio *et al.* 2005). In a study conducted by Elovainio *et al.* (2006), higher levels of depressive symptoms were associated with higher levels of CRP (C-reactive protein) among young adults. A similar finding was found in the Northern Finland 1966 Birth Cohort among men (Liukkonen *et al.* 2006), suggesting that an inflammatory process may contribute to the pathophysiology of depression.

## 2.4 Birth measures and depression

Some previous studies have suggested an association between low birth weight and later depression or psychological distress (Thompson *et al.* 2001, Gale & Martyn 2004, Wiles *et al.* 2005), but contradictory findings have also been presented (Osler *et al.* 2005). In a study conducted by Gale and Martyn (2004), birth weight and risk of psychological distress and depression at the ages of 16 and 26 years were examined. The results showed that women whose birth weight was  $\leq 3$  kg had an increased risk of depression at the age of 26 years compared with those who weighed  $>3.5$  kg, and men who weighed  $<2.5$  kg at birth were more likely to report a history of depression at the age of 26 years compared with men of normal birth weight.

Thompson *et al.* (2001) investigated the association between birth weight and depression in late life in the Hertfordshire birth cohort study of 882 subjects at the age of 68 years. They found that among men there was an association between low birth weight and risk of depression measured by the Geriatric Depression Scale while no association was found among women. In a Danish study of 12 270 men (Osler *et al.* 2005), no relation between birth dimensions and later hospital-treated depression was found. In another recent study of the Aberdeen Children of the 1950s low birth weight for gestational age was associated with adult psychological distress measured by four items from the 12-item GHQ (Wiles *et al.* 2005). The authors suggested that children born at

full term but having low birth weight are at higher risk of psychological distress in adulthood.

## **2.5 Menarche**

### ***2.5.1 Definition and the onset of menarche***

The first menstrual period in girls is called menarche. The mean age of menarche is around 13 years (Whincup *et al.* 2001), and it is controlled by genetic, environmental and psychosocial factors (Speroff *et al.* 1994, Adair 2001, Romans *et al.* 2003). In addition, growth in utero and childhood is associated with the age at menarche (Adair 2001, dos Santos Silva *et al.* 2002). The hormonal mechanism behind menarche consists of the development of positive estrogen feedback on the pituitary and hypothalamus (Speroff *et al.* 1994). According to Speroff *et al.* (1994), any female fulfilling the criteria of no period by the age of 16 regardless of normal growth and development should be evaluated as having the clinical problem of primary amenorrhea or delayed menarche.

### ***2.5.2 Menarche and depression***

Early age at menarche and early pubertal development has been shown to be associated with depression, psychosomatic symptoms and other psychopathology in adolescence (Aro & Taipale 1987, Hayward *et al.* 1999, Ge *et al.* 2001, Stice *et al.* 2001, Kaltiala-Heino *et al.* 2003). Aro and Taipale (1987) studied the impact of timing of puberty on psychosomatic symptoms among 14- to 16-year-old girls in a study sample of 935 subjects. Psychosomatic symptoms were more common among the earlier maturing girls. In a study conducted by Kaltiala-Heino *et al.* (2003) the relationship between pubertal timing and emotional and behavioural problems was studied. Among girls, early age at menarche was significantly associated with depression measured by the Beck Depression Inventory. This association between early maturing and increased psychopathology in adolescence has been proposed to be due to hormonal and morphological changes, genetic factors as well as the difficulty of moving into adolescence (Silberg *et al.* 1999). However, contradictory findings exist as well. In a study conducted by Bisaga *et al.* (2002) late menarche was found to be associated with depressive symptoms among adolescent girls. Regarding later age, Harlow *et al.* (1999) found that current depressive symptoms increased when the age at menarche decreased among subjects aged 36-44 years.

## 2.6 Overweight and obesity

### 2.6.1 Definition and epidemiology of overweight and obesity

According to the definition of the World Health Organization (WHO), individuals whose body mass index (BMI) is 25.0-29.9 kg/m<sup>2</sup> are classified as overweight and individuals whose body mass index is  $\geq 30.0$  kg/m<sup>2</sup> as obese (WHO 1988). With regard to children and adolescents, the 85<sup>th</sup> and 95<sup>th</sup> percentiles of body mass index for age and sex have been recommended as cut-off points of overweight and obesity (Barlow & Dietz 1998). However, Cole *et al.* (2000) published international cut-off points for body mass index for overweight and obesity by sex between ages 2 to 18 years in order to develop an internationally acceptable definition of child overweight and obesity. Data were obtained from six large nationally representative surveys on growth of subjects aged 6-18 years, and centile curves were drawn that at age 18 years passed the widely used cut-off points of 25 and 30 kg/m<sup>2</sup> for adult overweight and obesity. The cut-off points for children were provided by averaging all the six curves (Cole *et al.* 2000).

According to Seidell (1999), abdominal obesity should also be taken into account when evaluating health risks of obesity. Abdominal obesity reflects visceral, intra-abdominal fat and appears as growing waist circumference (Han *et al.* 1995). Abdominal obesity has traditionally been assessed by waist-to-hip ratio (Seidell 1999); however measuring only the waist circumference is a sufficient measure of abdominal obesity reflecting the amount of visceral fat (Han *et al.* 1995). Abdominal obesity is especially associated with type 2 diabetes mellitus, cardiovascular diseases and stroke (Han *et al.* 1995, Lakka *et al.* 2002b, Goodpaster *et al.* 2003, Suk *et al.* 2003).

The prevalence of obesity has been increasing in western countries among both adults and children and is nowadays a huge public health problem (Kuczmarski *et al.* 1994, Seidell 1995, Mokdad *et al.* 1999). As reviewed by Mustajoki *et al.* (2002), in the Mini-Finland survey in 1978-1980 12% of men and 18% of women were obese (body mass index  $\geq 30$  kg/m<sup>2</sup>). In 1997, the prevalence of overweight (body mass index 25.0-29.9 kg/m<sup>2</sup>) among 25- to 64-year-olds was 48.0% in men and 33.0% in women; and the prevalence of obesity 19.8% and 19.4%, respectively (Lahti-Koski *et al.* 2000). In the Health 2000 Study the prevalence of obesity among 30- to 64-year-old individuals assessed by the body mass index ( $\geq 30.0$  kg/m<sup>2</sup>) was 20.7% in men and 21.6% in women, and among individuals aged 65 years or older obesity was found in 21.2% of men and 31.3% of women (Reunanen *et al.* 2002). Abdominal obesity assessed by waist circumference ( $\geq 102$ cm in men,  $\geq 88$ cm in women) was seen among 30-to 64-year-old subjects in 31.9% of men and 41.7% of women, whereas among subjects 65 years or older the prevalence of abdominal obesity was as high as 40.0% in men and 66.1% in women (Reunanen *et al.* 2002). In the United States, the prevalence of obesity (defined as body mass index  $\geq 30.0$  kg/m<sup>2</sup>) has increased from 12.0% in 1991 to 17.9% in 1998 (Mokdad *et al.* 1999).

### ***2.6.2 Obesity, overweight and depression***

”The Jolly Fat” hypothesis was presented in the 1970s, when a positive association was found between obesity and low levels of anxiety in men and women, and low levels of depression in men (Crisp *et al.* 1976). After that several studies have been published on obesity and depression; some studies have found no significant association (Friedman & Brownell 1995), while other studies have reported a positive association between obesity and depression (Istvan *et al.* 1992, Simon *et al.* 2006). Recent studies have mostly observed an increased risk of depression among the obese (Roberts *et al.* 2000, Goodman & Whitaker 2002, Simon *et al.* 2006). However, most of the epidemiological studies concerning the association between obesity and depression have been cross-sectional (Friedman & Brownell 1995, Roberts *et al.* 2000).

One of the follow-up studies with prospectively collected data found that obesity predicted depression in a one-year follow-up when other variables were controlled for (Roberts *et al.* 2000). Noppa and Hällström (1981) followed a sample of middle-aged women for a six-year period and found that women who were more severely depressed at baseline were at greater risk for weight gain. Roberts *et al.* (2003) found in a two-wave, five-year-observational study of 2123 subjects 50 years and older from the Alameda County Study data that obesity at baseline was associated with increased risk of depression five years later, and that depression did not increase the risk of future obesity. Another study investigating the association between obesity and eight indicators of mental health using community residents 50 years and older showed that obese subjects were at increased risk of depression five years later (Roberts *et al.* 2002). Contradictory findings between men and women were found by Carpenter *et al.* (2000), who studied the relationship between relative body weight and clinical depression, suicide ideation and suicide attempts in an adult general population sample of 40 086 individuals. Among women, increased body mass index was associated with both major depression and suicide ideation, while among men lower body mass index was associated with major depression, suicide attempts and suicide ideation (Carpenter *et al.* 2000). A positive correlation between abdominal obesity and depressive symptoms was previously observed in a study of 59 middle-aged men (Ahlberg *et al.* 2002). In addition, in a recent cross-sectional epidemiological study of 9126 subjects conducted by Simon *et al.* (2006), obesity was associated with a significant increase in lifetime diagnosis of major depression.

With regard to children and adolescents, Pine *et al.* (2001) found that depression among 6 to 17 years old subjects was associated with an increased BMI in adulthood, even when participants with childhood obesity were excluded at baseline. Goodman and Whitaker (2002) showed that depressed adolescents were at increased risk of obesity in a one-year follow-up. In addition, in a study of 3101 subjects aged 11 to 17 years depressive symptoms were associated with obesity among both boys and girls (Richardson *et al.* 2006).

## 2.7 The metabolic syndrome

### 2.7.1 Definition and epidemiology of the metabolic syndrome

As reviewed by Laakso (2005), the metabolic syndrome was described as early as in the 1920s, but it was explicated unambiguously in 1988 by Gerald Reaven. The metabolic syndrome is also called syndrome X (Reaven 1988) or insulin resistance syndrome (Haffner *et al.* 1992). WHO presented a definition of the metabolic syndrome in 1998 and suggested that the metabolic syndrome is caused by insulin resistance (Alberti & Zimmet 1998). The WHO criteria of the metabolic syndrome are the following: glucose intolerance, impaired glucose tolerance or diabetes mellitus and/or insulin resistance together with two or more of the following criteria; 1. Elevated arterial blood pressure ( $\geq 140/90$  mmHg), 2. Elevated plasma triglycerides ( $\geq 1.7$  mmol/l; 150 mg/dl) or low plasma HDL-cholesterol ( $< 0.9$  mmol/l, 35 mg/dl in men;  $< 1.0$  mmol/l, 39 mg/dl in women), 3. Central obesity (waist-to-hip ratio in men  $> 0.90$ , in women  $> 0.85$  and/or body mass index  $> 30$  kg/m<sup>2</sup>, 4. Microalbuminuria (urinary albumin excretion  $\geq 20$   $\mu$ g/min.).

The National Cholesterol Education Program (Adult Treatment Panel III or ATP III) presented a definition of the metabolic syndrome in 2001. According to the ATP III criteria, a subject having 3 or more of the following criteria is defined as having the metabolic syndrome: 1. Abdominal obesity: waist circumference  $> 102$  cm in men and  $> 88$  cm in women; 2. High triglycerides:  $\geq 1.69$  mmol/L ( $\geq 150$  mg/dL); 3. Low high-density lipoprotein (HDL) cholesterol:  $< 1.04$  mmol/L ( $< 40$  mg/dL) in men and  $< 1.29$  mmol/L ( $< 50$  mg/L) in women; 4. High blood pressure:  $\geq 130/85$  mmHg; 5. High fasting glucose:  $\geq 6.1$  mmol/L ( $\geq 110$  mg/dL) (Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults 2001).

The most recent definition of the metabolic syndrome was presented by the International Diabetes Federation (IDF) to establish a diagnostic tool for the metabolic syndrome that is convenient to use in clinical practice and that can be used world-wide so that data from different countries can be compared (Alberti *et al.* 2006). The IDF criteria are based on the ATP-III criteria, but the diagnosis of the metabolic syndrome cannot be made without abdominal obesity (Laakso 2005). The IDF criteria are: 1. Abdominal obesity: waist circumference  $\geq 94$  cm in men and  $\geq 80$  cm in women (or body mass index  $\geq 30$  kg/m<sup>2</sup>), in addition at least two of the following 2. High triglycerides:  $\geq 1.7$  mmol/L ( $\geq 150$  mg/dL) or triglycerides lowering medication; 3. Low high-density lipoprotein (HDL) cholesterol:  $< 1.04$  mmol/L ( $< 40$  mg/dL) in men and  $< 1.29$  mmol/L ( $< 50$  mg/L) in women or medication for low HDL -concentration; 4. High blood pressure:  $\geq 130/85$  mmHg or antihypertensive medication; 5. High fasting glucose:  $\geq 5.6$  mmol/L ( $\geq 110$  mg/dL) or diabetes mellitus.

In Finland, the prevalence of the metabolic syndrome was studied in a population-based sample of 2049 subjects (FINRISK cohort) aged 45 to 64 years and in 522 subjects of the Finnish Diabetes Prevention Study (DPS) with impaired glucose tolerance using the definition of the World Health Organization (Ilanne-Parikka *et al.* 2004). In the FINRISK cohort, 38.8% of the men and 22.2% of the women had metabolic syndrome.

