THE ASSOCIATION BETWEEN ATOPIC DISORDERS AND DEPRESSION

The Northern Finland 1966 Birth Cohort Study

MARKKU TIMONEN

Department of Psychiatry,
Department of Public Health Science
and General Practice;
University of Oulu

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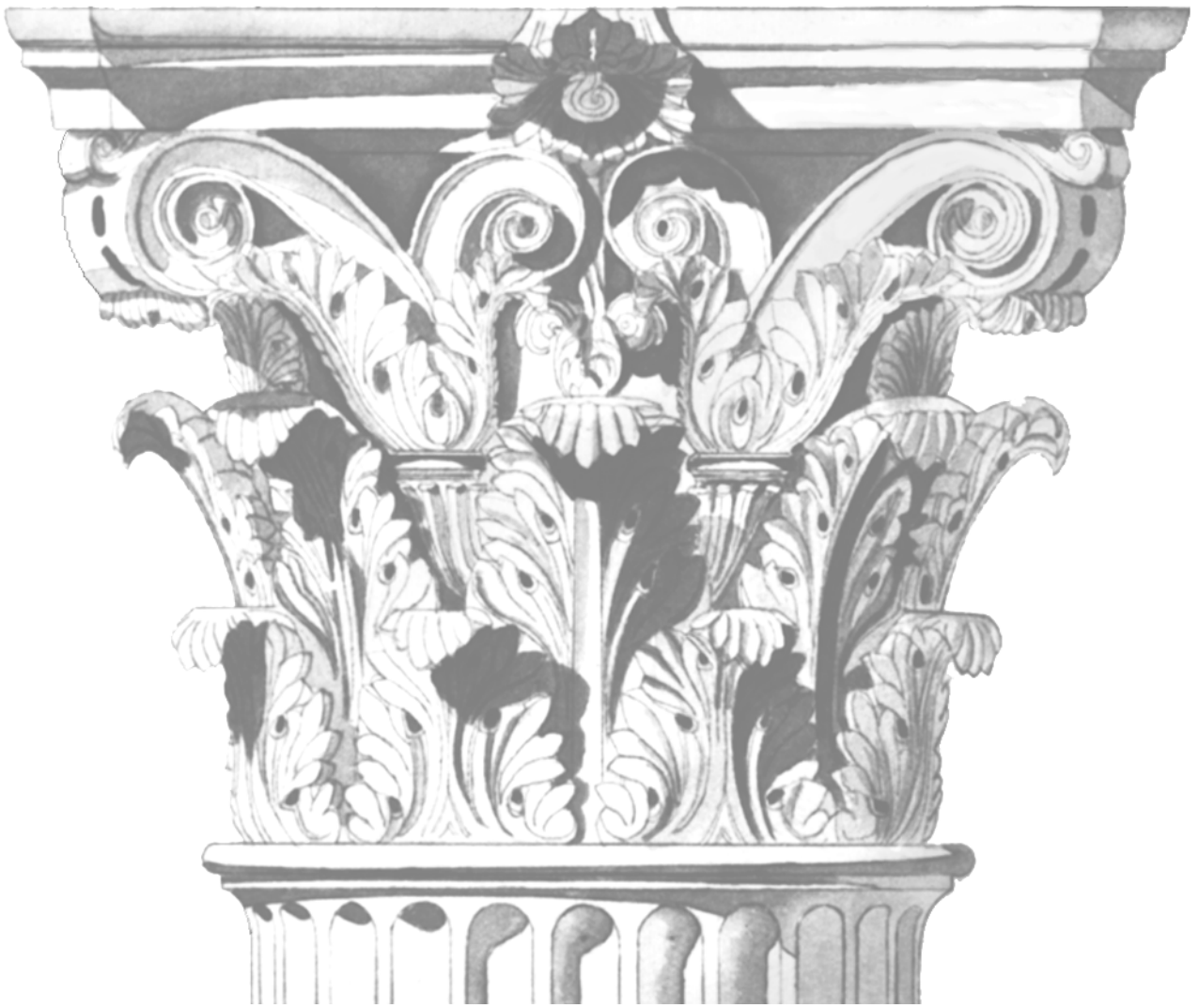

MARKKU TIMONEN

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Supervised by
Professor Pirkko Räsänen
Professor Juha Kinnunen

Reviewed by
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Professor Jari Tiihonen

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Department of Psychiatry, Department of Public Health Science and General Practice; University of Oulu, P.O.Box 5000, FIN-90014 University of Oulu, Finland
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Abstract

An excess of atopic allergies has been found in patients with depression, and conversely, increased amounts of depressive symptoms have been reported in patients with atopic disorders. Thus far, however, the findings have mainly been based on clinical samples. In this thesis, the association between atopic disorders and depression was investigated at epidemiological level by using data from the Northern Finland 1966 Birth Cohort.

An unselected cohort of 12058 liveborn children was followed prospectively from prenatal stages until 1997. During the 31-year follow-up, 6025 cohort members underwent skin prick tests. Data on lifetime depression diagnoses and atopic conditions were obtained from postal questionnaires and Finnish Hospital Discharge Registers, and the severity of the depressive symptoms was assessed with Hopkins Symptom Checklist-25. Information on the family histories of the atopic disorders was obtained from questionnaires of the 31-year follow-up.

Females with positive skin prick test responses and self-reported histories of allergic symptoms exhibited a 2.7-fold probability of developing lifetime depression. The corresponding probability increased in line with the increased severity of depressive symptoms in atopic but not in non-atopic females, ranging from 3.0 to 4.7-fold. Among males, the atopy-depression association was seen only in the highest depression scores, the odds ratio being up to 6.3-fold. While the most severe, hospital-treated manifestations of both disorders were considered, atopic disorders increased the risk of depression 3-fold independently of the subject's gender and sociodemographic characteristics. When investigating the effect of familial atopy on a child's depression, maternal atopy increased the probability of lifetime depression nearly 2-fold in females, and over 4-fold, when a female cohort member's own atopy was also present.

At epidemiological level, the presence of atopic conditions seemed to increase the probability of lifetime depression especially in females. Since both atopic disorders and depression are illnesses of major public health importance in Western countries, also the co-morbidity between these disorders should be seriously taken into account in clinical practice. Further investigations are called for in evaluating whether this association is specific to atopic disorders, since increased risks of depression have been noted in connection with many other physical diseases as well.

Keywords: allergic conjunctivitis, allergic rhinitis, allergy, asthma, atopic disorders, atopic eczema, atopy, cohort study, depression, depressive, hayfever, inheritance

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Vesala, Ylikiiminki, September 2003 Markku Timonen

Abbreviations

AD	Atopic dermatitis
B-cell	B lymphocyte
BDI	Beck Depression Index
CHAID	Chi-Squared Automatic Interaction Detector
CMI	Cornell Medical Index
CNS	Central Nervous System
CI	Confidence interval
CRH	Corticotropin-relasing hormone
DSM	Diagnostic and Statistical Manual of Mental Disorders
FHDR	Finnish Hospital Discharge Registers
GR	Glucocorticoid receptor
5-HIAA	5-hydroxyindoleacetic acid
HPA-axis	Hypothalamic-Pituitary-Adrenocortical -axis
HSCL-25	Hopkins Symptom Checklist-25
5-HT	5-hydroxytryptamine, serotonin
5-HTT	5-hydroxytryptamine transporter
ICD	International Classification of Diseases
Ig	Immunoglubulin (e.g., IgE)
IL	Interleukin (e.g., subtypes IL-1, IL-2, IL-4…)
INF-γ	Interferon-γ
MAO	Monoamine oxidase
MAS	Manifest Anxiety Scale
NK-cell	Natural Killer cell
OR	Odds ratio
PUFA	Polyunsaturated fatty acid
SCID-IV	Structured Clinical Interview for DSM-IV Axis I Disorders
SDS	Self-rating Depression Scale
SNS	Sympathetic nervous system
T-cell	T lymphocyte
Th-cell	T helper lymphocyte (e.g., subclasses Th1 and Th2)
TNF- β	Tumor necrosis factor β

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 Timonen M, Hakko H, Miettunen J, Karvonen JT, Herva A, Räsänen P, Koskinen O, Zitting P (2001) Association between atopic disorders and depression: Findings from the Northern Finland 1966 Birth Cohort Study. Am J Med Genet (Neuropsychiatr Genet) 105:216-217.

II Timonen M, Jokelainen J, Silvennoinen-Kassinen S, Herva A, Zitting P, Xu B, Peltola O, Räsänen P (2002) Association between skin test diagnosed atopy and professionally diagnosed depression: A Northern Finland 1966 Birth Cohort Study. Biol Psychiatry 52:349-355.

III Timonen M, Jokelainen J, Hakko H, Silvennoinen-Kassinen S, Meyer-Rochow VB, Herva A, Räsänen P (2003) Atopy and depression: Results from the Northern Finland 1966 Birth Cohort Study. Mol Psychiatry 8:738-744.

IV Timonen M, Jokelainen J, Herva A, Zitting P, Meyer-Rochow VB, Räsänen P (2003) Presence of atopy in first-degree relatives as a predictor of a female proband's depression: Results from the Northern Finland 1966 Birth Cohort. J Allergy Clin Immunol 111:1249-1254.

Contents

1 Introduction

The occurrence of atopic disorders has been increasing in Western countries in recent years (Konsensuslausuma 1998, Pekkanen *et al.* 2001a, Savolainen 2001, Hannuksela 2002). In Finland, about one million people (about 20% of the total population) are estimated to having some manifestation(s) of atopic disorders, e.g., asthma, allergic rhinitis/conjunctivitis, or atopic dermatitis (Savolainen 2001). Correspondingly, data from the Health 2000 study showed that 5% of adult Finns have suffered from major depression during the past 12 months (Pirkola *et al.* 2002). Major depression is one of the most important of all the illnesses leading to functional disability worldwide (Murray & Lopez 1997, Isometsä *et al.* 2000), and despite the increasing use of antidepressant medication, an upward trend in depression-related working disability has also been reported in Finland (Salminen *et al.* 1997, Herva 2002). Thus, both depression and atopic disorders are illnesses of major public health concern in Western countries (Konsensuslausuma 1998, Galil 2000, Isometsä *et al.* 2000).