The prevalence was 14.4% and 10.1% among subjects with normal glucose tolerance, 74.0% and 52.2% among subjects with impaired fasting glucose, 84.8% and 65.4% among subjects with impaired glucose tolerance, and 91.5% and 82.7% among subjects with type 2 diabetes mellitus, among men and women. In the DPS cohort 78.4% of the men and 72.2% of the women had metabolic syndrome (Ilanne-Parikka *et al.* 2004). In another study using WHO criteria in identifying the metabolic syndrome in Finland and Sweden (Botnia study) the prevalence of metabolic syndrome was 15% among men and 10% among women with normal glucose tolerance. The prevalence was 64% among men and 42% among women with impaired fasting glucose/impaired glucose tolerance, and 84% among men and 78% among women with type 2 diabetes mellitus (Isomaa *et al.* 2001). Lakka *et al.* (2002a) investigated the prevalence of the metabolic syndrome in a population-based cohort of 1209 Finnish men, the Kuopio Ischaemic Heart Disease Risk Factor Study. The prevalence of the metabolic syndrome ranged from 8.8% to 14.3%, depending on the definition. In the United States, the estimated prevalence of the metabolic syndrome among US adults aged 20 through 70 years was 23% among women and 24% among men using the ATP III definition (Ford *et al.* 2002). The prevalence of the metabolic syndrome is increasing all over the world; however, the prevalence varies markedly between different populations (Laakso 2005).

### **2.7.2 Pathogenesis of the metabolic syndrome**

The pathogenesis of the metabolic syndrome is not fully elucidated. There seem to be two main causative factors: insulin resistance and abnormal visceral fat distribution (central obesity). Other possible factors in the development of the metabolic syndrome are chronic inflammation, genetic profile, physical inactivity and ageing (Eckel *et al.* 2005).

Central obesity is closely related to insulin resistance (Alberti *et al.* 2006). It has been hypothesized that adipose tissue (particularly visceral adipose tissue) is a source of mediators (free fatty acids, tumour necrosis factor alfa, TNF- $\alpha$ ) that impair insulin action in target cells (Alberti *et al.* 2006). In addition, as reviewed by Laakso (2005), adipose tissue secretes adiponectin, which has been found to have antidiabetic, anti-atherosclerotic and anti-inflammatory functions. However, a profuse amount of adipose tissue decreases the production of adiponectin, which in turn deteriorates insulin sensitivity (Laakso 2005).

Insulin resistance has an important role in the pathogenesis of the metabolic syndrome and it is present in most individuals with metabolic syndrome (Laakso 2005). In people with insulin resistance, insulin lowers the level of blood glucose less than normal (Eckel *et al.* 2005). As reviewed by Reusch (2002), insulin resistance is associated with many components of the metabolic syndrome. In addition, insulin resistance has been found to be associated with diabetes mellitus and cardiovascular diseases (Reaven 1988). In the metabolic syndrome, insulin resistance is strongly associated with dyslipidemia and inflammatory state, less with hypertension or prothrombotic state (Alberti *et al.* 2006).

Furthermore, chronic inflammation has been suggested to be one underlying factor behind the metabolic syndrome. Elevated C-reactive protein levels have been found to be associated with several components of the metabolic syndrome correlating especially

with body fat (body mass index, waist circumference), insulin resistance and the number of metabolic abnormalities (Festa *et al.* 2000).

With regard to other important factors behind the metabolic syndrome, physical inactivity and unhealthy diet may contribute to obesity, and ageing often increases the amount of abdominal fat (Alberti *et al.* 2006). Genetic factors behind the metabolic syndrome are poorly understood (Laakso 2005).

### ***2.7.3 Metabolic syndrome, depression and anxiety***

Only a few studies have dealt with the association between affective or anxiety symptoms and the metabolic syndrome. Depressive symptoms have been shown to be associated with individual components of the metabolic syndrome in male twins with a mean age of 63 years (McCaffery *et al.* 2003). Räikkönen *et al.* (2002) found in a study of middle-aged women that depressive symptoms were associated with an elevated risk of developing the metabolic syndrome seven years later as well as with the presence of the metabolic syndrome; metabolic syndrome at baseline also predicted increased anxiety seven years later. Heiskanen *et al.* (2006) studied the prevalence of the metabolic syndrome in depressive outpatients, in addition to which the severity of depressive symptoms and general psychopathology were assessed. The prevalence of the metabolic syndrome was 36% among subjects who had earlier been treated for depression, and the metabolic syndrome was associated with current major depression. However, no associations were observed between the occurrence of the metabolic syndrome and scores for global psychopathology, the level of psychosocial functioning, alexithymia, life satisfaction or the level of hopelessness (Heiskanen *et al.* 2006).

With regard to younger individuals, in a study conducted by Kinder *et al.* (2004), young adult women with a history of a major depressive episode were twice as likely to have the metabolic syndrome compared to others. Depression in women was also associated with high blood pressure and high triglyceride level. There were no associations between depression and the metabolic syndrome among men (Kinder *et al.* 2004).

## **2.8 Summary of the reviewed literature**

Based on the reviewed literature, the existing findings about the impact of birth weight on later depression are to some extent contradictory. There have also been study design differences, including age of assessment of depression or definition of low and high birth weight. There is a lack of studies on whether high birth weight has an association with depression. In addition, in earlier studies on birth weight and depression maternal depression during pregnancy has not been taken into account as a confounding factor.

The association between menarcheal age and depression has mainly been studied in adolescent girls, and the existing findings are to some extent contradictory. There are no earlier studies investigating whether the menarcheal age is associated with depression in young adults, and only one survey regarding depression among premenopausal women.

Association between obesity and depression have been studied in several studies, most of which have been criticized for being cross-sectional. The relationship between obesity and depression does not seem to be simple as there are many physiological, behavioural and social variables linking obesity and depression. However, obesity is also increasing in younger age cohorts causing various health problems. More studies are therefore needed to better understand how it is associated with depression and other mental disorders. In obesity-depression studies especially abdominal obesity should be better observed, rather than only assessing obesity by body mass index, since abdominal obesity is associated with harmful metabolic disturbances.

The metabolic syndrome is increasingly prevalent due to increasing rates of obesity. It is known that both metabolic syndrome and depression are associated with cardiovascular diseases and diabetes mellitus. More information should be gathered on how metabolic syndrome is linked to depression.

### **3 Aims of the study**

The purpose of this study was to investigate depression in young adults with special reference to birth weight, age at menarche, obesity and metabolic syndrome. The numbers I-IV hereafter refer to the original publications:

The aims of the present study were:

1. To investigate whether there is an association between birth weight and depression (I).
2. To investigate whether there is an association between the age at menarche and depression (II).
3. To investigate whether there is a longitudinal association between obesity at the age of 14 years and depression at the age of 31 years and to investigate whether there is a cross-sectional association between obesity and depression in young adults at the age of 31 years (III).
4. To investigate whether metabolic syndrome and its components are associated with depressive and anxiety symptoms in a young adult population cohort (IV).

## **4 Material and methods**

### **4.1 Study population and data collection**

The foundation of this study was provided by the database of the Northern Finland 1966 Birth Cohort. The original Northern Finland 1966 Birth Cohort Study, nowadays called the Northern Finland Health and Well-being Study, was assembled by Professor (emerita) Paula Rantakallio, whose purpose was to investigate the risk factors for perinatal deaths and low birth weight. The original sample was collected from a geographically defined area of the two northernmost provinces of Finland. It consisted of an unselected birth cohort of 12 058 live births covering 96.3% of all deliveries in Northern Finland in the year 1966. The majority of the cohort members are Caucasians.

Information on sociodemographic characteristics of the mothers and the families as well as data on mothers' depression during pregnancy were collected at the antenatal clinic during midgestation. Data on birth weight and birth length were gathered immediately after birth (Rantakallio 1969). Information of biological, socioeconomic and health-related conditions as well as living habits and family characteristics of the cohort members have been collected prospectively through pre-natal stages up to the age of 31 (Rantakallio 1969, 1988).

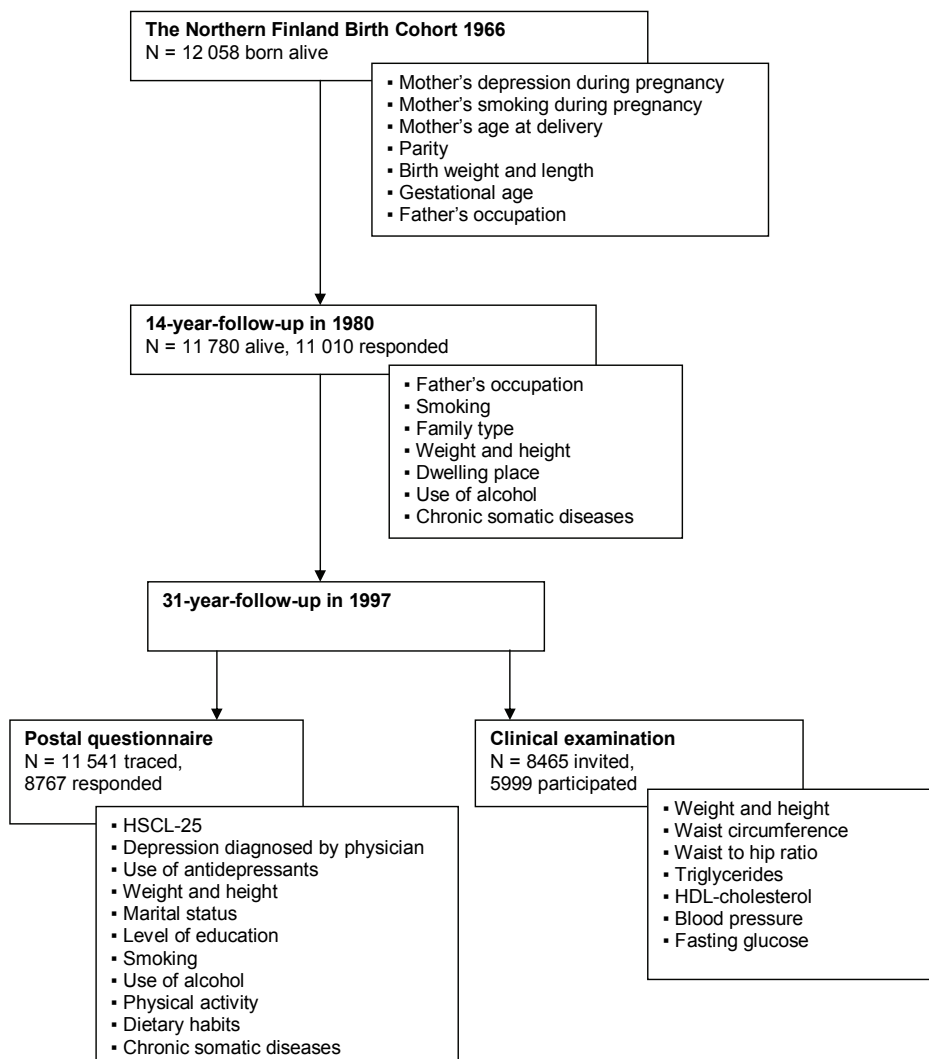
To date, three follow-up studies have been conducted. The first follow-up was performed at age of 1 year during routine postnatal clinic visit (1-year follow-up). Data were gathered on growth, development and health status of the children at that time (Rantakallio 1988).

The second follow-up of the total cohort was performed at the end of 1980 and in early 1981 (14-year follow-up) by sending a postal questionnaire to the subjects. At the age of 14 years, 11 780 subjects were alive and only 14 of them could not be traced. A postal questionnaire was sent to 11 766 subjects of which 11 010 subjects (93.6 %), 5455 girls and 5555 boys, responded. Information was gathered on cohort members' health, growth including height and weight, hobbies, living habits, school performance as well as family background variables and the social situation of the family (Rantakallio 1988).

The latest follow-up, called the Northern Finland Health and Well-being Study, was conducted during 1997-98 (Sorri & Järvelin 1998). A postal inquiry was sent to 11 541

members of the cohort, 75.3% of whom responded. In addition, 8465 cohort members who were living in Northern Finland or in the capital area of Helsinki were invited to a clinical examination, 70.9% of them participated in the examination.

The data collection procedure in the Northern Finland 1966 Birth Cohort Study and the main variables used in the original studies I-IV are presented in Figure 1.



**Fig. 1. The flowchart of the data collection procedure in the Northern Finland 1966 Birth Cohort Study and the main data used in the original publications I-IV.**

## 4.2 Variables

### 4.2.1 Outcome variables

#### 4.2.1.1 Current depression (HSCL-25) (I-IV)

In studies I-IV information on current depression was determined by the Hopkins Symptom Checklist-25 (HSCL-25), which is a 25-item shortened version of an originally 90-item questionnaire designed by Derogatis *et al.* (1973). The HSCL-25 was included in the postal questionnaire sent to the cohort members in 1997. The HSCL has been used in several versions of different lengths (16-90 items), all of which have been shown to have satisfactory validity and reliability as a measure of mental symptoms (Glass *et al.* 1978, Hough *et al.* 1990). The depression subscale has 13 items: feeling low in energy/slowed down, blaming him/herself for things, crying easily, loss of sexual interest or pleasure, feeling hopeless about the future, feeling blue, feeling lonely, thoughts of ending his/her life, feeling of being trapped or caught, worrying too much about things, feeling no interest in anything, feeling everything is an effort, feeling worthless (Winokur *et al.* 1984).

In the HSCL-depression subscale the subject assessed the presence and intensity of depressive symptoms over the previous week. The answers were scored on a scale from 1 (not bothered) to 4 (extremely bothered). The HSCL score was the sum of items divided by the number of items answered. In addition to two commonly used cut-off points, 1.55 and 1.75 (Hough *et al.* 1990, Nettelblatt *et al.* 1993, Sandanger *et al.* 1998), a cut-off point 2.01 was also used to define depression, as subjects scoring over 2.0 have been found to remain symptomatic for a longer follow-up time than subjects scoring under 2.0 (Winokur *et al.* 1994). The cut-off points 1.55, 1.75 and 2.01 have previously been used in this cohort (Timonen *et al.* 2003). As controls for depression subjects without depressive symptoms (HSCL score < 1.55) were used. In studies I and III three different cut-off points were used to define depression: 1.55, 1.75 and 2.01. In studies II and IV a cut-off point of 1.75 or over was used as an indicator of depression. Subjects were excluded from the sample if more than five items of the whole HSCL-25 were missing. Additionally, depression was not measured if four or more depression items were lacking. Missing data were not replaced.

#### 4.2.1.2 Self-reported physician-diagnosed lifetime depression (I-III)

In studies I-III data on self-reported lifetime-depression were gathered from the 31-year follow-up postal questionnaire. The subjects were asked “Have you ever been diagnosed by a physician as having depression or have you ever been treated by a physician because of depression (yes/no)”.

### 4.2.1.3 *Current use of antidepressants (II, III)*

In original studies II and III data on the current use of antidepressants were gathered from the 31-year follow-up postal questionnaire. The subjects were asked : “How often do you use the following medication?”, including antidepressants. The response categories were: 1) never, 2) occasionally and 3) regularly. The variable was dichotomised (original codes in parenthesis) 1) No (1) and 2) Yes (2-3).

### 4.2.1.4 *Current anxiety (IV)*

In study IV current anxiety was defined by the Hopkins Symptom Checklist-25 (HSCL-25). The anxiety subscale consists of 10 items: suddenly scared for no reason, feeling fearful, faintness, dizziness, or weakness, nervousness or shakiness inside, heart pounding or racing, trembling, feeling tense or keyed up, headaches, spells of terror or panic, feeling restless, can't sit still (Winokur *et al.* 1984). The answers were scored on a scale from 1 (not bothered) to 4 (extremely bothered). The HSCL score was the sum of items divided by the number of items answered. A cut-off point of 1.75 or over (Winokur *et al.* 1984, Hough *et al.* 1990) was used as an indicator of anxiety. Subjects were excluded from the sample if more than five items of the whole HSCL-25 were missing, and anxiety was not measured if three or more anxiety items were lacking. Missing data were not replaced.

## 4.2.2 *Exposure variables*

### 4.2.2.1 *Birth measures (I)*

Birth weight ( $\pm 5$  g) and birth length ( $\pm 1$  cm) were measured immediately after birth (Rantakallio 1969). Gestational age was defined by the mother's last menstrual period. Birth weight (g) was classified into three groups: low ( $< 2500$  g), normal (2500 g- 4499 g), and large ( $\geq 4500$  g) birth weight.

Intrauterine growth pattern was assessed by: (1) percentiles computed for all singleton boys and girls (birth weight relative to gestational age [BW-GA]), where birth weight was defined as appropriate for gestational age if weight was between the 11th and 89th percentiles, large if it was in the 90th percentile or above, and small if it was in the 10th percentile or below (Williams *et al.* 1992); and (2) ponderal index (birth weight/length<sup>3</sup>) as a measure of thinness.

#### 4.2.2.2 Age at menarche (II)

In study II, data on the age at menarche were gathered from the postal questionnaire sent to the subjects at the age of 31 years. The age at menarche was classified as 9-11 years/ 12-15 years /16 years or over. The cut off-point of 16 years for delayed menarche was used for clinical reasons. According to (Speroff *et al.* 1994), any female fulfilling the criteria of no period by the age of 16 regardless of normal growth and development should be evaluated as having the clinical problem of primary amenorrhea or delayed menarche.

#### 4.2.2.3 Overweight and obesity (III)

In study III, data on overweight and obesity at the age of 14 years were gathered from the postal questionnaire. The postal questionnaire sent to the subjects at the age of 14 years included questions about weight (kg) and height (cm). Overweight and obesity were assessed by the body mass index, kg/m<sup>2</sup> (BMI), which was calculated for each individual. At the age of 14 years overweight was defined as BMI between the 85<sup>th</sup> and the 95<sup>th</sup> percentiles separately for males (BMI = 21.45-23.42) and females (BMI = 21.63-23.80), and obesity was defined as BMI at or above the 95<sup>th</sup> percentile separately for males (BMI ≥ 23.43) and females (BMI ≥ 23.81), respectively. An internal definition, based on percentiles, was used, as has been done in previous studies on adolescent obesity and in this sample as well (Laitinen *et al.* 2001, Goodman & Whitaker 2002).

Data on overweight and obesity at the age of 31 years were gathered both from the postal questionnaire sent to the subjects in 1997-1998 and from the clinical examination in which weight, height and waist-to-hip ratio were measured. Body mass index (BMI) at the age of 31 years was calculated using the measured data of body weight (kg, in underwear) and height (cm, without shoes) obtained during the clinical examination, or the weight and height asked in the questionnaire if measured data from the clinical examination were not available. Weight and height were measured in 70% of the subjects. The self-reported and measured weight and height were almost identical (Pearson's correlation 0.98). The subjects were classified into four BMI categories according to the standard international classification (WHO 1998): underweight <18.5 kg/m<sup>2</sup>, normal weight 18.5-24.9 kg/m<sup>2</sup>, overweight 25.0-29.9 kg/m<sup>2</sup> (1586 males and 908 females), and obese ≥30.0 kg/m<sup>2</sup> (344 males and 378 females). These limits were the same for both males and females. Additionally, circumferences of waist (cm, at the level midway between the lowest rib margin and the iliac crest) and the hip (cm, at the widest trochanters) were measured during the clinical examination. Abdominal obesity was defined by the sex-specific waist-to-hip ratio (WHR) of the 85<sup>th</sup> percentile or greater (cut-off for males 97.0 cm and for females 87.7 cm) (WHO 1998).

Weight change was studied by dividing the subjects into three groups: "always overweight" (n=849, 440 men and 409 women), who were overweight or obese both at the ages of 14 and 31 years, "gained weight" (n=1989, 1253 men and 736 women), who had normal weight at the age of 14 years and overweight or obese at the age of 31 years, and "the others" (n=4376, 1750 men and 2626 women), who had normal weight at the

age of 14 and 31 years. There were only 82 males and 186 females who had lost weight; they were therefore combined with those who had normal weight at both the age of 14 and 31 years.

#### 4.2.2.4 *Metabolic syndrome (IV)*

In study IV, metabolic syndrome and metabolic risk factors were defined according to the National Cholesterol Education Program (Adult Treatment Panel III or ATP III) (Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults 2001). Subjects having 3 or more of the following criteria were defined as having the metabolic syndrome: 1. Abdominal obesity: waist circumference >102 cm in men and >88 cm in women; 2. High triglycerides:  $\geq 1.69$  mmol/L ( $\geq 150$  mg/dL); 3. Low high-density lipoprotein (HDL) cholesterol: <1.04 mmol/L (<40 mg/dL) in men and <1.29 mmol/L (<50 mg/L) in women; 4. High blood pressure:  $\geq 130/85$  mm Hg; 5. High fasting glucose:  $\geq 6.1$  mmol/L ( $\geq 110$  mg/dL).

Waist circumference was measured in the clinical examination as cm at the level midway between the lowest rib margin and the iliac crest. Blood samples were drawn during the clinical examination after overnight fasting from 22:00 until 8:00 - 11:00. Enzymatic determinations of serum triglycerides (Boehringer Mannheim, Germany) were done using a Hitachi 911 automatic analyser. HDL cholesterol was determined using the same analyser and the method published earlier (Sugiuchi *et al.* 1995). Blood pressure was also taken during the clinical examination. Two blood pressure readings were obtained and the average of the systolic and diastolic blood pressure readings was used in the analysis. Serum glucose level was measured by a glucose dehydrogenase method (Granutest 250, Diagnostica Merck, Darmstadt, Germany).

#### 4.2.3 *Confounding variables*

The confounding variables used in studies I-IV are presented in Table 1.

*Table 1. Confounding variables used in studies I-IV.*

Confounding variables	Original study
During pregnancy and delivery	
Father's occupation in 1966	I
Mother's smoking during pregnancy	I
Mother's depression during pregnancy	I
Mother's age at delivery	I
Parity	I
Gestational age of a cohort member in 1966	I
At the age of 14 years	
Father's occupation	II, III
Family type	II, III
Body mass index	II
Dwelling place	II
Smoking	II, III
Chronic somatic diseases	III
Use of alcohol	III
At the age of 31 years	
Level of education	III, IV
Marital status	III, IV
Chronic somatic diseases	III
Smoking	III, IV
Use of alcohol	III, IV
Physical Activity	III, IV
Dietary habits	III
Gender	IV

#### *4.2.3.1 Social class in 1966 and 1980*

The cohort members' social class in 1966 and 1980 was determined by the father's occupation and its prestige (Sosiaaliryhmitys 1954, Rantakallio 1969). In the highest class I the father's occupation has the highest prestige and requires academic education such as elementary school teachers, general practitioners, professional engineers and clergy. Class II included professionals with lower esteem and shorter education than in class I such as office managers. Class III consisted of skilled workers such as clerks and stewards, and class IV consisted of unskilled workers, e.g. office boys and night watchmen. Class V comprised farmers. In the original studies, the father's social class was re-categorized into three groups: classes I-II/classes III-IV/farmers.

#### *4.2.3.2 Tobacco exposure variables*

Information on mother's smoking was gathered during routine visits to the antenatal clinic (Rantakallio 1969, Rantakallio *et al.* 1992). The mother was asked whether she had

smoked during the last 12 months before pregnancy and whether she had changed her smoking habits in some way during pregnancy. The amount of cigarettes per day was also inquired. Mother's smoking was classified as "yes", if the mother had smoked during pregnancy (after the second month of pregnancy) and "no", if the mother did not smoke or had stopped smoking before pregnancy (Järvelin *et al.* 1997, Räsänen *et al.* 1999).

Information on smoking at the age of 14 years (studies II, III) was gathered from the postal questionnaire sent to the cohort members in 1980 (Rantakallio 1983). The subjects were asked "Do you smoke?". The response categories were: 1) Never, 2) I have tried once, 3) I have tried twice or more often, 4) I smoke occasionally, 5) I smoke about twice a week, 6) I smoke 1-5 cigarettes per day, 7) I smoke 6-10 cigarettes per day, and 8) I smoke more than 10 cigarettes per day. In studies II and III, the variable was dichotomised into two groups (original codes in parenthesis) 1) No (1-5) and 2) Yes (6-8).

Information on smoking at the age of 31 years (studies III, IV), was gathered from the postal questionnaire sent to the cohort members during the 31-year follow-up study. The subjects were asked: "Have you ever smoked during your lifetime?" If the answer was "yes", the cohort members were asked: "Do you smoke now?" The response categories were: 1) 7 days a week, 2) 5-6 days a week, 3) 2-4 days a week, 4) one day a week, 5) occasionally, and 6) never. In studies III and IV, the variable was dichotomised into (original codes in parenthesis) 1) Yes (1-4) and 2) No (5-6).

#### *4.2.3.3 Mother's depression during pregnancy*

The cohort members' pregnant mothers were asked at the antenatal clinic during midgestation whether they felt that their mood had been normal, depressed or very depressed during pregnancy. Mother's depression during pregnancy was categorized in study I as no depression versus depressed/very depressed (Rantakallio 1969).

#### *4.2.3.4 Mother's age at delivery and parity in 1966*

Mother's age at time of delivery was obtained from a questionnaire filled in at the maternity clinic. In study I, mother's age at delivery was classified as under 20 years, 20-35 years (ref), and 36 years or more.

Mother's parity (number of deliveries) in 1966 was classified in the study I as 1, 2-5 (ref), 6 or more.

#### *4.2.3.5 Gestational age in 1966*

In study I, gestational age was divided into two groups 1) 36 weeks or less and 2) 37 or more. The gestational age was calculated to the nearest week from the first day of the last menstrual period.

#### *4.2.3.6 Family type and marital status*

Family background was assessed by questionnaire in the 1980 follow-up (Moilanen & Rantakallio 1988). The questionnaire was sent to the cohort member, and if he/she did not answer, the questionnaire was forwarded to the custodial parent. The cohort member was asked at the age of 14 years if his/her mother/father was: 1) alive, 2) alive, but not living at home, 3) dead, or 4) unknown. In studies II and III, the families were divided into two- and single-parent families.

Information on the marital status at the age of 31 years was gathered from the postal questionnaire sent to the cohort members during the 31-year follow-up study. The subjects were asked about their marital status and the response categories were: 1) married, 2) cohabiting, 3) unmarried, 4) divorced, and 5) widowed. The variable was categorized in study III as not married or cohabiting/married or cohabiting.

#### *4.2.3.7 Body mass index in 1980*

Information on weight (kg) and height (cm) to calculate body mass index, kg/m<sup>2</sup> (BMI), was gathered from the postal questionnaire sent to the cohort members at the age of 14 years. BMI was classified into normal 18.5-24.9 kg/m<sup>2</sup>, overweight 25.0-29.9 kg/m<sup>2</sup> and obese  $\geq 30.0$  kg/m<sup>2</sup>.

#### *4.2.3.8 Dwelling place in 1980*

The dwelling place of the family in 1980 used in study II was defined as urban/rural.

#### *4.2.3.9 Chronic somatic diseases at the age of 14 and 31 years*

In study III, information on chronic somatic diseases was gathered from postal questionnaires at the age of 14 and 31 years. All chronic somatic diseases which were available in the data set were included separately in the 14-year follow-up phase (asthma, rheumatoid arthritis, diabetes mellitus, epilepsy, thyroid diseases, hypertonia, leukemia, kidney diseases, hemophilia) and in the 31-year follow-up phase (hypertonia, congenital heart failures, angina pectoris, diabetes mellitus, thyroid diseases, ulcer, epilepsy, rheumatoid arthritis, cancer).