Several lines of evidence suggest that there exists a link between atopic disorders and depression (Bell *et al.* 1991, Wamboldt *et al.* 1996, 1998, 2000, Hashiro & Okumura 1997, 1998, Cohen *et al.* 1998, Cuffel *et al.* 1999, Hurwitz & Morgenstern 1999, Brown *et al.* 2000, Centanni *et al.* 2000, Goethe *et al.* 2001). The majority of these atopy-depression studies are, however, based on clinical data settings including patients suffering from either depressive or atopic conditions, and the studies are furthermore heterogeneous in case definitions. There is a need for population-based investigations, which confirm the atopy-depression association at epidemiological level by using appropriate and accurate tools to define the presence of atopic disorders and depression.

Professor (emerita) Paula Rantakallio started the prospective Northern Finland 1966 Birth Cohort in order to describe and analyse the risk factors leading to perinatal deaths and low birth weight (Rantakallio 1969, 1988). The present study belongs to the psychiatric part of this ongoing follow-up project, called nowadays the Northern Finland Health and Well-being Study. This genetically homogeneous database made it possible to investigate the putative atopy-depression association at general population level. The presence of atopic disorders could be verified by objective measurements, i.e., skin prick test responses, and depression by different indicators, e.g., carefully validated hospital-treated depression diagnoses (Isohanni *et al.* 1997, Moilanen *et al.* 2003).

2 Review of the literature

2.1 Definition of atopy

The term "atopy" was first introduced by Coca and Cooke in the beginning of the 20th century as reviewed by Wamboldt *et al.* (1998). Originally the term "atopy" meant "unusual" (Abbas *et al.* 2000), and Coca and Cooke meant with that an inherited tendency, which was associated with hay fever, asthma and urticaria (Nikander 1999). These disorders have been called atopic disorders even though nowadays it is known that, for example, the etiology of urticaria is heterogeneous and that all patients with asthma are not suffering from atopic allergies. In addition, atopic dermatitis is defined to be an atopic disorder even though it was not included in the original definition (Nikander 1999). In older epidemiological studies, positive skin tests, high immunoglobulin E (IgE) levels, and atopy were treated as synonymous (Wamboldt *et al.* 1998). Nowadays, persons, who have a tendency to produce IgE antibodies in response to various environmental antigens and who exhibit strong immediate hypersensitivity response, are called atopic. In different individuals, atopy may manifest itself in different forms – e.g., asthma, atopic dermatitis (eczema), allergic rhinitis and allergic conjunctivitis (Kari & Hannuksela 1999, Abbas *et al.* 2000, Wamboldt *et al.* 2000). In clinical practice the presence of atopy requires both positive skin tests and clinical symptoms (Wamboldt *et al.* 1998).

2.2 Etiological factors of atopic disorders

It is known that both environmental and genetic factors play a role in the etiology of atopic disorders (Konsensuslausuma 1998). If an atopic allergy is present in both parents, the probability for their children to have some kind of atopic disorder is 60%-80%, but if only one of the parents is suffering from atopy, the corresponding probability is 30%-50%. If neither of the parents have an atopic phenotype, the probability for their children

to have an atopic allergy is only 15% (Savolainen 2001). In different populations, different possible candidate genes, which might have some connections with atopic disorders, have been found. Thus, it is obvious that atopic allergy is a genetically heterogeneous disorder (Konsensuslausuma 1998, Laitinen *et al.* 2000b, Savolainen 2001).

It is not definitely known, what exactly are those environmental factors, which determine whether a person develops an atopic allergy or not (Konsensuslausuma 1998). On the other hand, in addition to living in a farm environment during childhood/being a farmer's child (Kilpeläinen *et al.* 2000, Pekkanen *et al.* 2001b), also a low socioeconomical status of the family (Williams *et al.* 1994), high number of children in a family/mother's high parity (Strachan 1989, Pekkanen *et al.* 2001b), and an anthroposophic (Greek: wisdom about man; people who follow an anthroposophic way of life use antibiotics restrictively, have few vaccinations, and their diet usually contains live lactobacilli, which may affect the intestinal microflora) lifestyle of the family (Alm *et al.* 1999) have been found to be associated with a decreased risk of atopic allergies (Savolainen 2001, Hannuksela 2002).

2.3 Asthma bronchiale, atopic dermatitis, allergic rhinitis, and allergic conjunctivitis

2.3.1 Asthma bronchiale

The definitions of asthma and allergic diseases in general, have mainly been based on symptoms and a phenotype, which is why till now there have existed no widely accepted definitions for different allergic manifestations (Remes 1998). The knowledge about the characteristics of asthma has changed during the last decade and nowadays asthma is considered to be a chronic inflammatory disorder of the airways (Haahtela *et al.* 1999a).

Many cells play a role in the pathophysiology of asthma, particularly mast cells, eosinophils, and T-lymphocytes. The inflammation in the airways causes, to the patients suffering from asthma, recurrent episodes of wheezing, breathlessness, chest tightness, and cough. These symptoms are usually associated with reversible bronchial obstruction (Remes 1998, Harju 1999). According to its etiology, asthma can be divided into the extrinsic (allergic/atopic) and intrinsic (non-allergic) types (Nasr *et al.* 1981, Haahtela *et al.* 1999a, Laitinen *et al.* 2000a).

Asthma is the most prevalent chronic disease in childhood (Galil 2000), and childhood asthma is frequently, in fact in over 80% of the cases, associated with allergy (Remes & Korppi 1996). The proportion of atopic asthma decreases with the increase of age and in adulthood the asthma is in about 60% of all cases atopic in nature (Laitinen *et al.* 2000a).

With regard to psychiatric co-morbidity, increased rates of depression and depressive symptoms have been found in patients with asthma (Brown *et al.* 2000, Centanni *et al.* 2000, Goethe *et al.* 2001). On the other hand, higher than normal rates of IgE-mediated

allergies (including asthma) have been reported from patients with depression (Nasr *et al.* 1981, Sugerman *et al.* 1982).

2.3.2 Atopic dermatitis (AD)

Atopic dermatitis (AD) is a common inflammatory skin disorder. Its prevalence ranges from 5% to 13% among children in the industrialized Western countries. The frequency of AD has been noted to have increased, especially in urban areas, the estimated current incidence being even as high as 12% as reviewed by Buske-Kirschbaum *et al.* (2001).

The main symptoms of AD are dry skin, papules, lichenification, eczematous inflammation and an intense itching (Buske-Kirschbaum *et al.* 2001). In the majority of cases, AD begins in infancy. The pattern of AD varies with age, but a general dryness of the skin may persist throughout life. In infancy, AD usually starts on the face. During childhood the eczema is affecting mainly the elbow and knee flexures as well as wrist and ankles. In adults, eczema is distributed to the face, upper body, flexures and extremities. It has been estimated that symptoms of AD remit spontaneously before the age of 10 in the majority of the affected children (Hunter *et al.* 1990, Kalimo & Hannuksela 1999). However, symptoms may relapse in stressful life situations, which are often accompanied by an exacerbation of AD (Hunter *et al.* 1990, Buske-Kirschbaum *et al.* 2001). It has been suggested that psychosocial stress and skin condition in AD are bidirectionally related, and eventually, via a vicious circle of emotional stress and worsening skin condition the situation may also lead to the chronification of AD symptoms (Buske-Kirschbaum *et al.* 2001).

2.3.3 Allergic rhinitis and allergic conjunctivitis

Allergic rhinitis, like asthma, is an inflammatory disorder of the airways (Malmberg & Rinne 1999). The cardinal symptoms of allergic rhinitis are sneezing, watery nasal discharge and nasal obstruction. In addition, many patients who are suffering from allergic rhinitis also have eye symptoms; allergic conjunctivitis is known to be commonly associated with allergic rhinitis (Remes 1998, Abbas *et al.* 2000). Allergic rhinitis can be divided into the seasonal (hay fever) and nonseasonal allergic rhinitis.

In Finland, pollen from broad-leaved trees, grasses and the composite flowers are the commonest allergens causing the typical symptoms of seasonal allergic rhinitis, whereas animal dusts and dust mites are the most prevalent allergens behind the nonseasonal allergic rhinitis (Malmberg & Rinne 1999). In respect to the psychiatric co-morbidity, allergic rhinitis has been found to be associated with high rates of depression and anxiety disorders (Cuffel *et al.* 1999).

Allergic conjunctivitis is a common cause of conjunctivitis in general. It can be the only manifestation of atopic allergy, but usually it is associated with allergic rhinitis, atopic eczema or asthma (Kari & Hannuksela 1999).

2.4 Trends in the occurrence of atopic disorders

There is a world-wide variation in the prevalence of atopic disorders. High prevalence rates seem to be present in Australia and Western Europe and low rates in Asia and Eastern Europe (Remes 1998, Harju 1999, Dunder *et al.* 2001). Further, evidence has been accumulating to indicate that the prevalence of atopic disorders has been increasing in recent decades in Western countries, including Finland (Harju *et al.* 1998, Konsensuslausuma 1998, Remes 1998, Galil 2000, Pekkanen *et al.* 2001a, Savolainen 2001, Vartiainen *et al.* 2002). Earlier, because only few of the studies investigating the presence of atopic disorders used objective measurements in repeated surveys, there was a critical debate about whether the observed increased rates were true or biased due to many possible confounders (Magnus & Jaakkola 1997, Remes 1998). At present, there is a consensus about the upward trend in the occurrence of atopic disorders (Konsensuslausuma 1998, Pekkanen *et al.* 2001a, Savolainen 2001, Hannuksela 2002). In Finland, it has been suggested that 15%-20%, 2%-6% and 2%-5% of adult people are nowadays suffering from allergic rhinitis, asthma and atopic dermatitis, respectively. The corresponding figures for children are 20%-25%, 5%-7% and 15%-19%, respectively (Haahtela *et al.* 1999b). Thus, it has been estimated that nowadays about one million Finnish people are suffering from asthma, allergic rhinitis or atopic dermatitis (Savolainen 2001).

2.5 Some biological aspects of atopic disorders

Atopic disorders are immunological diseases. The following basic mechanisms behind the pathophysiology of the immune system in atopic disorders are presented in order to make understandable the putative psycho-neuroimmunological mechanisms behind the association between atopic and depressive disorders.

2.5.1 Regulation of immunity

Immunity is a state of resistance, or protection from pathogenic micro-organisms (Kelley 2001). The immune system can be divided into innate (antigen-nonspecific) and acquired (adaptive/antigen-specific) immunity. Innate immunity is present at all times in normal individuals, and is thus fully functional before infectious agents enter the body. An adaptive immune response is a specific reaction of the body to the challenge by an immunogen. Immune responses are contributed by antigen-presenting cells, such as monocytes/macrophages, which are components of innate immunity, and on the other hand by T helper (Th) lymphocyte subclasses Th1 and Th2, which are involved in acquired immunity (Elenkov & Chrousos 1999, Elenkov *et al.* 2000, Kelley 2001, Schwarz *et al.* 2001). These Th subclasses secrete a distinct cytokine profile (Figure 1):

Th1 cells produce mainly interleukin-2 (IL-2), tumor necrosis factor β (TNF- β), and interferon-γ (INF-γ), all three of which promote cellular immunity. Th2 cells secrete primarily IL-4, IL-5, IL-10 and IL-13, all of which favour humoral immunity (Elenkov *et al.* 2000, Buske-Kirschbaum *et al.* 2001).

Naive (antigen-inexperienced) Th0 cells are precursors of Th1 and Th2 cells (Figure 1). IL-12, which is produced by antigen-presenting cells, is a major inducer of Th1 shift, and thus is favouring cellular immunity, whereas IL-4 and IL-10, while stimulating Th2 differentiation, are promoting humoral immunity by stimulating the growth and activation of mast cells and eosinophils, the differentiation of B cells into antibody-secreting B cells, and B cell immunoglobulin to switch to IgE. Th1 and Th2 responses inhibit each other (Elenkov & Chrousos 1999, Elenkov *et al.* 2000).

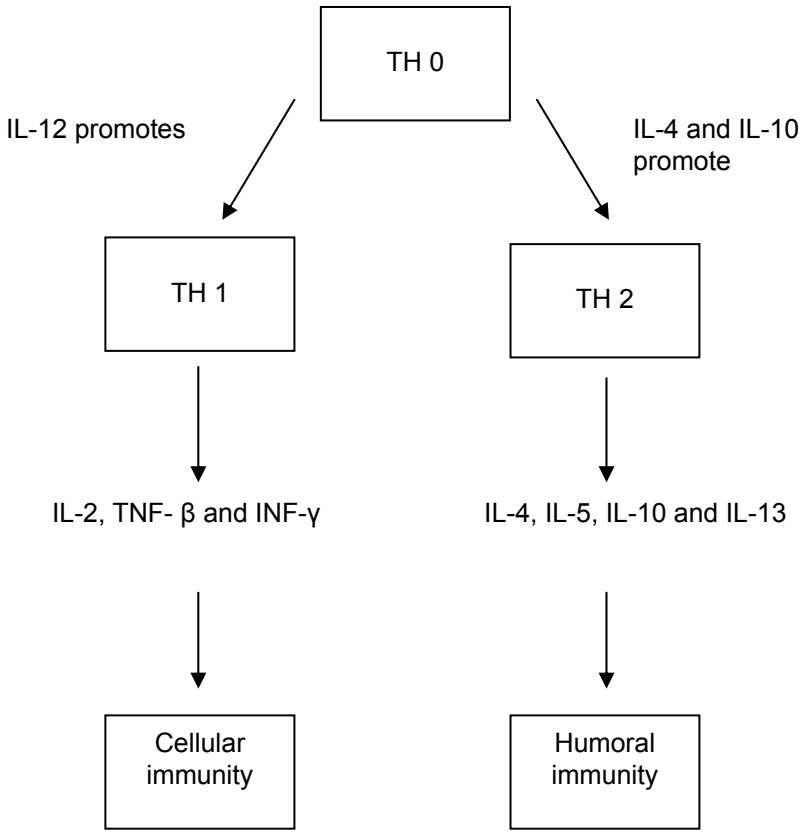

Fig. 1. Differentiation into Th1 or Th2 subsets from naive Th0 cells and corresponding cytokine patterns and effector mechanisms. Modified from the illustration of Elenkov & Chrousos (1999).

2.5.2 Immediate hypersensitivity

In atopic patients, naive Th0 cells are stimulated by an environmental allergen to differentiate into Th2 cells. IL-4, produced by Th2 cells, is required for the differentiation of B cells to produce high levels of IgE specific for that antigen. IgE binds to the circulating basophils and mast cells in different tissues. When these cell-associated antibodies are cross-linked by antigen, the cells are activated and they rapidly release preformed mediators – e.g., biogenic amines such as histamine – stored in the cytoplasmic granules of the mast cells and basophils. In addition, a rapid synthesis of lipid-derived mediators – prostaglandins and leukotrienes – and cytokines takes place. The biogenic amines and lipid mediators are responsible for the acute phase reaction of immediate hypersensitivity while they cause increased vascular permeability, vasodilatation as well as bronchial and visceral smooth muscle contraction. Cytokines and lipid mediators contribute to an allergic inflammation, which is part of the late phase reaction beginning 2 to 4 hours after the acute phase reaction. The late phase reaction achieves its maximum in about 24 hours and then it gradually subsides (Abbas *et al.* 2000, Buske-Kirschbaum *et al.* 2001). The most severe manifestation of the immediate hypersensitivity is anaphylaxis, in which airways can be restricted to the point of asphyxiation and a cardiovascular collapse can occur, which can lead to a person's death (Abbas *et al.* 2000).

2.5.3 Allergen-specific T-cell memory

The foetal immune response is dominated by Th2 cytokines (Prescott *et al.* 1998). It has been suggested that this Th2 polarization is an evolutionary adaptation and aimed to protect the foeto-placental unit against the toxic effects of proinflammatory cytokines such as INF-γ (Lin *et al.* 1993, Prescott *et al.* 1998). Further, it has also been shown that virtually all newborn infants have a Th2-skewed immunity (Prescott *et al.* 1998). In healthy, non-atopic individuals, this Th2 dominance is shifted toward the Th1 cytokine phenotype during early childhood whereas the long term Th2-skewed allergen-specific immunologic memory is being developed among atopic persons (Prescott *et al.* 1998, 1999).

2.6 Definition of depression

There exist different forms of depression and depression can manifest itself in different grades of severity. In general, depressive feeling is an emotion that is universally experienced by virtually everyone at some time in life. Depressive feeling can be a normal emotional reaction e.g., in different normative crises during an individual's life-cycle (Isometsä 1999, Stahl 2001). Depressive feeling can also manifest itself as a special

symptom in different mental or somatic disorders (Aalto-Setälä 2002). As an illness, depression is a socially debilitating syndrome including clusters of symptoms (i.e., vegetative, cognitive, behavioural, and physical features as well as impairment of impulse control in behaviour), only one symptom of which is abnormality of mood (Stahl 2001). In depressive disorders, one has lost the sense of control of one's mood and affects: Patients suffering from depressive disorders might experience loss of energy and interest, they have feelings of guilt/worthlessness, and difficulties in concentrating. They also might have loss of appetite, insomnia or hypersomnia, and frequently experience thoughts of death or suicide/suicidal behaviour. In the most severe form of depression, i.e., major depression with psychotic features, patients also have delusions or hallucinations (Kaplan *et al.* 1994).

Throughout the history of psychiatry, there have existed a number of different classifications of depression (Tamminen 1993). With regard to diagnosing depression, contemporary epidemiological surveys nowadays usually conceptualize depression as a diagnosis, based on the criteria of diagnostic systems such as DSM-IV (the fourth edition of Diagnostic and Statistical Manual of Mental Disorders) diagnostic classification (American Psychiatric Association 1994) or ICD-10 (International Classification of Disorders) (World Health Organization 1992) as reviewed by Aalto-Setälä (2002). In the DSM-IV, for example, the following depression diagnoses are given: Major depressive disorder, dysthymia, adjustment disorder with depressed mood and depressive disorder not otherwise specified (American Psychiatric Association 1994). In addition to structured or semi-structured diagnostic instruments, there are several rating scales designed to ascertain depressive symptoms, the value of which is well established in obtaining estimates of symptom prevalence in the population and for screening purposes (Aalto-Setälä 2002).

2.7 Prevalence of depression

As with atopic disorders (Konsensuslausuma 1998, Galil 2000), also depressive disorders (Galil 2000, Isometsä *et al.* 2000) are illnesses of major public health importance in many Western societies, Finland included. As reviewed by Lehtinen and Joukamaa (1994), according to population surveys conducted in different countries, the prevalence of clinically defined depression varies from 2.6% to 5.5% (mean 4.0%) and from 6.0% to 11.8% (mean 7.9%) in men and in women, respectively. In addition, the occurrence of depressive symptoms is far more common among both genders when compared with depressive disorders, their prevalence ranging from 18% to 34% and from 10% to 19% for females and males, respectively. Thus, both depressive symptoms and depressive disorders are among women about twice as common as in men. In the Mini Finland Health Survey, a study population (n=8000) representative of the whole Finnish adult population, the mean prevalence of depression was 3.9% among males and 6.0% in females (Lehtinen & Joukamaa 1994).