#### *4.2.3.10 Use of alcohol at the age of 14 and 31 years*

Alcohol consumption at the age of 14 years was investigated by a postal questionnaire (Rantakallio 1983). The cohort members were asked "Do you drink alcohol?" and the answers were classified into four categories: 1) Never, 2) I have tried once, 3) I have tried twice or more often, 4) I drink alcohol at some time every month, and 5) I drink alcohol

every week (Rantakallio 1983, Isohanni *et al.* 1993). In study III the variable was dichotomized into (original codes in parenthesis) 1) No (1-3) and 2) Yes (4-5).

In studies III and IV, information of the use of alcohol at the age of 31 years was gathered from the postal questionnaire. Questions on alcohol use measured the average frequency of consumption of beer, wine and spirits during the last year, and the usual amount of each consumed on one occasion. The amount of alcohol consumed per day was calculated and converted into grams of absolute alcohol (Laitinen *et al.* 2004). Subjects were divided into light < 15 g/day, moderate 15-40 g/day and heavy > 40 g/day drinkers.

#### *4.2.3.11 Level of education*

In studies III and IV, cohort members' social status at the age of 31 years was based on data on the level of education which was obtained from the registers of Statistic Finland at the end of the year 1997 and divided into three groups: basic  $\leq 9$  years, secondary 10-12 years and tertiary > 12 years level.

#### *4.2.3.12 Physical activity*

Information on physical activity was gathered from the postal questionnaire of the 31-year follow-up phase. Physical activity was defined as regular vs. nonregular. Regular physical activity was defined as consisting of exercise that makes the subject become breathless and to sweat at least mildly at least two to three times a month or more often.

#### *4.2.3.13 Dietary habits*

Information on cohort members' dietary habits were gathered from the postal questionnaire at the age of 31 years. Cohort members were asked to consider their habitual food consumption during the previous 6 months. In study III, diet was considered unhealthy when it included daily or almost daily consumption of sausages, and less frequent consumption of rye bread or crisp bread, fresh vegetables and salads, berries or fruit, one point being assigned to each of these counts, so that a sum of four-five points indicated an unhealthy diet and three or less a healthy diet (Laitinen *et al.* 2004).

### **4.3 Statistical methods**

In studies I-IV, as a preliminary method to study the association between variables cross-tabulation was used, with Pearson's Chi square test for independence to evaluate statistical significance. Multivariate binary logistic regression analyses were used to

explore the associations between the outcome and exposure variables adjusting for the confounding variables presented in Table 1 to obtain adjusted odds ratios.

In study IV, the inter-correlations between HSCL depression and HSCL anxiety were determined by Spearman's correlation coefficients. Spearman's partial correlation coefficients were used to examine the relationships between the components of the metabolic syndrome and psychological distress adjusting for gender. The analyses in study IV were also performed excluding subjects with angina pectoris and diabetes mellitus.

P-values <0.05 and odds ratios with 95% confidence intervals not including 1 were considered as statistically significant. The statistical analyses were performed using the SAS system version 8.2 for Windows in the original study II (SAS Institute, Cary, NC, 1999), and the SPSS system version 11.5 for Windows in the original studies I, III and IV (SPSS Inc., 2001).

#### **4.4 Ethical considerations and personal involvement**

Permission for gathering data for the entire Cohort was obtained from the Ministry of Social Welfare and Health Affairs in 1993. The research plan for the 31-year follow-up study design of the Cohort named the Northern Finland Health and Well-being Study (Sorri & Järvelin 1998) was reviewed by the Ethics Committee of the Faculty of Medicine, University of Oulu on June 17, 1996. This permission by the Ethics Committee of the Faculty of Medicine, University of Oulu covers the present study as well. During the 31-year follow-up, the cohort members have been given a complete description of the study and they have had the chance to refuse participating in the study. A written informed consent was obtained from all participants.

This study has been approved by the Postgraduate Research Committee of the Faculty of Medicine, University of Oulu, on 31 November 2000 as part of the Northern Finland Health and Well-being Study. The author of this thesis has participated in the Northern Finland Birth Cohort as a researcher since 1999. The author has been accorded permission to use the data and has participated in study design, data analysis and reporting the results in all original studies I – IV. The contribution of the author in all original studies has been central; the author has had original ideas for the studies and has written the first and last versions of papers I-IV.

## **5 Results**

### **5.1 Birth measures and depression**

The prevalence of current depression measured by the HSCL-questionnaire (HSCL depression sum score 1.75 or above compared to subjects scoring 1.74 or below) was 11.6% among men and 17.1% ( $p < 0.01$ ) among women. Current depression at age 31 also associated significantly with female gender as well as three characteristics at birth in 1966: maternal depression, smoking during pregnancy and primiparity (Table 2; I: Table 1). Lower mean birth weight was associated with female gender, maternal depression, mother's smoking during pregnancy, mother's young age ( $< 20$  years), low social class, small gestational age and primiparity.

#### ***5.1.1 Birth measures and current depression at age 31***

Among men there were no statistically significant associations between any of the body size measures at birth and current depression (Table 3; I: Table 2). Women with high birth weight ( $\geq 4500$ g) had a higher risk for current depression using all cut-off points, adjusted ORs varying from 1.96 to 2.16. However, no significant association was seen when birth weight relative to gestational age was used as a predictor for current depression, although there was a tendency towards a positive association between large for gestational age babies and current depression with a cut-off point of 2.00 in the HSCL-25 depression subscale ( $p = 0.066$ ). Among females high ponderal index was also associated with current depression with cut-off point 1.75 (adjusted OR 1.38, 95%CI 1.08-1.77).

*Table 2. Characteristics of the study population by mean birth weight and current HSCL-depression in the 31-year follow-up of the Northern Finland 1966 Birth Cohort (I: Table 1).*

Characteristics at birth in 1966	Participants N	Mean birth weight (g)	p-value*	HSCL- depression, cut-off 1.75 N (%)	p-value**
<b>Gender</b>					
Male	4007	3558	<0.001	466 (11.6)	<0.001
Female	4332	3434		740 (17.1)	
<b>Maternal depression</b>					
No	7087	3499	0.032	986 (13.9)	0.003
Depressed/very depressed	1081	3462		187 (17.3)	
<b>Maternal smoking</b>					
No	6497	3525	<0.001	905 (13.9)	0.021
Yes	1666	3376		269 (16.1)	
<b>Mother's age</b>					
< 20	747	3326	<0.001	106 (14.2)	0.770
20-35	6389	3496		918 (14.4)	
36 or more	1203	3586		182 (15.1)	
<b>Father's social class in 1966</b>					
I-II	2031	3554	<0.001	274 (13.5)	0.213
III-IV	4600	3455		690 (15.0)	
V	1680	3528		233 (13.9)	
<b>Gestational age</b>					
< 38	646	2908	<0.001	90 (13.9)	0.932
38-42	6951	3537		1005 (14.5)	
>42	460	3712		67 (14.6)	
<b>Mother's parity</b>					
1	2660	3351	<0.001	354 (13.3)	0.047
2-5	4672	3544		683 (14.6)	
6 or more	991	3637		163 (13.6)	

\*Student's t-test or one-way ANOVA.

\*\*Pearson's chi-square test.

Table 3. Birth measures and current depression at age 31 years measured by HSCL-25 in the Northern Finland 1966 Birth Cohort (I: Table 2).

Birth measures	Total N	HSCL-score		HSCL-score		HSCL-score	
		1.55-4.00 (vs. no depression) <sup>a</sup>	OR (95%CI) <sup>b</sup> , p-value	1.75-4.00 (vs. no depression) <sup>a</sup>	OR (95%CI) <sup>b</sup> , p-value	2.01-4.00 (vs. no depression) <sup>a</sup>	OR (95%CI) <sup>b</sup> , p-value
		n (%) of cases	n (%) of cases	n (%) of cases	n (%) of cases	n (%) of cases	n (%) of cases
Birth weight (g)							
Men							
< 2500	3766	677 (18.0)	432 (12.3)	161 (5.0)			
2500 – 4499	108	19 (17.6)	12 (11.9)	7 (7.3)	1.07 (0.54-2.09), 0.855	1.43 (0.58-3.51), 0.432	
≥ 4500	3501	624 (17.8)	396 (12.1)	146 (4.8)	Ref.	Ref.	
Women							
< 2500	157	34 (21.7)	24 (16.3)	8 (6.1)	1.40 (0.89-2.22), 0.146	1.29 (0.61-2.72), 0.506	
2500 – 4499	4043	1051 (26.0)	690 (32.9)	272 (8.3)			
≥ 4500	137	32 (23.4)	24 (18.6)	8 (7.1)	0.99 (0.61-1.62), 0.965	0.85 (0.39-1.87), 0.691	
BW-GA <sup>c</sup>							
Men							
≤10% (small)	3820	984 (25.8)	641 (18.4)	254 (8.2)	Ref.	Ref.	
11-89% (appropriate)	86	35 (40.7)	25 (32.9)	10 (16.4)	2.14 (1.31-3.49), 0.002	2.16 (1.08-4.34), 0.030	
≥90 (large)	3766	677 (18.0)	432 (12.3)	161 (5.0)			
Women							
≤10% (small)	338	66 (19.5)	42 (13.4)	19 (6.5)	1.21 (0.79-1.59), 0.520	1.41 (0.85-2.33), 0.183	
11-89% (appropriate)	3041	536 (17.6)	344 (12.1)	124 (4.7)	Ref.	Ref.	
≥90 (large)	387	75 (19.4)	46 (12.8)	18 (5.5)	1.07 (0.76-1.491), 0.703	1.16 (0.69-1.94), 0.572	
BW-GA <sup>c</sup>							
Men							
≤10% (small)	4043	1051 (26.0)	690 (18.7)	272 (8.3)			
11-89% (appropriate)	358	81 (22.6)	55 (16.6)	20 (6.7)	0.87 (0.64-1.18), 0.378	0.82 (0.51-1.32), 0.404	
≥90 (large)	3246	838 (25.8)	548 (18.5)	213 (8.1)	Ref.	Ref.	
BW-GA <sup>c</sup>							
Men							
≤10% (small)	439	132 (30.1)	87 (22.1)	39 (11.3)	1.22 (0.94-1.57), 0.140	1.41 (0.98-2.03), 0.066	

Table 3. Continued.

Birth measures	Total N	HSLC-score		HSLC-score		HSLC-score	
		1.55-4.00 (vs. no depression) <sup>a</sup> n (%) of cases	OR (95%CI) <sup>b</sup> , p-value	1.75-4.00 (vs. no depression) <sup>a</sup> n (%) of cases	OR (95%CI) <sup>b</sup> , p-value	2.01-4.00 (vs. no depression) <sup>a</sup> n (%) of cases	OR (95%CI) <sup>b</sup> , p-value
<b>Ponderal Index</b>							
<b>(weight/height<sup>3</sup>)</b>							
<b>Men</b>							
≤ 10 percentile	3731	673 (18.0)		429 (12.3)		160 (5.0)	
11 – 89 percentile	428	88 (20.6)	1.23 (0.95-1.60), 0.110	59 (14.8)	1.32 (0.97-1.78), 0.077	25 (6.8)	1.49 (0.94-2.34), 0.086
≥ 90 percentile	2975	529 (17.8)	Ref.	333 (12.0)	Ref.	119 (4.6)	Ref.
<b>Women</b>							
≤ 10 percentile	328	56 (17.1)	0.93 (0.68-1.25), 0.630	37 (12.0)	0.98 (0.68-1.41), 0.922	16 (5.6)	1.23 (0.72-2.11), 0.453
11 – 89 percentile	4010	1041 (26.0)		685 (18.7)		270 (8.3)	
≥ 90 percentile	171	83 (24.9)	0.98 (0.75-1.28), 0.878	61 (19.6)	1.13 (0.84-1.52), 0.427	25 (9.1)	1.18 (0.76-1.84), 0.452
	3618	824 (25.5)	Ref.	527 (18.0)	Ref.	207 (7.9)	Ref.
	221	134 (29.7)	1.22 (0.98-1.52), 0.071	97 (23.4)	1.38 (1.08-1.77), 0.010	38 (10.7)	1.37 (0.95-1.98), 0.092

<sup>a</sup>No depression = HSLC-25 depression subscale score less than or equal to 1.54. <sup>b</sup>Odds ratios and 95% confidence intervals after adjustment for father's social class in 1966 (I-II=highest, III-IV=lowest, V=farmers), and mother's depression during pregnancy (no, depressed/very depressed) mother's smoking during pregnancy (no, yes), mother's age at child's birth (<20, 20-35 (ref), 36 or more), parity (1, 2-5 (ref), 6 or more), gestational age (36 weeks or less, 37 or more). <sup>c</sup>Birth weight relative to gestational age.