2.8 Etiological factors and biological aspects of depressive disorders

Depression is known to be a multifactorial disease by origin. Different biological, genetical and psychosocial factors are known to be behind the psychopathology of depressive disorders (Isometsä 1999, Kaplan *et al.* 1994). The etiological factors presented in this chapter are considered to be the most relevant ones in the context of this thesis.

Several lines of evidence – family, twin and adoption studies – suggest that major depression is a familial disorder and that in the majority of the cases in which a tendency of familial preponderance is noticed, it is caused by genetic factors (Kendler & Aggen 2001). It has been estimated that among first degree relatives (parents, siblings or children) of persons suffering from depressive disorders the occurrence of unipolar depression varies from 6.4% up to even 29.4% (Isometsä 1999). In addition, in a large twin study, genetic factors have recently been shown to play a greater role in the etiology of major depression among females than in males (Kendler *et al.* 2001a). The concept of psychosocial/environmental factors behind the etiology of depression is based on the fact that the onset of depression is often preceded by stressful life events and/or crises of a person's life-cycle (Isometsä 1999). The overall sensitivity to the depressogenic effects of stressful life events seems to be equal for both genders, even though the psychosocial stressors themselves, preceding major depression in adulthood, differ between genders (Kendler *et al.* 2001c).

2.8.1 Some biological aspect of depression

2.8.1.1 Biogenic amines

There are many biological theories attempting to explain the pathophysiology behind depressive disorders. One of the earliest is the so called monoamine-hypothesis, which was introduced in the 1960s (Isometsä 1999). Since then, evidence has been accumulating to indicate that the dysregulation of biogenic amines is associated with depressive disorders. Serotonin and norepinephrine are the most important biogenic amines, which are known to be behind the psychopharmacology of depression (Kaplan *et al.* 1994). The disorganized catecholamine and serotonin metabolisms have formed also a basis for the development of drugs against depression over several decades (Horrobin & Bennet 1999).

Dopamine, epinephrine and norepinephrine are classified as catecholamines. They are all synthesized from tyrosine. In addition to the fact that the dopamine hypothesis has been the leading neurochemical hypothesis for schizophrenia, there has also been some evidence that dopamine might be associated with the pathophysiology of depressive disorders. Low levels of dopamine metabolites have been found in depressed patients in several previous studies (e.g., Kaplan *et al.* 1994).

When compared with epinephrine, norepinephrine is considered to be the more important neurotransmitter in psychiatry (Kaplan *et al.* 1994). The *locus ceruleus*, which is located bilaterally in the dorsal pons near the floor of the fourth ventricle, is the most important noradrenergic nucleus in the brain. The *locus ceruleus* has connections to many areas of the central nervous system (CNS), including the hippocampus, the amygdala, the hypothalamus, the limbic system, and the cerebral cortex (Kaplan *et al.* 1994, Kaye *et al.* 2000). In noradrenergic neurons, dopamine is converted to norepinephrine by dopamine β–hydroxylase. Thereafter it is stored in synaptic vesicles until it is released during the depolarization of the neuron. As with dopamine, also norepinephrine is deactivated either by uptake from the synaptic cleft back into the presynaptic neuron or via the metabolism by monoamine oxidase (MAO) and by catechol-O-methyltransferase. There exist many subtypes of the α –adrenergic receptors and of the β−adrenergic receptors, by which catecholamines are mediating their effects on the target cells. In reference to these receptors, the knowledge in the field of molecular biology is rapidly increasing. For example, presynaptic α_2-adrenoreceptrors are known to be acting as autoreceptors and noradrenergic neurotransmission is under the control of these receptors. Stimulation of these receptors results in a decrease in the amount of released norepinephrine (Kaplan *et al.* 1994, Isometsä 1999). The MAO inhibitors and the tricyclic antidepressants are blocking the metabolism and the uptake of the norepinephrine, respectively, whereas, e.g., α_2-adrenoreceptror antagonists are blocking the presynaptic α_2-adrenoreceptros. Thus, the immediate effect of these drugs is to enhance noradrenergic neurotransmission (Kaplan *et al.* 1994, de Boer 1995). In spite of the intensive work in this field, the exact role of norepinephrine behind the pathophysiology of depression has still remained unclear (Kaplan *et al.* 1994).

Serotonin (5-HT, i.e., hydroxy tryptamine) is synthesized from tryptophan in the axonal terminals of the serotonergic neurons. Most of the serotonergic nuclei of the brain are situated in the brainstem with median and dorsal raphe nuclei being one of the most important ones (Kaplan *et al.* 1994). The main metabolite of 5-HT is 5-hydroxyindoleacetic acid (5-HIAA). The concentration of 5-HIAA in the cerebrospinal fluid of depressed patients has been shown to be lowered in numerous previous studies, indicating decreased serotonergic metabolism during depression (Kaplan *et al.* 1994, Mann & Malone 1997, Isometsä 1999). In the most simplified form, the monoamine-hypothesis meant that depression is associated with too low a level of serotonin in the CNS. Nowadays it is known that the monoamine-hypothesis has proved to be incorrect in this simplified form (Kaplan *et al.* 1994, Isometsä 1999). While there exist numerous different 5-HT receptor subtypes, which mediate the effects of 5-HT, there is only one 5-HT transporter (5-HTT), which takes the 5-HT up from the synaptic cleft and returns it into the presynaptic neuron. Therefore, the modulation of 5-HTT is an important mechanism to influence the serotonergic neurotransmission (Mösner *et al.* 2001). Likewise in the noradrenergic neurotransmission, MAO inhibitors and tricyclic antidepressants are blocking the metabolism and the uptake of serotonin, respectively (Kaplan *et al.* 1994). The introduction of selective serotonin re-uptake inhibitors has improved the safety and has reduced adverse effects, but not efficacy in the treatment of depression when compared with tricyclic antidepressants and MAO inhibitors (Kaplan *et al.* 1994, Anderson 2000).

5-HT is also an important mediator of bidirectional interactions between the nervous and the immune systems (Mössner & Lesch 1998; Mössner *et al.* 2001). As reviewed by Mössner and Lesch (1998), the CNS can, via the autonomic nervous system, induce the neural release of 5-HT to the immune system. 5-HT receptors and the 5-HTT are distributed widely in immune cells and 5-HT is known to have various immunological effects.

2.8.1.2 Omega-3 fatty acids and depression

The theories of the pathophysiology of depression, which are based on disorders in catecholamine and serotonin metabolism, have been criticized, because they are inadequate to provide a full explanation for the depression (Kaplan *et al.* 1994, Horrobin & Bennet 1999); Many patients fail to respond to drugs developed on the basis of those theories. There has therefore been a search for other mechanisms, which could explain the biological backgrounds behind depression. Disturbances in fatty acid metabolism have been suggested to provide one mechanism, which could also serve as a plausible theory behind the pathophysiology of depression (Horrobin & Bennet 1999). Several lines of evidence have been put together and collectively suggest that diminished omega-3 fatty acid intake or concentrations are associated with unipolar depressive disorders: A reduction in omega-3 polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid and docosahexaenoic acid, has been noted in plasma, serum phospholipids, or red cell membranes of depressive patients (Adams *et al.* 1996, Seko 1997, Peet *et al.* 1998, Maes *et al.* 1999). Secondly, previous findings in a cross-national analysis showed a highly significant inverse relationship between prevalence of major depression and fish consumption (Hibbeln 1998). By using a postal questionnaire survey, a higher consumption of fish has recently been shown to be associated with a reduced risk of major depression in two large general population samples (Tanskanen *et al.* 2001a, 2001b). A significant gender difference was found in another of these surveys, infrequent female fish-consumers being more depressive than frequent (more than once a week) consumers (Tanskanen *et al.* 2001b). Recently, highly purified ethyl eicosapentaenoic acid was shown to be effective in improving major depression in two randomized, placebo-controlled studies (Peet & Horrobin 2002, Nemets *et al.* 2002).

On the other hand, as reviewed by Maes and Smith (1998), it has been suggested that changes in 5-HT receptor number and function caused by changes in PUFAs, could also provide the theoretical rationale connecting fatty acids with the current receptor and neurotransmitter theories of depression. With regard to immunological effects, dietary fatty acids are known to have important effects on immune and inflammatory processes as reviewed previously (Kelley 2001, Maes & Smith 1998).

2.8.1.3 Hypothalamic-pituitary-adrenocortical-axis

Among other neuropeptides, corticotropin-relasing hormone (CRH) is synthesized in the paraventricular nucleus of the hypothalamus. CRH is released into the portal circulation via which it enters the anterior lobe of the pituitary gland, where it then induces the synthesis and release of corticotropin. The biosynthesis and the release of corticosteroids from the adrenal cortex are stimulated by corticotropin (Holsboer 2001). The effects of the glucocorticoids, the end products of this hypothalamic-pituitary-adrenocortical (HPA)-axis, are mediated by intracellular receptors including glucocorticoid receptors (GRs), which play also an essential role in the feedback regulation of the HPA-axis (Pariante & Miller 2001).

Hypercortisolism and dysfunction of GRs are usually present in depression (Murphy 1997, Holsboer 2001, Pariante & Miller 2001). It has remained undefined, where exactly in the HPA -axis this dysfunction arises (Jiang *et al.* 2000). However, there is evidence CRH is hypersecreted from hypothalamic as well as from extrahypothalamic neurons in depression (Arborelius *et al.* 1999), and HPA-axis alterations are suggested to be secondary to the hypersecretion of the CRH (Pariante & Miller 2001). In addition, recent evidence shows that cytokines might be causing GR resistance (Pariante & Miller 2001).

With regard to immunological effects, it has been found that glucocorticoids, the end products of the HPA-axis, selectively suppress cellular immunity and favour humoral immune responses, and that glucocorticoid receptor binding affinity has been found to be reduced in atopic diseases (Clayton *et al.* 1995, Elenkov *et al.* 1999, Leung 2000, Nimmagadda *et al.* 1997).

2.8.2 Immunological alterations in depression

2.8.2.1 Immunological alterations in stress and in depression

As mentioned earlier, stressful life events play an important role in the etiology of depressive disorders (Isometsä 1999, Olff 1999) and it has been suggested that depression may be conceived as a component of chronic stress (Olff 1999). It is also known that psychological stress modulates the immune system and changes are seen in many immune parameters (Olff 1999, Maddock & Pariante 2001). In addition, there are several similarities in the immune alterations in times of chronic stress and depression (Olff 1999). Even though the findings are to some extent heterogeneous, there is now quite reliable evidence that depressed patients are likely to exhibit changes in major immune cell classes with an increase in total white blood cell counts and a relative increase in the numbers of neutrophils. Further, the relative number of lymphocytes has been shown to be reduced in patients with depression. Depression has also been found to be associated with a suppression of mitogen-induced lymphocyte proliferation and with a reduction of Natural Killer (NK) cell activity (Irwin 1999).

2.8.2.2 Cytokines and "sickness behaviour"

With regard to immune parameters, depression has also been shown to be associated with an excessive secretion of proinflammatory cytokines, such as IL-1, IL-6 and TNF (Maes *et al.* 1998, Maddock & Pariante 2001). Proinflammatory cytokines regulate the acute phase reaction, which is an early immune reaction against invading organisms (Maddock & Pariante 2001).

During an immune response, proinflammatory cytokines such as IL-1β and IL-6, which also are involved in the local inflammatory responses in atopic disorders (Abbas *et al.* 2000), are also capable to induce a non-specific systemic reaction to inflammation – a so-called syndrome of "sickness behaviour" (Dantzer 2001, Schwarz *et al.* 2001). As reviewed by Dantzer (2001), cytokines can affect the brain via both the afferent neurons of the vagus nerves and by direct targeting to the brain regions such as the amygdala after diffusing to the brain side of the blood-brain barrier at the circumventricular organs and the choroid plexus. In addition, cytokines do not always have to reach the brain from the periphery (directly or indirectly), because most cytokines, including IL-1, IL-4 and IL-6, can be synthesized and released within the central nervous system (Kronfol & Remic 2000). The "sickness behaviour" shares many features with major depression, including anhedonia, fatigue, loss of appetite, reduced activity, altered sleep patterns, social withdrawal, decreased libido, and depressed mood (Dantzer 2001, Maddock & Pariante 2001, Musselman *et al.* 2001). The overlap of symptoms in sickness behaviour with depression has led to the concept that cytokines secreted during stress would serve as an important etiological factor behind the pathophysiology of depressive disorders (Maes & Smith 1998, Musselman *et al.* 2001).

2.8.2.3 The concept of psycho-neuro-immunology

Psycho-neuro-immunology is a paradigm, which began to develop in the 1970s. It evaluates the complex interactions which are involved in the body-mind connection including nervous, endocrine, and immune systems, and the contribution of psychosocial factors as well as behavioural processes to these interactions (Bonneau *et al.* 1998, Kaye *et al.* 2000). The CNS and the immune system are two of the main adaptive systems of the human body (Elenkov *et al.* 2000). During an immune response, the CNS and the immune system communicate with each other in order to maintain homeostasis in the body (Elenkov *et al.* 2000, Kronfol & Remick 2000). Two major pathways, the HPA-axis and the sympathetic nervous system (SNS) are involved in this bidirectional interaction (Mössner & Lesch 1998, Elenkov *et al.* 2000). Cytokines play also a crucial role in this interaction. Besides acting as chemical messengers between immune cells, they can serve also as mediators between immune system and the brain (Kronfol & Remick 2000, Dantzer 2001).

2.9 Earlier studies concerning the association between atopic disorders and depression

As reviewed by Galil (2000), associations between asthma and psychiatric symptoms were explained with the help of psychoanalytic theories earlier in the 20th century: it was, for example, suggested that asthma was caused by an excessive dependence on the mother and that it was precipitated by traumatic separations. Ever since genetic factors behind both asthma and depression have become evident, these earlier psychoanalytic explanations have largely been abandoned (Galil 2000).

2.9.1 Allergic symptoms in patients with depression

Higher than normal rates of IgE-mediated allergies have been reported in patients with depression (Nasr *et al.* 1981, Sugerman *et al.* 1982). Nasr *et al.* (1981) evaluated the personal and family history of bronchial asthma and/or allergic rhinitis from 82 psychiatric patients (58 inpatients and 24 psychiatric clinic outpatients). Psychiatric diagnoses were based upon the 3rd edition of the Research Diagnostic Criteria. A semi-structured interview was conducted to explore the relationship between physical and mental problems. The cases of intrinsic asthma were excluded from the analyses since they were not likely to be allergic in nature. A statistically significantly ($p<0.005$) higher incidence of atopic disorders was found in affective patients (16/48) than in schizophrenic patients (2/34).

Sugerman *et al.* (1982) compared IgG, IgA, IgM, IgE, and IgD antibodies in adult alcoholic, depressive, and schizophrenic patients with those of adult, healthy controls. Total above mentioned and specific IgE antibodies were assessed, using 12 inhalant and 21 food allergens. No statistically significant differences were observed in the total immunoglobulin results between patients and controls. However, significant differences were found between the groups for allergen specific-IgE with depressive patients giving the greatest number of positive test results.

2.9.2 Depression in patients with atopic disorders

2.9.2.1 Depression in patients with atopic dermatitis

Hashiro and Okumura (1997) investigated anxiety (manifest anxiety scale, MAS), depression (self-rating depression scale, SDS), and psychosomatic symptoms (Cornell Medical Index, CMI) in 45 patients with atopic dermatitis and 34 normal controls. On the MAS, the atopic dermatitis group did not show any statistical difference from the normal

controls. When compared with the controls, the SDS and the CMI produced statistically significantly higher scores ($p<0.05$ and $p< 0.01$, respectively) in patients with atopic dermatitis. With regard to SDS, 44.4% of the patients with atopic dermatitis had scores of 40 or more (indicating a depressive state including depressive neurosis, but no major depression), the corresponding percentage being 29.4% in the normal controls. After classifying atopic patients in three degrees of severity (mild, moderate and severe), the patients with moderate symptoms were more depressive than the normal controls ($p< 0.01$). The authors concluded that the patients with atopic dermatitis were more depressive and psychosomatic symptom-prone than the normal control individuals.

2.9.2.2 Depression in patients with asthma

In a study conducted by Centanni *et al.* (2000), the anxiety and depression level was tested with State Trait Anxiety Inventory and ZUNG questionnaires in a population of 80 asthmatic patients. Fourty patients with chronic viral hepatitis B or C, and 40 healthy subjects were recruited as control groups, and, thereafter stratified according to sex, age and education to parallel the asthmatic sample. The results showed that asthmatic patients had statistically significantly higher scores both in State Trait Anxiety Inventory ($p< 0.05$) and ZUNG ($p< 0.05$) when compared with controls. In the ZUNG questionnaire, 27 asthmatic patients (33.8%), 10 patients with liver disease (25%) and 5 healthy controls (12.5%) had higher scores than the cut-off point (40 out of 80), indicating higher traits of depression. With regard to both questionnaires, in the asthmatic and healthy populations females had higher scores ($p<0.05$ and $p<0.01$, respectively) when compared with men, whereas among patients with liver disease, the two subgroups showed no gender difference. The limitation of this study was that allergic and non-allergic asthma was not analyzed separately.

Brown *et al.* (2000) conducted structured clinical interviews (SCID-IV) on 32 inner city outpatients with moderate to severe asthma to identify current and past psychiatric illnesses. They found that 25% of their study material had current major depressive disorder, but the majority of them (75%) did not receive antidepressants. The investigators called for interventions aimed at identifying and treating psychiatric disorders among asthmatic outpatients.

Further, in a study conducted by Goethe *et al.* (2001) the prevalence of depressive symptoms was assessed also in a sample of inner-city asthma patients. By using the Center for Epidemiologic Studies Depression Scale, 55% out of 307 asthma patients had scores in excess of the cut-off point for depression (Goethe *et al.* 2001).

2.9.3 Other studies concerning atopy-depression association

Bell and colleagues (1991) conducted a questionnaire study in a nonclinical sample of 379 college students, examining the possible association between depression and IgE-

mediated allergies. Measures included self-reports of the histories of depression and allergic disorders, and specific environmental allergens as well as ratings of affective symptoms of depression (4-point scale). Of the subjects, who had ever received a professional diagnosis of depression (n=17), 71% also indicated a history of some type of allergic disorder; the difference being statistically significant ($p<0.05$) when compared with non-depressive students. The findings were comparable and significant, when the sample was restricted to those with histories of professional allergy diagnoses as well. Furthermore, when the entire sample was divided into four depression groups on the basis of frequency of self-rated current depression (from rarely depressed=1 to frequently depressed=4), the most depressed group had a much higher frequency of asthma than did the less depressed group. Thus, the authors suggested that dysfunctions of the immune system could play a role behind the degree of severity of the depression.

Cohen *et al.* (1998) followed prospectively a cohort of over 700 randomly selected children from early childhood (ages 1-10 years in 1975) to young adulthood in 1992. In 1975, mothers of these children were interviewed to obtain the health status and a range of other factors relevant to the children's well-being. The follow-up interviews were conducted in 1983, 1985-1986 and 1991-1993. In 1983 and 1986, parent and child interviews were done and the presence of psychiatric disorders was assessed by using a modification of the Diagnostic Interview Schedule for Children. In 1992, only the young adults were investigated in respect of the psychiatric disorders by using an expanded Diagnostic Interview Schedule for Children. Strong positive associations were found between the preceding atopic disorders and a subsequent new-onset of major depressive disorder with the odds ratio reaching even up to 6.41 (95% CI 2.42-16.46) from early childhood to adolescence and still being 1.88 (95% CI 1.07-3.30) from childhood to adulthood.