*Table 4. Birth measures and self-reported physician-diagnosed lifetime depression at age 31 years in the Northern Finland 1966 Birth Cohort (I: Table 3).*

Birth measures	n	n (%) with self-reported physician-diagnosed depression	Crude OR (95% CI), p-value	Adjusted OR (95% CI) <sup>a</sup> , p-value
<b>Birth weight (g)</b>				
Men	3774	136 (3.6)		
< 2500	109	6 (5.5)	1.60 (0.69-3.72), 0.273	1.53 (0.58-4.00), 0.391
2500 – 4499	3506	123 (3.5)	Ref.	Ref.
≥ 4500	159	7 (4.4)	1.27 (0.58-2.76), 0.552	1.34 (0.60-2.96), 0.475
Women	4054	208 (5.1)		
< 2500	138	8 (5.8)	1.13 (0.55-2.34), 0.744	1.22 (0.56-2.67), 0.616
2500 - 4499	3830	198 (5.2)	Ref.	Ref.
≥ 4500	86	2 (2.3)	0.44 (0.11-1.79), 0.250	0.46 (0.11–1.89), 0.281
<b>BW-GA<sup>b</sup></b>				
Men	3774	136 (3.6)		
≤10% (small)	337	16 (4.7)	1.38 (0.81-2.37), 0.238	1.35 (0.78-2.32), 0.285
11-89% (appropriate)	3047	106 (3.5)	Ref.	Ref.
≥90 (large)	309	14 (3.6)	1.03 (0.59-1.82), 0.911	1.05 (0.59-1.88), 0.848
Women	4054	208 (5.1)		
≤ 10%	361	15 (4.2)	0.76 (0.44-1.31), 0.323	0.76 (0.44–1.31), 0.762
11-89%	3252	175 (5.4)	Ref.	ref.
≥ 90%	441	18 (4.1)	0.75 (0.46-1.23), 0.251	0.77 (0.47–1.27), 0.304
<b>Ponderal Index<sup>c</sup></b>				
Men	3739	133 (3.6)		
≤ 10%	429	20 (4.7)	1.36 (0.84-2.22), 0.213	1.34 (0.81-2.21), 0.252
11-89%	2978	103 (3.5)	Ref.	Ref.
≥ 90%	332	10 (3.0)	0.87 (0.45-1.68), 0.671	0.85 (0.44-1.65) 0.633
Women	4021	206 (5.1)		
≤ 10%	334	16 (4.8)	0.92 (0.54-1.55), 0.751	0.91 (0.53-1.55) 0.727
11-89%	3235	168 (5.2)	Ref.	Ref.
≥ 90%	452	22 (4.9)	0.93 (0.59-1.48), 0.769	0.96 (0.61-1.52), 0.857

<sup>a</sup>Odds ratios after adjustment for father's social class in 1966 (I-II=highest, III-IV=lowest, V=farmers), and maternal depression during pregnancy (no, depressed/very depressed), maternal smoking during pregnancy (no, yes), mother's age at child's birth.

<sup>b</sup>Birth weight relative to gestational age.

<sup>c</sup>Weight/height<sup>3</sup>.

### ***5.1.2 Birth measures and physician-diagnosed depression at age 31***

Birth weight and birth weight relative to gestational age (BW-GA) were not associated with physician-diagnosed depression among either men or women (Table 4; I: Table 3). No associations were found when ponderal index was assessed by  $\leq 10^{\text{th}}$  percentiles and  $\geq 90^{\text{th}}$  percentiles. However, males with a ponderal index belonging to the lowest 5 percentile had an elevated risk (adjusted OR 1.95, 95%CI 1.07-3.56) for physician-diagnosed depression even after controlling for characteristics at birth, while no association was found among women.

## **5.2 Age at menarche and depression at the age of 31 years**

12.2% (n=482) of the subjects had menarche at the age of 9-11 years, 84.5% (n=3340) at the age of 12-15 years and 3.3% (n=130) at the age of 16 years or later. Women with menarche at the age of 16 years or later had a higher likelihood of depression at the age of 31 years than the other women according to all three depression indicators (Table 5; II: Table 1). The likelihood of depression was 1.8-fold in current depression, 2.8-fold in the use of antidepressants and 2.1-fold in self-reported physician-diagnosed depression in women with menarche at the age of 16 years or later. After adjusting for confounders the association between current depression and late menarche remained, but the use of antidepressants and depression diagnosed by physician did not have a significant association with the age at menarche.

*Table 5. The association of menarcheal age with the prevalence (%), OR with 95% confidence intervals) of self-reported depressive symptoms<sup>a</sup>, use of antidepressants and lifetime depression diagnosed by physician at 31 years in the Northern Finland 1966 Birth Cohort (II: Table 1).*

Menarche age	Current depression <sup>a</sup> N=666			Use of antidepressants N=69			Depression diagnosed by physician N=206		
	%	Crude OR (95% CI)	Adjusted <sup>c</sup> OR (95% CI)	%	Crude OR (95% CI)	Adjusted <sup>d</sup> OR (95% CI)	%	Crude OR (95% CI)	Adjusted <sup>e</sup> OR (95% CI)
9-11 (N=482)	18.7	1.2 (0.9,1.5)	1.1 (0.9,1.4)	1.2	0.7 (0.3,1.7)	0.8 (0.3,1.9)	5.6	1.1 (0.7,1.6)	1.1 (0.7,1.7)
12-15 (N=3340)	16.3	1.0 <sup>b</sup>	1.0 <sup>b</sup>	1.7	1.0 <sup>b</sup>	1.0 <sup>b</sup>	5.0	1.0 <sup>b</sup>	1.0 <sup>b</sup>
16- (N=130)	25.4	1.8 (1.2,2.6)	1.7 (1.1,1.6)	4.6	2.8 (1.2,6.6)	1.9 (0.7,5.5)	10.0	2.1 (1.2,3.8)	1.8 (0.9,3.6)

<sup>a</sup>Measured by HSCL-25 depression subscale at the age of 31 years, cut-off 1.75. <sup>b</sup>Reference category. <sup>c</sup>Adjusted for smoking (yes/no), body mass index (BMI = body mass index, kg/m<sup>2</sup>, normal/overweight/obese; 18.5-24.9 kg/m<sup>2</sup>/25.0-29.9 kg/m<sup>2</sup>/≥30.0 kg/m<sup>2</sup>), social class (I-II=highest, III-IV=lowest, V=farmers), family type (single-parent, two-parent family) and dwelling place (urban, rural) at the age of 14 years.

### **5.3 Obesity and depression**

The prevalence of depression measured by the HSCL-25 using the cut-off point 1.75 was 11.6% among males (n=468) and 17.2% among females (n=761) ( $p<0.01$ ). Seventy-two of the males (1.8%) and 76 of the females (1.7%) were using antidepressants at the time of the clinical examination. Of the males using antidepressants, 34 reported the type of the antidepressant, including 6 cases (17.7%) using tricyclic or other antidepressants causing weight gain. Of the females using antidepressants, 49 reported the type of the antidepressant, including 8 cases (16.3%) using tricyclic or other antidepressants causing weight gain. Depression had been diagnosed by a physician in 146 (3.6%) males and in 233 (5.3%) females.

#### ***5.3.1 BMI at 14 years and depression at 31 years***

Obesity at the age of 14 years associated with depressive symptoms at the age of 31 years; among males using the cut-off point 2.01 in the HSCL-25 (adjusted OR 1.97, 95%CI 1.06-3.68), among females using the cut-off point 1.75 (adjusted OR 1.64, 95%CI 1.16-2.32) (Table 6; III: Table 1). Overweight or obesity did not associate with physician-diagnosed depression or the use of antidepressants in adulthood.

Table 6. Obesity measured by the body mass index (kg/m<sup>2</sup>) at the age of 14 years and depression at the age of 31 years in the Northern Finland 1966 Birth Cohort (III: Table I).

BMI at 14 years	HSLC depression, cut-off 1.55 <sup>a</sup>			HSLC depression, cut-off 1.75 <sup>a</sup>			HSLC depression, cut-off 2.01 <sup>a</sup>		
	N (%)	Crude Odds Ratio OR (95% CI)	Adjusted Odds Ratio <sup>b</sup> OR (95% CI)	N (%)	Crude Odds Ratio OR (95% CI)	Adjusted Odds Ratio <sup>b</sup> OR (95% CI)	N (%)	Crude Odds Ratio OR (95% CI)	Adjusted Odds Ratio <sup>b</sup> OR (95% CI)
<b>Males</b>									
Below 85%	530 (17.6)	1 <sup>c</sup>		334 (11.1)	1 <sup>c</sup>		117 (4.5)	1 <sup>c</sup>	
85% to 95%	62 (17.9)	1.02 (0.76-1.36)	1.01 (0.75-1.37)	35 (10.1)	0.91 (0.63-1.32)	0.93 (0.64-1.35)	9 (3.1)	0.67 (0.34-1.33)	0.67 (0.33-1.34)
Above 95%	35 (19.8)	1.15 (0.79-1.69)	1.08 (0.72-1.61)	24 (13.6)	1.26 (0.80-1.96)	1.18 (0.73-1.89)	13 (8.4)	1.94 (1.07-3.52)	1.97 (1.06-3.68)
<b>Females</b>									
Below 85%	840 (24.7)	1 <sup>c</sup>		553 (16.3)	1 <sup>c</sup>		223 (8.0)	1 <sup>c</sup>	
85% to 95%	118 (29.4)	1.27 (1.01-1.59)	1.20 (0.95-1.53)	73 (18.2)	1.19 (0.90-1.56)	1.13 (0.85-1.51)	31 (9.8)	1.25 (0.84-1.86)	1.18 (0.78-1.78)
Above 95%	61 (30.5)	1.34 (0.98-1.82)	1.33 (0.97-1.83)	49 (24.5)	1.63 (1.16-2.29)	1.64 (1.16-2.32)	18 (11.5)	1.49 (0.89-2.47)	1.55 (0.93-2.59)

<sup>a</sup>Vs. no depression, HSLC-score < 1.55. <sup>b</sup>Logistic regression analysis, adjusted for father's social class (I-II=highest, III-IV=lowest, V=farmers), family type (single-parent, two-parent family), smoking (yes/no), use of alcohol (yes/no) and chronic somatic diseases (yes/no) at the age of 14 years. <sup>c</sup>Reference category.

### ***5.3.2 BMI at 31 years and depression at 31 years***

In the cross-sectional analyses of 31-year-old males underweight men had a 2.48- to 6.10-fold likelihood of having depressive symptoms compared to men with normal weight when using different HSCL cut-off points (Table 7; III: Table 2). The finding remained significant using the cut-off point 2.01 when the analyses were adjusted for potential confounders. Overweight was not significantly associated with HSCL depression among males. Overweight or obesity did not associate statistically significantly with physician-diagnosed depression among males. The proportion of those who used antidepressants was 2.49-fold higher among obese than among normal weighted men, and this association remained significant after adjusting for the confounders (OR 2.21, 95%CI 1.12-4.37).

Among the females, there were no significant associations between obesity or overweight and depression measured by the HSCL questionnaire (Table 7; III: Table 2). The proportion of those who used antidepressants was 2.63-fold higher among the underweight women compared to women with normal weight, but the finding did not remain significant after adjusting for confounders (OR 2.49, 95%CI 0.85-7.27). The proportion of those who used antidepressants was 2.18-fold higher among obese women than among normal weighted women, although this finding did not reach statistical significance after adjusting for confounders (OR 2.00, 95%CI 0.95-4.19). Obesity or overweight among females did not associate with physician-diagnosed lifetime depression.

Table 7. Obesity measured by the body mass index (kg/m<sup>2</sup>) and depression at the age of 31 years in the Northern Finland 1966 Birth Cohort (III: Table 2).

BMI at 31 years	HSCl depression, cut-off 1.55 <sup>a</sup>		HSCl depression, cut-off 1.75 <sup>a</sup>		HSCl depression, cut-off 2.01 <sup>a</sup>	
	N (%)	Crude Odds Ratio OR (95% CI)	N (%)	Crude Odds Ratio OR (95% CI)	N (%)	Crude Odds Ratio OR (95% CI)
<b>Males</b>						
Under 18.5	10 (34.5)	2.48 (1.14-5.37)	8 (27.6)	3.07 (1.33-7.09)	6 (24.0)	6.10 (2.38-15.65)
18.5-24.9	361 (17.5)	1 <sup>c</sup>	233 (11.3)	1 <sup>c</sup>	88 (4.9)	1 <sup>c</sup>
25.0-29.9	284 (17.9)	1.03 (0.87-1.22)	174 (11.0)	0.97 (0.79-1.20)	56 (4.1)	0.83 (0.59-1.17)
≥ 30	76 (22.1)	1.34 (1.01-1.76)	51 (14.8)	1.39 (1.00-1.93)	20 (6.9)	1.44 (0.87-2.38)
<b>Females</b>						
Under 18.5	37 (25.9)	1.09 (0.75-1.60)	26 (18.2)	1.16 (0.75-1.80)	12 (10.2)	1.32 (0.71-2.43)
18.5-24.9	713 (24.5)	1 <sup>c</sup>	472 (16.0)	1 <sup>c</sup>	192 (7.9)	1 <sup>c</sup>
25.0-29.9	261 (28.7)	1.26 (1.07-1.49)	170 (18.7)	1.24 (1.02-1.51)	74 (10.3)	1.33 (1.00-1.76)
≥ 30	112 (29.6)	1.32 (1.04-1.67)	80 (21.2)	1.42 (1.09-1.86)	28 (9.5)	1.22 (0.81-1.86)

<sup>a</sup>Vs. no depression, HSCl-score < 1.55. <sup>b</sup>Logistic regression analysis, adjusted for level of education (basic ≤ 9 years, secondary 10-12 years and tertiary > 12 years level), marital status (not married or cohabiting/married or cohabiting), chronic somatic diseases (yes/no), smoking (yes/no), use of alcohol (light < 15 g/day, moderate 15-40 g/day and heavy > 40 g/day), physical activity (regular/nonregular) and dietary habits (healthy/unhealthy) at the age of 31 years. <sup>c</sup>Reference category.

### ***5.3.3 Abdominal obesity at 31 years and depression at 31 years***

Among men, abdominal obesity, as estimated by the WHR 85<sup>th</sup> percentile, was significantly associated with depression at all HSCL-25 cut-off points (Table 8; III: Table 3). Compared to subjects with no abdominal obesity, the abdominally obese men had a 1.67- to 2.64-fold likelihood of depressive symptoms. After adjusting for confounders the association remained significant at the cut-off point 2.01.

After adjusting for confounders, obese men had a 2.07-fold probability of physician-diagnosed depression (adjusted OR 2.07, 95%CI 1.23-3.47) and the proportion of those who used antidepressants was 2.63-fold higher among obese men compared to men without abdominal obesity (adjusted OR 2.63, 95%CI 1.33-5.21). In female subjects, no association was found between abdominal obesity and depression after adjusting for confounders (Table 8; III: Table 3).

### ***5.3.4 Weight change and depression at 31 years***

As seen in Table 9 (III: Table 4), no associations between weight change and depression were found among males. Among females, always overweight subjects had 1.5 times higher likelihood of current depressive symptoms in the HSCL-questionnaire at all cut-off points compared to normal-weighted subjects. The result was significant after adjusting for confounders at cut-off points 1.55 and 1.75 (Table 9; III: Table 4). The proportion of those who used antidepressants was 2.17-fold higher among women who had gained weight compared to women who had stayed normal-weighted (adjusted OR 2.17, 95%CI 1.28-3.68). Weight gain or being always overweight was not associated with physician-diagnosed depression among women.

Table 8. Obesity measured by the waist-to-hip ratio and depression at the age of 31 years in the Northern Finland 1966 Birth Cohort (III: Table 3).

WHR	HSCL depression, cut-off 1.55 <sup>a</sup>			HSCL depression, cut-off 1.75 <sup>a</sup>			HSCL depression, cut-off 2.01 <sup>a</sup>		
	N (%)	OR (95% CI)	Adjusted Odds Ratio <sup>b</sup> OR (95% CI)	N (%)	OR (95% CI)	Adjusted Odds Ratio <sup>b</sup> OR (95% CI)	N (%)	OR (95% CI)	Adjusted Odds Ratio <sup>b</sup> OR (95% CI)
<b>Males</b>									
WHR at 31 years									
Below 85%	367 (15.4)	1 <sup>c</sup>		224 (9.4)	1 <sup>c</sup>		74 (3.6)	1 <sup>c</sup>	
Above 85%	97 (23.3)	1.67 (1.29-2.16)	1.26 (0.95-1.67)	68 (16.3)	1.91 (1.42-2.57)	1.38 (0.99-1.93)	31 (8.9)	1.64 (1.71-4.08)	1.76 (1.08-2.88)
<b>Females</b>									
WHR at 31 years									
Below 85%	611 (24.8)	1 <sup>c</sup>		400 (16.3)	1 <sup>c</sup>		166 (8.2)	1 <sup>c</sup>	
Above 85%	116 (26.7)	1.10 (0.88-1.39)	0.99 (0.79-1.27)	73 (16.8)	1.06 (0.80-1.40)	0.96 (0.72-1.29)	33 (9.4)	1.16 (0.78-1.71)	0.99 (0.65-1.51)

<sup>a</sup>Vs. no depression, HSCL-score < 1.55. <sup>b</sup>Logistic regression analysis, adjusted for level of education (basic ≤ 9 years, secondary 10-12 years and tertiary > 12 years level), marital status (not married or cohabiting/married or cohabiting), chronic somatic diseases (yes/no), smoking (yes/no), use of alcohol (light < 15 g/day, moderate 15-40 g/day and heavy > 40 g/day), physical activity (regular/nonregular) and dietary habits (healthy/unhealthy) at the age of 31 years. <sup>c</sup>Reference category.

Table 9. Weight change from 14 to 31 years and depression at the age of 31 years in the Northern Finland 1966 Birth Cohort (III: Table 4).

Weight change	HSCL depression, cut-off 1.55 <sup>a</sup>			HSCL depression, cut-off 1.75 <sup>a</sup>			HSCL depression, cut-off 2.01 <sup>a</sup>		
	N (%)	Crude Odds Ratio OR (95% CI)	Adjusted Odds Ratio <sup>b</sup> OR (95% CI)	N (%)	Crude Odds Ratio OR (95% CI)	Adjusted Odds Ratio <sup>b</sup> OR (95% CI)	N (%)	Crude Odds Ratio OR (95% CI)	Adjusted Odds Ratio <sup>b</sup> OR (95% CI)
<b>Males</b>									
Always overweight <sup>e</sup>	80 (18.2)	1.04 (0.79-1.37)	1.01 (0.76-1.34)	51 (11.6)	1.03 (0.74-1.43)	1.02 (0.72-1.44)	19 (5.0)	1.00 (0.60-1.68)	0.99 (0.58-1.69)
Gained weight <sup>d</sup>	221 (17.6)	1.00 (0.83-1.21)	1.01 (0.83-1.23)	135 (10.8)	0.95 (0.76-1.20)	0.97 (0.76-1.23)	41 (3.8)	0.75 (0.60-1.68)	0.76 (0.51-1.12)
Others <sup>e</sup>	308 (17.6)	1 <sup>c</sup>		198 (11.3)	1 <sup>c</sup>		76 (5.0)	1 <sup>c</sup>	
<b>Females</b>									
Always overweight <sup>e</sup>	129 (31.5)	1.45 (1.15-1.82)	1.41 (1.12-1.78)	84 (20.5)	1.46 (1.12-1.91)	1.40 (1.06-1.85)	34 (10.8)	1.47 (0.99-2.17)	1.44 (0.96-2.17)
Gained weight <sup>d</sup>	195 (26.5)	1.13 (0.94-1.37)	1.13 (0.93-1.37)	135 (18.3)	1.22 (0.98-1.51)	1.19 (0.95-1.48)	54 (9.1)	1.21 (0.88-1.66)	1.25 (0.90-1.74)
Others <sup>e</sup>	634 (24.1)	1 <sup>f</sup>		409 (15.6)	1 <sup>f</sup>		165 (7.6)	1 <sup>f</sup>	

<sup>a</sup>Vs. no depression, HSCL-score < 1.55. <sup>b</sup>Logistic regression analysis, adjusted for father's social class (I-II=highest, III-IV=lowest, V=farmers), family type (single-parent, two-parent family), smoking (yes/no), use of alcohol (yes/no) and chronic somatic diseases (yes/no) at the age of 14 years. <sup>c</sup>BMI at 14 years ≥ 85<sup>th</sup> percentile and BMI at 31 years ≥ 25.0 kg/m<sup>2</sup>. <sup>d</sup>BMI at 14 years < 85<sup>th</sup> percentile and BMI at 31 years ≥ 25.0 kg/m<sup>2</sup>. <sup>e</sup>Reference category.

## 5.4 Metabolic syndrome, depression and anxiety

The prevalence of the metabolic syndrome was 5.8% in the whole sample (6.8% in males and 4.8% in females,  $p=0.002$ , Fisher's exact test). The prevalence of depression was 13.5% (10.4% in males and 16.5% in females,  $p<0.001$ , Fisher's exact test), and the prevalence of anxiety 8.1% (6.7% and 9.5%,  $p<0.001$ , Fisher's exact test). The mean HSCL-25 depression score was 1.36,  $SD \pm 0.37$  (1.31,  $SD \pm 0.33$  in males and 1.41,  $SD \pm 0.39$  in females) and the mean HSCL-25 anxiety score 1.31,  $SD \pm 0.31$  (1.28,  $SD \pm 0.29$  in males and 1.34,  $SD \pm 0.33$  in females). The inter-correlation between depressive and anxiety symptoms was 0.668 (0.663 in males and 0.662 in females).

The components of the metabolic syndrome, HSCL-25 depression and HSCL-25 anxiety were first analysed as continuous measures. As seen in Table 10 (IV: Table 1), Spearman's partial correlation coefficients between the components of the metabolic syndrome and depressive and anxiety symptoms as continuous measures were low, varying from -0.062 to 0.041 for depression and from -0.033 to 0.046 for anxiety. The positive correlation between glucose level and psychological distress vanished when subjects with angina pectoris or diabetes mellitus were excluded from the analyses.

*Table 10. Spearman's partial correlations of the components of the metabolic syndrome with anxiety depressive and symptoms as continuous measures in the Northern Finland 1966 Birth Cohort (IV: Table 1).*

Variable <sup>a</sup>	Mean	SD	HSCL depression		HSCL anxiety	
			correlation <sup>b</sup>	p-value	correlation <sup>b</sup>	p-value
Waist (cm)	83.81	12.13	0.024	0.071	0.017	0.20
Triglycerides (mmol/L)	1.17	0.72	0.022	0.11	0.035	0.011
HDL-cholesterol (mmol/L)	1.55	0.38	0.015	0.28	-0.005	0.71
Glucose (mmol/L)	5.05	0.38	0.041	0.003	0.046	0.001
Systolic blood pressure (mm Hg)	125.17	13.50	-0.062	<0.001	-0.033	0.013
Diastolic blood pressure (mm Hg)	77.65	11.65	-0.033	0.013	-0.009	0.48

<sup>a</sup>N = 5287-5691. <sup>b</sup>Adjusted by gender.

When multivariate binary logistic regression analyses were used, metabolic syndrome did not associate with depression or anxiety (Table 11; IV: Table 2). Of the components of the metabolic syndrome high waist circumference (>102 cm in males and >88 cm in females) associated with depression (OR 1.30, 95%CI 1.05-1.61), but the association vanished when adjusted for gender, smoking, alcohol consumption, marital status, level of education and physical activity. On the other hand, high blood pressure associated inversely with depression (adjusted OR=0.80, 95%CI 0.66-0.97). The results regarding Table 11 (IV: Table 2) did not change substantially if subjects with angina pectoris or diabetes mellitus were excluded from the analyses.

Table 11. The crude and adjusted<sup>d</sup> odds ratios of depression and anxiety symptoms in subjects with metabolic risk factors and metabolic syndrome in the Northern Finland 1966 Birth Cohort (IV: Table 2).

Variable	HSCCL-25 depression (cut-off 1.75)				HSCCL-25 anxiety (cut-off 1.75)							
	c/d	N (%)	Crude Odds Ratio		Adjusted Odds Ratio		c/d	N (%)	Crude Odds Ratio		Adjusted Odds Ratio	
			OR	95% CI	OR	95% CI			OR	95% CI	OR	95% CI
Waist > 88/102	736/5648	120 (16.3)	1.30	1.05-1.61	1.06	0.85-1.33	736/5648	65 (8.8)	1.12	0.85-1.47	0.82	0.61-1.10
Trigly. ≥ 1.69	916/5341	121 (13.2)	1.01	0.82-1.25	0.98	0.78-1.23	916/5341	80 (8.7)	1.15	0.89-1.48	1.03	0.78-1.36
HDL < 1.04/1.29	609/5402	77 (12.6)	0.94	0.73-1.22	0.87	0.67-1.13	609/5402	45 (7.4)	0.92	0.67-1.26	0.87	0.63-1.21
BP ≥ 135/85	1762/5667	197 (11.2)	0.74	0.63-0.88	0.80	0.66-0.97	1762/5667	124 (7.0)	0.82	0.66-1.01	0.82	0.65-1.04
Gluc. ≥ 6.1	151/5322	24 (15.9)	1.26	0.81-1.97	1.17	0.73-1.89	151/5322	10 (6.6)	0.82	0.43-1.58	0.60	0.29-1.26
MS <sup>b</sup>	325/5691	39 (12.0)	0.87	0.62-1.23	0.76	0.53-1.09	325/5691	23 (7.1)	0.86	0.56-1.32	0.71	0.45-1.12

<sup>a</sup>Adjusted by gender, smoking (yes/no), alcohol consumption (light < 15 g/day, moderate 15-40 g/day and heavy > 40 g/day), marital status (not married or cohabiting/married or cohabiting), level of education (basic ≤ 9 years, secondary 10-12 years and tertiary > 12 years level) and physical activity (regular/non-regular).

<sup>b</sup>Metabolic syndrome, A TP III criteria. <sup>c</sup>Total number of subjects fulfilling the criteria. <sup>d</sup>Number of subjects whose data were available.

## **6 Discussion**

### **6.1 Main findings**

The findings of study I differed among the two genders. Males with a ponderal index in the lowest 5 percentile showed an elevated risk of physician-diagnosed depression in young adulthood. On the contrary, among women high birth weight and high ponderal index were found to be associated with a higher risk of self-reported depressive symptoms at the age of 31 years.

The results of study II showed that adolescents with delayed menarche had two- to three-fold greater likelihood of depression at the age of 31 years than other girls. The result was essentially the same by all the three indicators of depression: the HSCL-25, the use of antidepressants and depression diagnosed by a physician. However, two out of the three indicators of depression were not significantly associated with this phenomenon after adjusting for confounders.

In study III teenage obesity was shown to be associated with depressive symptoms at the age of 31 years. In addition, abdominal obesity among 31-year-old males was associated with increased likelihood of depression assessed by three different indicators of depression. Further, female subjects who were overweight/obese both at the age of 14 and 31 years had an elevated risk of having depressive symptoms at the age of 31 years.

As shown in study IV, no clear association was found between the metabolic syndrome and symptoms of depression and anxiety in the study population of 31-year-old young adults.

### **6.2 Discussion of the results**

#### ***6.2.1 Birth weight and depression (I)***

Among men, our finding that small body size at birth measured by ponderal index is associated with lifetime depression is in line with the findings of Gale and Martyn

(2004), as they found that men who weighed < 2500 g at birth were more likely to report a history of depression at the age of 26 years compared with men of normal birth weight. Further, in the Hertfordshire birth cohort study of 882 subjects at the age of 68 years (Thompson *et al.* 2001), an association was found among men between low birth weight and elevated risk of later depression measured by the Geriatric Depression Scale. The finding is in line with our study, although in this study the association between small body size and depression among men was only found in the case of very low ponderal index. In addition, in the Hertfordshire birth cohort study it was not possible to adjust for many potential confounding factors, e.g. maternal depression. In a Danish study of 12 270 men (Osler *et al.* 2005) no relation between birth dimensions and later hospital-treated depression was found. Compared with the present study, the measurement of depression may have been more valid since the diagnoses were based on hospital case note diagnoses confirmed by a psychiatrist. However, as only hospital-treated depressions were included, the results may not be generalized to the whole population as most of the people suffering from depression are not treated in hospital. In another recent study of the Aberdeen Children of the 1950s, low birth weight for gestational age was associated with adult psychological distress measured by four items from the 12-item General Health Questionnaire (Wiles *et al.* 2005). The authors suggested that children born at full term but having low birth weight are at higher risk for psychological distress in adulthood. The study was conducted pooling both genders, so we do not know whether there were differences between genders, as was found in the present study.