In a cross-sectional analysis of survey data from 6836 adults between the ages of 20 and 39, Hurwitz and Morgenstern (1999) examined the associations of allergic conditions with depression and low-back pain. A history of depression was obtained from the Diagnostic Interview Schedule. Study subjects responded to questions regarding history of asthma, hay fever and other allergies (i.e., history of insect reaction, food reaction, pet allergy and history of shot/test reaction). The investigators found that respondents with both asthma and hay fever were twice as likely to have been diagnosed with major depression in the past 12 months (OR=2.06, 95% CI 1.32-3.21 and OR=2.03, 95% CI 1.28-3.20, respectively) than those without these illnesses. The corresponding odds ratio was 1.87 (95% CI 1.25-2.79) if respondents had a history of any allergy/allergic reaction.

While investigating economic consequences of co-morbid depression, anxiety, and allergic rhinitis in a database of over 600000 privately insured persons, Cuffel *et al.* (1999) found that allergic rhinitis was associated with increased rates of depression and anxiety disorders, the OR of depressive disorders being approximately 1.7-fold (95% CI 1.63-1.73) in the allergic rhinitis sample when compared with the non-allergic rhinitis sample. In addition, co-morbid allergic rhinitis, depression and anxiety were associated with increased health and mental health expenditures. Interestingly, prescription treatment of allergic rhinitis was found to moderate the increased expenditures associated with co-morbidity (Cuffel *et al.* 1999).

2.9.4 Genetic studies

2.9.4.1 Atopy in family members of a proband suffering from depression

There are few studies that investigate the presence of atopic disorders in relatives of patients suffering from depression. However, as described in chapter 2.9.1, Nasr *et al.* (1981) evaluated the personal and family histories of bronchial asthma and/or allergic rhinitis from 82 psychiatric patients. With regard to familiality, they found that the rate of atopy in first-degree relatives of the patients suffering from bipolar and unipolar depression was statistically significantly ($p<0.005$) higher than that of the relatives of the schizophrenic patients (13.5% vs. 5.5%). The authors suggested that the high rate of concurrence of atopic disorders and affective illness might be indicative of the existence of a genetic association/a common pathophysiological mechanism between these disorders.

2.9.4.2 Depression in family members of an atopic proband

Likewise, there are only a few studies in which the association of depression in family members of an atopic proband has been investigated. In support of the genetic linkage hypothesis it has been, however, noted that mothers of asthmatic children exhibited statistically significantly ($p=0.01$) higher rates (45.4%) of depression when compared with controls (27.7%) (Davis 1977). It has been, however, suggested that this link could also have environmental explanations, such as family interactional processes (Wamboldt *et al.* 1996, 2000, Galil 2000). Wamboldt *et al.* (1996) found that first degree relatives of adolescents with severe asthma had also statistically significantly ($p=0.003$ in male relatives and $p<0.001$ in female relatives) higher rates of depression when compared with those of non-ill comparison samples obtained from previously reported studies. This clearly supported the notion of a genetic association between these disorders (Galil 2000).

2.9.4.3 Twin studies

Twin-studies, based on non-clinical samples, are also suggesting a common genetic rather than an environmental etiology of these two disorders (Wamboldt *et al.* 1998, 2000). In a community sample of 207 twin pairs (children, whose mean age was 7 years and 7 months) the association between atopy and behavioural symptoms was investigated by using parent report questionnaires. The children's behaviour was assessed with the help of the Child Behavior Checklist. The atopy score was derived from questioning the parent about whether a doctor had ever said that the child had allergies to pollen, food, or medicines, or whether a doctor diagnosed the child as having asthma or treated the child

as a consequence of allergy shots. The results suggested that a common additive genetic effect accounts for 77% of the covariance between atopic symptoms and the symptoms of anxiety or depression (Wamboldt *et al.* 1998) Recently, Wamboldt *et al.* (2000) demonstrated the existence of an association between self-reported indices of atopic illness and at least moderate depression, according to the Beck Depression Index (BDI), in a large sample of Finnish adult twins. The authors estimated that 64% of the association between atopy and depression were due to additive genetic effects but, as the authors pointed out themselves, their measures to ascertain allergic status - a tabulation of up to three diagnoses of allergic disorders derived from questionnaire responses - were crude and a single BDI score provided only a very limited approximation of lifetime depression (Wamboldt *et al.* 2000).

2.9.5 Other factors related to atopy-depression association

As reviewed by Wamboldt *et al.* (2000) there exist also certain environmental factors, which could conceivably influence both disorders. Of the family interactional processes, parent-child conflict/parental criticism has been shown to be associated with both asthma and depression (Hermanns *et al.* 1989, Schobinger *et al.* 1992, Asarnow *et al.* 1993, 1994, Wamblodt *et al.* 2000).

With regard to sociodemographic factors, a prevalence of depression has been shown to be associated with decreasing social class (Lehtinen & Joukamaa 1994). On the other hand, belonging to an unprivileged social class has been noted to be related to lower incidences of allergies (Williams *et al.* 1994). In previous Finnish surveys, depression has been shown to be most prevalent in the most heavily populated areas of the country, i.e., in southern Finland, and in cities (Väisänen 1975, Lehtinen & Joukamaa 1994). Furthermore, as presented in chapter 2.2, having experienced a farm environment during childhood had been noted to be correlated with lower incidences of allergies (Kilpeläinen *et al.* 2000). Large numbers of children in a family and mother's high parity were found to be associated with decreased risks of atopic allergies (Strachan 1989, Pekkanen *et al.* 2001b), but an increased probability of depressive disorders (Kemppainen *et al.* 2000).

In previous studies, also exposure to tobacco smoke *in utero*, and current own smoking activities have been shown to be associated with atopic disorders (Backer *et al.* 2002, Devereux *et al.* 2002) and depression (Fergusson *et al.* 1998, Dierker *et al.* 2002). However, also opposite results regarding the effect of exposure to tobacco smoke on atopic sensibilization have been published: the prevalences of allergic asthma and allergic rhino-conjunctivitis have been shown to be decreased with increasing exposure to tobacco smoke in an adult Swedish study population (Hjern *et al.* 2001). In addition, children, who had been exposed to tobacco smoke in childhood, were noted to have lower risks for atopic disorders (Hjern *et al.* 2001, von Linstow *et al.* 2002).

2.10 The associations between other physical disorders and depression

It is evident that depression is associated also with a wide range of physical illnesses other than atopic disorders (Horrobin & Bennet 1999, Evans & Charney 2003, Katon 2003). As reviewed by Horrobin & Bennet (1999) and Katon (2003), studies of patients with e.g., diabetes mellitus, coronary artery disease, and certain neurologic illnesses have reported higher rates of major depression than in patients without these disorders. A recent meta-analysis of studies of major depression in patients with diabetes showed that the odds of major depression in the diabetes group was twice (OR=2.0, 95%CI 1.8-2.2) that of the nondiabetic group (Anderson *et al.* 2001, Katon 2003). Further, rates of major depression have been shown to vary between 17% and 27% in patients with coronary artery disease (for a review, see Rudisch & Nemeroff 2003). In addition, the prevalence of major depression has been found to be 20%-30% and 16%-30% in patients with Parkinson's disease and multiple sclerosis, respectively (for a review, see Katon 2003).

The relationship between depression and certain physical illnesses is probably bidirectional in nature: physical illness may be a risk factor for depression because of psychosocial stressors, functional impairment, and other biological mechanisms on the one hand, but, on the other, depression may serve as an etiologic factor in the onset and course of somatic illness as reviewed by Evans & Charney (2003). Even though the physical illness may have a direct pathophysiologic effect on the brain (i.e., multiple sclerosis), or have indirect physiologic effects (i.e., increasing cytokine levels that affect the brain), the exact mechanisms behind the associations between physical illnesses and depression have largely remained unclear (Horrobin & Bennet 1999, Joynt *et al.* 2003, Katon 2003). It is also possible that both certain somatic illnesses and depression are attributable to some third factor, being behind the pathophysiology of both disorders (Horrobin & Bennet 1999).

2.11 Summary of the reviewed literature: what is known and what should be studied?

Both depression and atopic disorders are illnesses of major public health concern in many Western societies. During the last few decades, evidence has been accumulating to indicate that there exist an association between these two disorders. There are several theories attempting to explain the co-occurrence of atopic disorders and depression: Firstly, since atopic allergy itself is an IgE-mediated immune system disorder and depression has been shown to be associated with changes in altered immunity, it could be postulated that certain immune mediators, for example cytokines, could contribute to the mechanism behind both allergic and depressive symptoms. Secondly, in both disorders there exist many other common biochemical features, such as changes in the function of the HPA-axis. Thirdly, psychosocial/environmental factors can also play a role, assuming a common etiology behind these disorders, because it is known that e.g., parental

criticism is associated with both disorders. Finally, it has recently been postulated that a majority of the association between atopic disorders and depression is likely due to common genetic effects. On the other hand, the association between atopic disorders and depression might be non-specific, and therefore could be explained by some third factor, because, e.g., increased risks of depression have been noted in connection with many other physical diseases than atopic disorders as well. Any associations between physical disorders other than atopic disorders and depression are, however, beyond the scope of this thesis.

Most of the previous studies that concern themselves with the association between atopic disorders and depression are, however, based on restricted data sample settings, in which the association between the two disorders has been investigated by studying patients suffering from either depressive or atopic symptoms. Thus, there is a need for large epidemiological studies with general population databases to investigate this putative atopy-depression association.