Our finding that women with high birth weight had a higher likelihood of self-reported depressive symptoms at the age of 31 years is not in line with the 1970 British Cohort Study, where women whose birth weight was  $\leq 3000$  g had an increased risk of depression measured by the 12-item General Health Questionnaire at the age of 26 years. The birth weight of these women, however, was not associated with self-reported history of depression at the age of 26 years, which is in line with our findings of birth weight and physician-diagnosed lifetime depression (Gale & Martyn 2004). Furthermore, in the Hertfordshire birth cohort study, an association between low birth weight and risk of later depression was not found among women (Thompson *et al.* 2001). However, the differences in depression measures in these studies may have contributed to the varying findings.

One important limitation in the previous studies on the association between birth weight and depression was that it was not possible to take into account maternal depression during pregnancy. In addition, to the best of our knowledge, there are no studies on high birth weight and later depression; the main focus has previously been on exploring whether low birth weight is associated with later depression.

As far as the author knows, the finding that high birth weight is associated with later depression has not been reported earlier. Studies investigating birth weight, cardiovascular diseases and diabetes mellitus have found that both low and high birth weight may cause an increased risk; the association has been found to be J- or U-shaped (Osmond *et al.* 1993, Wei *et al.* 2003). As depression has also been found to be associated with diabetes (Musselmann *et al.* 2003) and cardiovascular diseases (Carney *et al.* 2002), there may be a common risk factor which may have its origin in foetal life.

The results of this study differ by gender; among women high birth weight and high ponderal index predicted later depression, while among men thinness at birth measured

by ponderal index at birth was associated with later depression. Gender differences have also been found in earlier studies on this topic. Thompson *et al.* (2001) found an association between low birth weight and later depression among men, but not among women, while Gale and Martyn (2004) reported an increased risk of depression among women aged 26 years, but not among men. Based on these findings, there may be a gender difference in the foetal origins of depression between men and women.

Mother's depression during pregnancy may lead to a lower birth weight of the offspring (Paarlberg *et al.* 1999), which was also found in the present study. Maternal depression is a stressful condition, which may affect the hypothalamic-pituitary-adrenal axis of the child (Goodman & Gotlib 1999). In this study, subjects whose mothers had been depressed during pregnancy had a significantly higher risk of depression at the age of 31 years. The finding of a positive association between low ponderal index and later depression in men and high birth weight and later depression in women did not disappear when maternal depression was adjusted for. In addition, mother's depression may have an influence on the developmental psychosocial environment of the child and constitute a risk factor for later depression.

### ***6.2.2 Age at menarche and depression (II)***

There are very few longitudinal studies exploring the association between age at menarche and later depression and no earlier studies regarding young adults. Concerning later age there is only one earlier study on the association between menarcheal age and later depression in adulthood. Harlow *et al.* (1999) conducted a study on premenopausal women and found in contrast to this study that current depressive symptoms increased when the age at menarche decreased. However, the finding was not observed for past depression. In addition the subjects in the study of Harlow *et al.* were aged 36 to 44 years, 6 to 14 years older than in this study.

The existing findings with regard to the association between menarcheal age and depression in adolescent girls are contradictory. The findings in several earlier studies suggest that girls with early menarche and early pubertal development have a higher risk of depression and other psychopathology in adolescence (Graber *et al.* 1997, Hayward *et al.* 1999, Ge *et al.* 2001, Stice *et al.* 2001, Kaltiala-Heino *et al.* 2003). In contrast to this, and in line with the findings in the present study, Bisaga *et al.* (2002) found that late menarche was associated with elevated depressive symptoms among high school girls when chronological age and other risk factors were controlled for. It should be kept in mind, however, that none of these studies on adolescent females have followed the subjects over the years; previous longitudinal studies in this area are thus lacking.

The association between age at menarche and psychopathology has been proposed to be due to hormonal and morphological changes, genetic factors as well as the difficulty in transition to adolescence (Angold *et al.* 1999, Silberg *et al.* 1999). Stice *et al.* (2001) have proposed the reason to be that the girls may be confronted by new stressors and expectations because of their fast maturation while they are not at all psychologically ready. According to Cyranowski *et al.* (2000), adolescent depression can be explained by the interaction of various biological and social factors.

One possible explanation for the findings in the present study may be the protective effect of estrogen. Serum estrogen levels have been suggested to be higher for several years among women with early menarche compared with women with later menarche (Apter *et al.* 1989, Madigan *et al.* 1998). As reviewed by McEwen and Alves (1999), estrogen has neuroprotective effects in the brain and it regulates the serotonergic system. In addition, estrogen has been found to be effective in reducing depression symptoms in postpartum depression (Ahokas *et al.* 2001) and to be an effective treatment of depression among perimenopausal women (Soares *et al.* 2001, Rasgon *et al.* 2002). Women with early menarche may thus in the long run benefit from the positive effects of estrogen on the central nervous system. However, several other individual protective as well as risk factors - biological, psychological and social - such as childhood adverse experiences related to depression must be taken into account in further studies. In addition, the subjects may possibly have had other health problems in adolescence, such as eating disorders, which might have led to late menarche and might confound this relationship. In this study the physical health of the subjects in adolescence was not studied.

Changes in estrogen levels occur in menarcheal age, premenstrually and especially in the postpartum period, and thereafter through perimenopause. These periods are also characterized by mood changes (Burt & Stein 2000). Based on the present study, from a lifecourse perspective higher estrogen levels may be a protective factor against depression. Several possible confounders, both biological and psychosocial, could not explain the main finding of the association of late menarche and later depression. On the other hand, depression in adolescence could not be assessed, but the findings of the study add an important consideration to earlier literature, suggesting that adolescents with delayed menarche might have an increased risk of depression already during early adulthood.

### **6.2.3 Obesity and depression (III)**

The finding that obesity at the age of 14 years predicted depressive symptoms is in line with the earlier results of Roberts *et al.* (2000) and Roberts *et al.* (2003). In addition, depression in childhood and adolescence has been found to be associated with an increased BMI in adulthood, even when participants with childhood obesity were excluded at baseline (Pine *et al.* 2001). Thus, there may be a bi-directional relationship between adolescent obesity/depression and adulthood obesity/depression. However, in this study we did not have the possibility to assess depression in adolescence. Based on this study it is impossible to assess whether it is merely depression in adolescence which predicts recurrent/persistent depressive symptoms at the age of 31 years, rather than obesity at the age of 14 years. Among adolescents a thin and beautiful body is idealized, especially among girls (Toro *et al.* 2005). As body image, the individual, subjective sense of the body, develops in adolescence, overweight or obesity may easily have a negative influence on subjective well-being at that vulnerable age (Rierdan & Koff 1997, Pesa *et al.* 2000). In addition, early onset of obesity has been suggested to increase the risk of body dissatisfaction and impair self-esteem later in life (Wardle *et al.* 2002). Further, in a

recent cross-sectional study among adolescents depression has been found to be associated with obesity (Richardson *et al.* 2006).

In the cross-sectional analyses at the age of 31 years, underweight men (BMI under 18.5 kg/m<sup>2</sup>) were more commonly depressed than those with normal weight at the age of 31 years; there was an increase in the ORs with increasing severity of depressive symptoms. Carpenter *et al.* (2000) found an association among men between being underweight and having an increased risk of clinical depression and suicidal tendencies. In addition, in a study conducted by Kress *et al.* (2006), an association between being underweight and depressive symptoms was found among men. Thus, being underweight and male may have a special psychological meaning: men may prefer a large, muscular body rather than a thin one, and having a low body weight may be associated with a poorer body image and may also increase the risk for depression. In addition, as weight loss is one possible symptom of depression the possibility of bi-directional causality must be taken into consideration. Depression may cause weight loss by reduced appetite, being underweight may thus also be a consequence of depression.

The association between abdominal obesity and depression in men was found by all three depression indicators. A possible physiological mechanism behind abdominal obesity and depression may be stress (Rosmond *et al.* 1998, Faith *et al.* 2002, Bhagwagar *et al.* 2003, Stunkard *et al.* 2003) and cortisol secretion which is regulated by the hypothalamic-pituitary-adrenal (HPA) axis (Faith *et al.* 2002, Stunkard *et al.* 2003). Increased levels of serum cortisol have been observed both during stress (Rosmond *et al.* 1998) and depression (Bhagwagar *et al.* 2003).

As a way to cope with stress some individuals are prone to consume alcohol and eat unhealthy foods (Laitinen *et al.* 2002), which is associated with abdominal obesity (Laitinen *et al.* 2004), and depression (Greenfield *et al.* 2002). This was supported in this study by the observation that crude odds ratios decreased when analyses were controlled for unhealthy behaviours. It has been shown that physical inactivity is closely related to the development of abdominal obesity (Laws *et al.* 1990, Trichopoulou *et al.* 2001, Laitinen *et al.* 2004), and physical inactivity may decrease psychological well-being (Sexton *et al.* 2001). Regular physical activity has been suggested to be associated with psychological well-being (Hassmén *et al.* 2000, Leppämäki *et al.* 2006). In addition, unhealthy dietary habits involving for example infrequent consumption of fruit, berries and vegetables have been shown to be associated with abdominal obesity (Laitinen *et al.* 2004). These foods contain a lot of folic acid, for example, and their low intake may predispose to psychiatric disorders such as depression (Alpert *et al.* 2000). Furthermore, infrequent consumption of fish resulting in a low intake of omega-3 fatty acids has been found to be associated with depression (Tanskanen *et al.* 2001, Timonen *et al.* 2004). On the other hand, depressed subjects may have poor appetite, and their diet might be inadequate and unbalanced. Abdominal obesity might thus be an indicator of unhealthy habits associated with depression, but the direction of the causality between abdominal obesity and depression cannot be exactly assessed in this cross-sectional study setting.

When the influence of weight change on depression was studied, it was found that always overweight female subjects had 1.5 times more commonly current depressive symptoms in the HSCL questionnaire at all cut-off points compared to normal-weighted subjects. Among men there were no associations. The finding supports the hypothesis that

being overweight or obese may have a greater influence on well-being among women than among men.

The use of antidepressants was quite rare compared to the result from the HSCL questionnaire. When assessing depression by the HSCL-25, the prevalence of depressive symptoms was 12% in males and 17% in females, while only 2% of males and females used antidepressants. There is a strong likelihood that the subjects using antidepressants had more severe depression than those having depressive symptoms measured by the HSCL-25. That is also why the results are somewhat inconsistent depending on the assessment of depression. In addition, an association between weight gain and depression was found among women who used antidepressants. Some antidepressive drugs such as tricyclics and mirtazapine often produce weight gain, while SSRIs do not cause weight gain (Aronne & Segal 2003). The proportion of antidepressant users was also high among men with obesity, measured both by the BMI and WHR. The antidepressants may have contributed to the increase in obesity, although in this study most of the subjects who reported the type of the antidepressant did not use drugs causing weight gain. Thus, when treating depression with antidepressive drugs it is important to take into account the possible influence on weight and to choose a drug which does not cause weight gain.

#### ***6.2.4 Metabolic syndrome and depression (IV)***

The overall prevalence of the metabolic syndrome among the study subjects was lower than in earlier observations in young adults (6.8% vs. 8.4% in men, 4.8% vs. 8.4% in women) (Kinder *et al.* 2004). Compared to earlier studies on this topic, the results regarding the metabolic syndrome and depression were to some extent controversial. Kinder *et al.* (2004) found in a cross-sectional study of 3186 males and 3003 females aged 17 to 39 that the prevalence of the metabolic syndrome was elevated among women with a life-time history of depression as assessed by the Diagnostic Interview Schedule. It must, however, be remembered that the definition of depression was different from our definition. In men, Kinder *et al.* (2004) found no association between metabolic syndrome and depression, which is in line with our findings. Furthermore, our findings also disagree with those of a study concerning middle-aged women, in which depressive symptoms were associated with the co-occurring metabolic syndrome; in addition, metabolic syndrome at baseline predicted increased anxiety seven years later (Räikkönen *et al.* 2002). However, the latter study was based on middle-aged subjects, among whom the presence of other physical diseases, such as coronary artery disease, might have affected the relationship between metabolic syndrome and psychological distress.

In the present study, of the components of the metabolic syndrome, blood pressure associated inversely with depression when analysed as a continuous measure even after adjusting for confounders. A growing body of earlier research has reported the independent role of depression in predicting the onset of cardiovascular disease (Katon *et al.* 2003, Lett *et al.* 2004). Since cardiovascular disease is a hypertension-related condition, it is reasonable to hypothesize that depression may also be associated with hypertension. However, the findings regarding the relationship between depression and hypertension have been controversial (Barrett-Connor and Palinkas 1994, Meyer *et al.*

2004, Scalco *et al.* 2005), albeit recent follow-up studies indicate that preceding depression predicts later hypertension (Jonas *et al.* 1997, Davidson *et al.* 2000, Meyer *et al.* 2004). Possible explanations for our findings might be the young age of the cohort members among whom the prevalence of hypertension is relatively low. In addition, our research frame was cross-sectional in nature, and as hypertension develops over the course of years, the strongest connection between depression and hypertension may come out in later life. For example, the follow-up time in earlier studies showing a positive association between antecedent depression and later hypertension was 5 to 16 years (Jonas *et al.* 1997, Davidson *et al.* 2000, Meyer *et al.* 2004).