The interpretation between different studies concerning the association between atopic disorders and depression is hampered due to differences in definitions of depression/depressive symptoms; many different rating scales have been used in case definitions. Whether the strength of the association between atopic disorders and depression is dependent on the severity of depression is, in addition, a very sparsely studied area. Therefore, the association should be investigated according to different grades of severity of depressive symptoms, e.g., self-reported depression in the general population versus severe depression requiring hospital admission. Earlier studies are also heterogeneous in terms of defining atopy, and the presence of atopic disorders is not necessarily verified by objective measurements such as skin prick test responses.

Even though there exist a few investigations which show an increased rate of depression especially among mothers of atopic children, and even though it has been suggested that a majority of the association between atopy and depression is due to additive genetic effects, there is a considerable lack of studies investigating the putative genetic linkage between atopy in first degree relatives and depression of a proband.

3 Aims of the present study

The purpose of this study was to investigate the association between atopic disorders and depression by using a large, general population birth cohort. The numbers I-IV hereafter refer to the original publications.

The aims of the present study were:

1. To examine the association between lifetime hospital admissions due to atopic disorders and depression (I).
2. To study, whether atopy verified by skin prick tests is associated with self-reported professionally diagnosed depression (II).
3. To investigate whether the association between atopic disorders and depression is dependent on the severity of depressive symptoms assessed with Hopkins Symptom Checklist-25, and/or whether it is dependent on the gender of a person (III).
4. To investigate, whether there is an association of parental atopy and sibling's atopy with depression of a proband (IV).

4 Materials and Methods

4.1 The Northern Finland 1966 Birth Cohort

4.1.1 Data collection

The foundation for the present thesis was provided by the database of the Northern Finland 1966 Birth Cohort. Originally, the Northern Finland 1966 Birth Cohort, called nowadays the Northern Finland Health and Well-being Study, was assembled by Professor (emerita) Paula Rantakallio. She aimed to describe and analyse the risk factors for perinatal deaths and low birth weight. This database is based on the unselected, genetically homogenous general population: In the two northernmost Finnish provinces, i.e., Oulu and Lapland, 96% of all women (n=12068), with an expected date of delivery falling between 1st January and 31st December, were evaluated. They gave birth to 12058 liveborn infants. The majority of the cohort members are Finns, with less than 1% being Lapps and Gypsies (nowadays often referred to as "Roma"). A variety of biological, socioeconomic and health conditions as well as living habits and family characteristics of the cohort members have been collected prospectively from pre-natal stages up to the age of 31 (Rantakallio 1969, 1988; Rantakallio *et al.* 1995, 1997).

4.1.2 The follow-ups

The follow-up of the cohort members has been continued until these days, and the data thus collected have regularly been linked to national registers, e.g., hospital discharge registers. Until the end of 2001 three main follow-up surveys have been conducted. The first follow-up was performed when a cohort member was one year old (1-year follow-up) in 1967. Data on growth, development and health status of the children at that time was gathered (Rantakallio 1988).

The second follow-up of the cohort (14-year follow-up) was conducted at the end of 1980 and in early 1981 by using postal questionnaires. Each child and their families were asked about the child's health, growth, hobbies, living habits, school performance, as well as the social situation of the family and family background variables (Rantakallio 1988, Järvelin *et al.* 1997). The response rates in this survey reached up to 97%. By the age of 14 years, 278 cohort members had died. Thus, the number of the cohort members alive at that time was 11780 (Rantakallio 1988).

The latest follow up was conducted during 1997-98 (Sorri & Järvelin 1998). In this 31-year follow-up survey, postal questionnaires were sent to 11541 cohort members, and the response rate was 75.3%. All those, who were living in northern Finland or in the capital area, were invited to a clinical examination (n=8463) and 71.2% attended.

The data collection procedure in the Northern Finland 1966 Birth Cohort Study and the main data used in the original publications I-IV are presented in Figure 2.

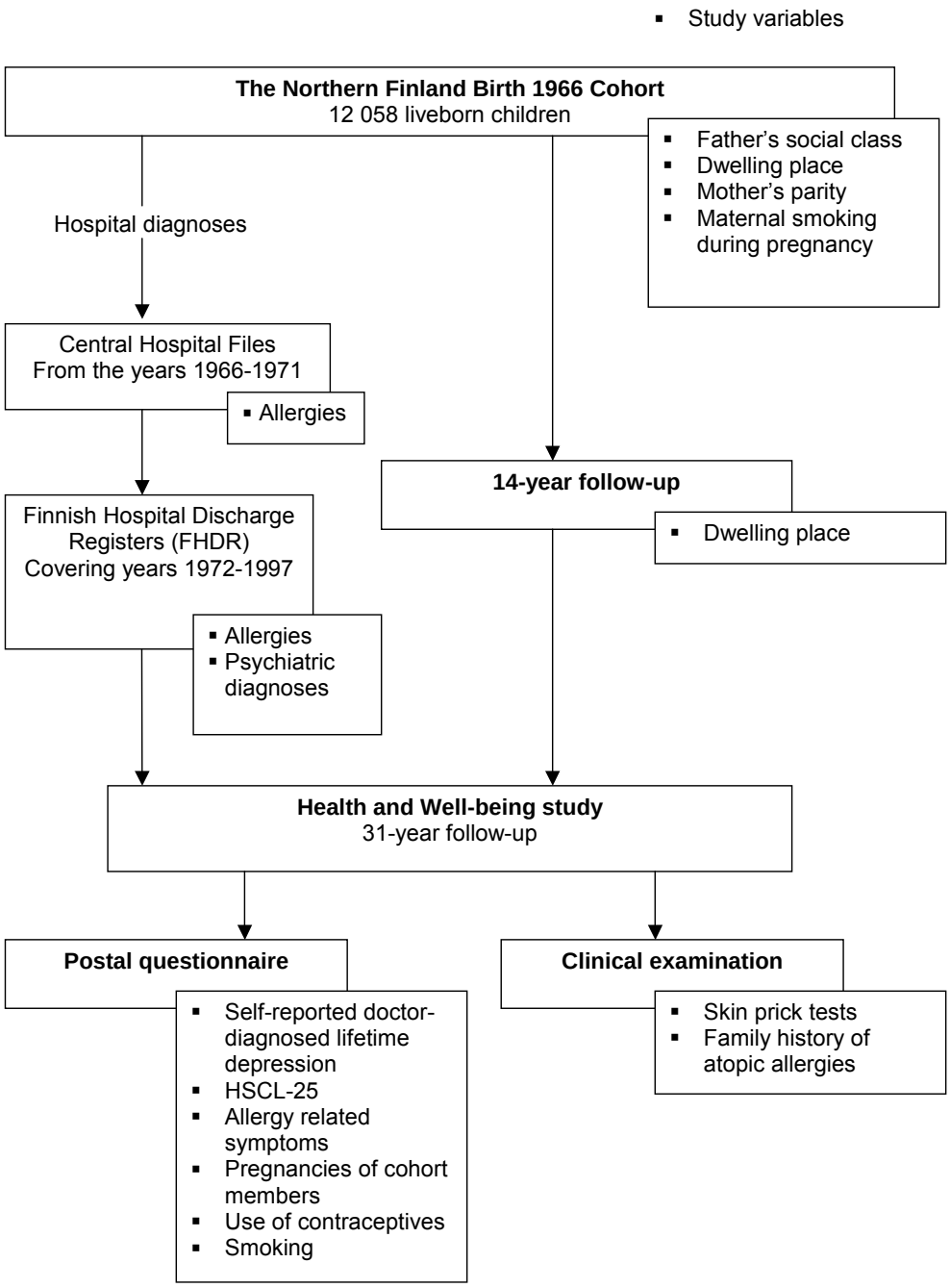

Fig. 2. The flowchart of the data collection procedure in the Northern Finland 1966 Birth Cohort Study and the main data used in the original publications I-IV.

4.2 Variables

4.2.1 Outcome variables

4.2.1.1 Hospital-treated depression (I, IV)

In Finland, diagnoses have been coded according to the International Classification of Diseases (ICD-7, up to 1968; ICD-8, 1969-1986; ICD-9, 1987-1995; ICD-10 1996 and thereafter) (World Health Organization 1967, 1977, 1993). From 1972 hospital diagnoses were obtained from the hospital discharge register maintained by the Finnish National Board of Health and later from the Hospital Care Register maintained by the National Research and Development Center for Welfare and Health until the end of 1997. These Finnish Hospital Discharge Registers (FHDR) cover all treatment episodes in general, mental, military, prison and private hospitals, as well as the inpatient wards of local health centers nation-wide. The FHDR contains the personal and hospital identification codes, data on age, gender, length of stay, and primary diagnosis at discharge, together with three subsidiary diagnoses. These register data have been shown to be of sufficiently high accuracy to be used in research (Poikolainen 1983, Keskimäki & Aro 1991, Näyhä 1992, Mähönen *et al.* 2000).

All cohort members having been admitted to a hospital during 1982-1997 (aged 16 to 31 years) due to a psychiatric disorder (i.e., ICD-8 290-309, 7092; ICD-9 290-316) were identified from the FHDR. Further, their hospital case notes were collected and the FHDR diagnoses were carefully validated by re-checking them against DSM-III-R criteria (American Psychiatric Association 1987, Isohanni *et al.* 1997, Moilanen *et al.* 2003).

In the original publications I and IV, those subjects who fulfilled the diagnostic criteria of major depression (DSM-III-R codes 296.2-296.3), depressive disorder Not Otherwise Specified (311.00) or dysthymia (300.40) were defined to suffer from hospital-treated depression.

4.2.1.2 Self-reported doctor-diagnosed lifetime depression (II, III, IV)

In the original publications II-IV, data on self-reported lifetime doctor-diagnosed depression were obtained from the postal questionnaires of the 31-year follow-up survey. Cohort members were asked the following question: “Have you ever been diagnosed by a doctor as having depression or have you ever been treated by a doctor because of depression (yes/no).”