This study showed a positive correlation between glucose level and depression. With regard to anxiety, a positive correlation was found concerning triglyceride and glucose levels, and a negative correlation regarding systolic blood pressure. Albeit being statistically significant, it must, however, be emphasized that these correlations were very small per se. In addition, the correlations between glucose level and depression and glucose level and anxiety vanished when subjects with angina pectoris and diabetes mellitus were excluded from the analyses, which is not surprising taking into account that the association between diabetes and depression is already well established (Musselmann *et al.* 2003). Thus, the findings of the present study are inconsistent with those of male twin data showing an association between the individual components of the metabolic syndrome and depression (McCaffery *et al.* 2003). However, the study subjects in the twin study were middle-aged, which is likely to have affected the result.

## 6.3 Methodological considerations

### 6.3.1 Study participants

The participation rate in the study was high. During the 14-year follow-up, 11 780 subjects were alive and of them only 14 could not be traced. 11 010 subjects responded of the postal inquiry, which is 93.6% of the cohort. During the 31-year follow-up in 1997-98, a postal inquiry was sent to 11 541 members of the cohort, and 75.3% of the cohort members responded. Of the 8465 subjects invited to the clinical examination at the age of 31 years, 70.9% (5999 subjects) participated.

In study I the eligible study population was compared with the reminding alive members (29%) of the cohort at the age of 31 years. There were no significant differences in birth weight between participants and non-participants of cohort members. Non-participants as compared to participants were, however, more commonly males than females (60% vs. 48%). In study II, 12.6% of the subjects did not participate due to information missing on age at menarche or on depression. In study III, 25.6% of the subjects of whom both weight and height at the age of 14 years was known did not participate due to information of depression was missing. Obesity was, however, more prevalent among non-participating males than among participating males (7.0% obese vs. 5.0% obese). In females no significant differences were found. In study IV, 5.0% of the subjects participating the clinical examination were not included in the analyses due to

they had no data available on depression and anxiety, did not have data available on more than two components of the metabolic syndrome, had not fasted overnight before the blood samples were taken or were pregnant.

### ***6.3.2 Strengths of the study***

The major strength of this study was its design: a large, population-based prospective birth-cohort follow-up study. The Northern Finland 1966 Birth Cohort includes an unselected birth cohort of 12 058 live births, covering 96.3% of all deliveries in Northern Finland in the year 1966. Since then, data on biological, socioeconomic and health conditions, living habits and family characteristics of the cohort members have been collected prospectively from antenatal stages up to the age of 31 years (Rantakallio 1969, 1988). The study population consists exclusively of Caucasians, selection bias being thus unlikely.

The prospective follow-up study gave the opportunity to examine longitudinally the associations between birth weight, menarche and obesity at the age of 14 years and depression at the age of 31 years. Since there were a lot of data collected during a 31-year follow-up time, it was possible to use several confounding factors which could influence these associations. In this study it was possible to use for the first time data on maternal depression during pregnancy as a confounding factor when studying the association between birth weight and depression.

Depression could be measured in three different ways: by using the HSCL-25 and the use of antidepressants as a measure of current depression and by using self-reported physician-diagnosed depression as a measure of lifetime depression. The HSCL-25 has previously been found to be a valid instrument for screening psychiatric cases in the Nordic countries including Finland, and in this database, too (Joukamaa *et al.* 1994, Veijola *et al.* 2003). The HSCL-25 has also been found to be a moderate tool in a two-stage field study with structured interview for DSM-III-R as a diagnostic instrument (Veijola *et al.* 2003), and comparison with the GHQ has shown comparable sensitivity and specificity (Goldberg *et al.* 1976). Compared with the Montgomery-Åsberg-Depression Rating Scale as well as with the diagnostic criteria of depression, HSCL-25 was found to be a sensitive case-finder of depressive disorders (Frojdth *et al.* 2004).

Moreover, all the subjects of the present study were young 31-year-old adults, the age at which the prevalence of cardiovascular diseases is low. Thus, in studying the association between metabolic abnormalities and depression the possibility of the relationship being affected by cardiovascular diseases was low.

### ***6.3.3 Limitations of the study***

The present study includes several limitations. Despite the longitudinal study setting there was no information on depression in adolescence, as depression was not measured during the 14-year follow-up study. Thus, it was not possible to assess whether depression in adolescence predicts later depression or to study the association between age at menarche

and depression in adolescence. In addition, due to the lack of information on adolescent depression, the directionality of the associations between obesity in adolescence and in young adulthood at the age of 31 years could not be truly determined. It was also not possible to investigate whether depression predicts metabolic abnormalities or the metabolic syndrome. Further, it was not possible to use adolescent depression as a confounding factor.

In addition, self-report questionnaires, such as HSCL-25, give very limited data on lifetime depression. It provides information on depressive symptoms at one time point. Depressive symptoms may be predictive of major depression, but they are not the equivalent of physician-diagnosed depression. Thus, using a clinical interview would have been a more valid instrument in assessing depression. In addition, by using the HSCL-25 questionnaire as a measure of depression, comorbidity of other mental disorders could not be assessed.

The use of antidepressive drugs was also a measure of current depression. In addition, this measure of depression was also self-reported, and may thus not be valid. Subjects may not have reported all antidepressive drugs they had used, or they may have simultaneously used other psychotropic drugs such as neuroleptics. In addition, antidepressive drugs may also be used in other indications than depression, for example in social phobia or obsessive compulsive disorder. Lifetime depression was assessed by asking the subjects whether they had ever been diagnosed by a physician as having depression. This assessment of depression was self-reported as well, and it was not possible to determine at what time point the subject had been depressed and how severe the depression had been. Furthermore, the used depression assessments “the use of antidepressants” and “the physician-diagnosed depression can be possible for only part of the depressive subjects as there exists subjects that are not diagnosed or treated by a physician although being depressed. Thus, the found risk estimations may be conservative.

Data on hormonal profiles such as oestrogen and testosterone levels were lacking for purposes of this study. It was not possible to find out if there was an association between oestrogen levels and depression, not longitudinally or cross-sectionally. For this reason it was not possible to make any valid biological inferences from the reported findings other than to observe that the findings deserve prospective investigation.

Furthermore, age at menarche was asked retrospectively and it may therefore not be exact. It has, however, been shown that women remember their first menstrual bleeding quite well (Bean *et al.* 1979, Madrigal 1991). In addition, the validity of self-reported body weight and height data at the age of 14 years could not be evaluated in this cohort. It is probable that obese subjects might have underreported their body weight. Because we used an internal definition based on percentiles in classifying overweight and obesity, this underreporting probably does not cause classification bias. In addition, obesity was slightly more common among subjects lost from the follow-up than among participants. As both the more obese and the more depressed may be at risk of not attending surveys (Andersson & Rossner 1997, Sonawalla *et al.* 2002), this may limit the generalization of the results to the whole population.

## **7 Conclusions**

### **7.1 Main conclusions of the results**

This thesis adds new considerations to the literature regarding depression in young adults with special attention to birth weight, age at menarche, obesity and metabolic syndrome. Both longitudinal and cross-sectional research frames were used in order to highlight the relationship of these biological factors with depression.

In the longitudinal study design high birth weight, late age at menarche, adolescent obesity and weight gain among females increased the risk of depression at the age of 31 years. These results suggest that biological factors exist in adolescence and even at birth that may have an impact on later psychological well-being. However, as depression is considered a biopsychosocial disease and is usually caused by several aetiological factors affecting an individual's state of mind, many confounding factors may have affected these relationships between these biological factors and depression. Adolescence is a particularly sensitive time of life during which an individual meets many social, psychological and biological changes that may have a profound influence on mental health later in life.

In the cross-sectional study, risk of depression was higher among males with abdominal obesity. This higher risk may be explained by physiological mechanisms, but the impact of many psychosocial factors must be remembered. The finding that the metabolic syndrome showed no association with depression is interesting; due to the lack of studies on this topic, it also needs more research. As depressed subjects are at higher risk for cardiovascular diseases and diabetes mellitus, the possible common risk factors such as abdominal obesity should be better accommodated.

### **7.2 Clinical implications**

As depression in its different forms is a common public health problem causing a lot of suffering, often adding to working disabilities and complicating several somatic diseases,

the somatic features related to depression must also be taken into account when recognizing and treating both depression and physical diseases.

Obesity and overweight are also huge problems in western countries today. Based on the findings in this thesis, obesity in adolescence seems to be a risk factor for later psychological well-being. Therefore, careful attention should be paid to obesity and overweight among adolescents. It would be important to find ways of preventing obesity and overweight among children and adolescents, for example by guiding them towards healthier diets and by developing physical education at schools so as to make it more inspiring. These expedients against obesity should be carried out by parents, teachers and health care professionals.

Obesity in adulthood was also a risk factor for depression, with abdominal obesity among men being especially detrimental. Given the other medical hazards of obesity, in clinical practice special attention should be paid to abdominal obesity. Measuring the circumference of waist is an easy and cheap method and should nowadays be included in standard physical examinations in general practice and occupational health care. Based on the newest criteria of the metabolic syndrome (Alberti *et al.* 2006), abdominal obesity is probably the most important criterion of the metabolic syndrome, which is why recognizing individuals with abdominal obesity is important. In clinical practice, when treating patients with abdominal obesity, the potential of co-occurring depression should be observed. In addition, when treating patients with antidepressants, doctors should prefer antidepressants that do not cause weight gain.

With regard to age at menarche, there seems to be an increased risk of depression among subjects with delayed menarche. Thus, in clinical practice at clinics where subjects with late menarche are treated, it is important to take into account the increasing risk for later depression if the woman has had delayed menarche.

It is difficult to study separately the psychological and biological effects behind depression. However, information on causes and effects would be important in clinical practice and preventive work. Depression should be screened for more routinely by health care professionals both in general practice and special health care, especially among patients with other medical problems. Given the fact that many depressive patients are still without appropriate treatment, the threshold for the treatment of depression should be as low as possible.

### **7.3 Research implications**

Based on earlier studies and the findings from this study, the findings regarding birth weight and later depression are more or less ambiguous. There is still need for studies in large birth cohorts on whether birth weight is associated with later depression, taking also into account mother's depression during pregnancy. In future studies, more information should also be gathered on whether high birth weight is a risk factor for later depression. In addition, it would also be important to study the association between birth weight and depression by observing other pre- and perinatal factors together with birth weight.

The finding that late age at menarche was associated with depression in adulthood should be replicated in future research. In addition, serum oestrogen levels should be

measured and studied to see whether there is an association between serum oestrogen levels, age at menarche and depression.

There are many studies on obesity and depression, most of them cross-sectional, which is why longitudinal studies on the relationship between obesity and depression are needed. In longitudinal studies the possible causal relationship could be better understood, i.e., does obesity cause depression or vice versa. Measuring serum cortisol levels in studies on obesity and depression would clarify the possible hormonal relationships in this area. In addition, more information is needed on abdominal obesity and depression.

The metabolic syndrome and its effects on physical health have been investigated in many studies, but less is known about the metabolic syndrome and psychological health. Although an association between the metabolic syndrome and psychological distress in a sample of 31-year-old young adults was not found in this study, future studies should be carried out in large longitudinal population-based cohorts in order to better highlight the putative association of metabolic syndrome with depression. In addition, an important topic would be to assess mental disorders by more specific diagnostic criteria, and to take into consideration the comorbidity of mental disorders in different age cohorts. In general, when studying cardiovascular diseases and the risk factors for these diseases, depression should also be taken into account.

Being an ongoing study, the Northern Finland 1966 Birth Cohort database will in the future provide the possibility to explore longitudinally risk and protective factors of depression in older age groups. An interesting future research area would be to investigate whether depression at the age of 31 years is associated with obesity, metabolic abnormalities or somatic diseases among middle-aged individuals.

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## Original publications

- I Herva A, Pouta A, Hakko H, Läksy K, Joukamaa M & Veijola J. Birth weight and depression at 31 years age: the Northern Finland 1966 Birth Cohort Study. Manuscript.
- II Herva A, Jokelainen J, Pouta A, Veijola J, Timonen M, Karvonen JT & Joukamaa M (2004) Age at menarche and depression at the age of 31 years: findings from the Northern Finland 1966 birth cohort study. *J Psychosom Res* 57: 359-362.
- III Herva A, Laitinen J, Miettunen J, Veijola J, Karvonen JT, Läksy K & Joukamaa M (2006) Obesity and depression: results from the longitudinal Northern Finland 1966 Birth Cohort Study. *Int J Obes* 30: 520-527.
- IV Herva A, Räsänen P, Miettunen J, Timonen M, Läksy K, Veijola J, Laitinen J, Ruokonen A & Joukamaa M (2006) Co-occurrence of metabolic syndrome with depression and anxiety in young adults: the Northern Finland 1966 Birth Cohort Study. *Psychosom Med* 68: 213-216.

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893. Trias, Tuulikki (2006) Inter-twin and parent-twin relationships and mental health. A study of twins from adolescence to young adulthood
894. Ala-Mursula, Leena (2006) Employee worktime control and health
895. Turpeinen, Miia (2006) Cytochrome P450 enzymes—*in vitro*, *in vivo*, and *in silico* studies
896. Vuorialho, Arja (2006) Costs and effectiveness of hearing aid rehabilitation in the elderly
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901. Riekkö, Riitta (2006) Late dermal effects of breast cancer radiotherapy
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