4.2.1.3 Hopkins Symptom Checklist-25 (HSCL-25) (III)

In the original publication III, information of depressive symptoms was determined through Hopkins Symptom Checklist-25 (HSCL-25), which is a 25-item shortened version of an 90-item questionnaire designed by Derogatis *et al.* (1973). HSCL-25 was included to the postal questionnaires of the 31-year follow-up survey. A depression subscale consists of 13 items: feeling low in energy/slowed down, blaming yourself for things, crying easily, loss of sexual interest or pleasure, feeling hopeless about the future, feeling blue, feeling lonely, thoughts of ending your life, feeling of being trapped or caught, worrying too much about things, feeling no interest in anything, feeling everything is an effort, feeling worthless (Winocur *et al.* 1984).

Cohort members estimated the severity of their depressive symptoms on a four-point scale ranging from 1 ("not at all") to 4 ("extremely"). Responses were summed and divided by the number of answered items to generate a "depression mean score" ranging from 1.0 to 4.0. This mean score was utilized to categorize the cohort members to subgroups according to the severity of their depressive symptoms. In addition to two commonly used mean scores of 1.55 and 1.75 (Nettelbladt *et al.* 1993, Sandanger *et al.* 1998), a cut-off point of 2.01 was also used in the original publication III, because it is known that duration of symptoms is an essential factor in the diagnosis of major depressive disorder, and because Winocur *et al.* (1984) have found that patients, who were considered to be highly symptomatic (i.e., had a score over 2.0), showed more consistent ratings over a whole follow-up period than subjects with lower scores (e.g., cut-off point <2.0).

4.2.2 Exposure variables

4.2.2.1 Hospital-treated atopic disorder (I)

Hospital diagnosed atopic disorders of cohort members up to the age of 31 years were collected from central hospital files by the research group covering the years 1966-1971 (Moilanen & Rantakallio 1988), and extracted from the FHDR between the years 1972-1997. Cohort members, who had at least one of the following diagnoses: bronchial asthma (ICD-9 code 493), allergic rhinitis (477), or atopic eczema (691), were identified and considered to have an atopic disorder in the original publication I.

4.2.2.2 Skin prick tests (II, III, IV)

In the 31-year follow-up survey, skin prick tests to three of the most common allergens in Finland (i.e., cat, birch, and timothy grass) and the house dust mite (*Dermatophagoides pteronyssinus*) were carried out. Histamine dihydrochloride (10 mg per ml) and diluent of

the allergen extracts were used as positive and negative controls, respectively. After 15 minutes, skin reactions to each allergen were recorded as the average of the maximum wheal diameter and the diameter perpendicular to the maximum value. In the original publication II, subjects with a wheal reaction ≥3 mm (i.e., skin prick test positive) to one or more of the four allergens tested were considered to be "atopic", based on the biological approach in that paper. In the publications III and IV, the term "positive skin prick test response" was preferred to the term "atopic", because the concept of atopic disorder was considered in a more clinical sense in those papers. All prick-tested subjects had a positive reaction to histamine, but subjects with positive reactions to the negative control were rejected.

4.2.2.3 Symptoms of allergy (II, III)

In clinical practice, the presence of atopy requires not only a positive skin prick test response but also clinical symptoms of allergy (Wamboldt *et al.* 1998). Therefore, data on a cohort member's lifetime history of allergic diseases were gathered from postal questionnaires of the 31-year follow-up survey. Each person was asked to evaluate if, "he/she has ever had the following allergy-related symptoms or diseases: asthma, allergic rhinitis, atopic eczema, and/or allergic conjunctivitis.(yes/no)?" Symptoms of allergies were considered to be present if a cohort member had at least one of these self-reported allergic disorders/symptoms.

4.2.2.4 Family history of atopy (IV)

Data on the family histories of atopies were obtained through questionnaires included in the 31-year follow-up survey and posing the following, separate questions: "Have your a) father, b) mother or c) "any of your siblings" suffered from asthma, allergic rhinitis, or atopic eczema (yes/no)?". Parental/sibling atopy were considered to be present if at least one of the parents/at least one sibling had or had had asthma, allergic rhinitis or atopic eczema.

4.2.2.5 Self-reported doctor-diagnosed clinical history of allergic disorders (IV)

In the original publication IV, data on self-reported doctor-diagnosed clinical histories of allergic disorders were obtained from the postal questionnaires of the 31-year follow-up survey. Cohort members were asked the question: "Have you ever been diagnosed by a doctor as having or having had the following allergy-related symptoms or diseases: asthma, allergic rhinitis, atopic eczema, and/or allergic conjunctivitis, or have you ever

been treated by a doctor due to the following allergy-related symptoms or diseases: asthma, allergic rhinitis, atopic eczema, and/or allergic conjunctivitis (yes/no)?". Clinical history of allergic disorders was considered to be present if a cohort member had ever had at least one of these self-reported doctor-diagnosed allergic disorders/symptoms.

4.2.3 Confounding variables

The confounding variables used in the original publications I-IV are presented in Table 1. A father's social class, the dwelling place and a mother's parity were used as potential confounding factors, because in previous studies, they were shown to be associated with atopic disorders (Kilpeläinen *et al.* 2000, Pekkanen *et al.* 2001b, Williams *et al.* 1994) and depression (Kemppainen *et al.* 2000, Lenzi *et al.* 1993, Väisänen 1975).

Table 1. Confounding variables used in the original publications (I-IV)

Confounding variables	Original publication
Father's social class in 1966	I-IV
Dwelling place in 1966	II-IV
Mother's parity in 1966	II-IV
Cohort member's hospital-diagnosed psychiatric diseases	II
Pregnancy of a cohort member (in females)	II
Use of oral contraceptives (in females).	II
Dwelling place in 1980	I
Gender of a cohort member	I
Maternal smoking during pregnancy	IV
Cohort member's regular daily smoking at the age of 31	IV

4.2.3.1 Father's social class in 1966

A father's social class in 1966 was defined according to the father's occupation and its prestige in 1966 (Sosiaaliryhmitys 1954, Rantakallio 1969, Rantakallio 1979). In the highest social stratum, class I, the father's occupation has the highest prestige and usually required academic education. Examples of occupations in social class I are elementary school teachers, general practitioners, professional engineers and priests. Fathers from social class II were professionals with lower valuation and shorter education than in class I, e.g., office managers and ship's engineers. Social class III consisted of skilled workers like clerks and stewards, and class IV contained unskilled workers like night watch men and office boys as well as persons on a disability pension. Farmers formed social class V. In all original publications, the father's social class was re-categorized to three subgroups: classes I-II/classes III-IV/farmers.

4.2.3.2 Dwelling place in 1966 and in 1980

The dwelling place in 1966 was defined according to the place of residence of the mother at the time of delivery, and it was divided into urban/rural categories in the original publications II-IV (Rantakallio 1969, Rantakallio *et al.* 1992). The dwelling place of the family in 1980 (urban/rural) was used in the original publication I (Rantakallio *et al.* 1992).

4.2.3.3 Mothers parity in 1966

A mother's parity (number of deliveries) in 1966 was used in the original publications II-IV. Parity status was defined as grand multiparity (Juntunen 1997, Kemppainen *et al.* 2000), if the mother had undergone six or more deliveries (yes/no).

4.2.3.4 Hospital-diagnosed psychiatric diseases

Hospital-diagnosed psychiatric diseases (yes/no) were also used as a potential confounder in the original study II, because psychiatric disorders had been shown to be associated with physical illnesses (Mäkikyrö *et al.* 1998), and because of the high amount of co-morbidity between depression and other psychiatric disorders (Beekman *et al.* 2000, Kessler *et al.* 1996, Kool *et al.* 2000, Zisook *et al.* 1999). Psychiatric diagnoses (i.e., ICD-8 290-309, ICD-9 290-316, and ICD-10 F00-F69) of cohort members were obtained from the FHDR, and thereafter validated in detail as described in chapter 4.2.1.1 (Isohanni *et al.* 1997, Moilanen *et al.* 2003). In the original publication II, hospital-diagnosed psychiatric diseases were defined to be present if a cohort member had been admitted to hospital due to any of the above mentioned psychiatric disorders at least once before the age of 32.

4.2.3.5 Pregnancy and the use of oral contraceptives

Reproductive experience causes long-term psychological and physiological effects (Hucke *et al.* 2001). Further, female sex hormones may play a role in the mechanisms associated with both depression (Freeman 2001, Joffe & Cohen 1998) and atopic disorders (Balzano *et al.* 2001, Stubner *et al.* 1999). Therefore, the following variables were used as potential confounding factors in females in the original study II: a) a pregnancy of a cohort member (at least one pregnancy before the age of 31, yes/no), and b) the use of oral contraceptives (yes/no). This information was extracted from the postal questionnaires of the 31-year follow-up survey.

4.2.3.6 Tobacco exposure variables

In previous studies, also exposure to tobacco smoke *in utero* and current own smoking have been shown to be associated with atopic disorders (Backer *et al.* 2002, Devereux *et al.* 2002) and depression (Fergusson *et al.* 1998, Dierker *et al.* 2002). Therefore, maternal smoking during pregnancy (yes/no) (Rantakallio *et al.* 1992, Järvelin *et al.* 1997, Räsänen *et al.* 1999) and a cohort member's regular daily smoking at the age of 31 were used as potential confounding factors in the original publication IV.

Details with regard to the variable of maternal smoking during pregnancy had been obtained from the mothers of the probands during the time of their pregnancies and their visits to the antenatal clinics, and also after the delivery (Rantakallio 1969, Rantakallio *et al.* 1992). Maternal smoking was classified as "yes", if the mother had smoked during the pregnancy (after second month of the pregnancy) and "no" if the mother did not smoke or had stopped before the pregnancy (Järvelin *et al.* 1997, Räsänen *et al.* 1999).

Data on a cohort member's regular daily smoking habits at the age of 31 were obtained through postal questionnaires of the 31-year follow-up survey by posing the following questions: "Have you ever smoked in your life?" If the answer was "yes", then cohort members were questioned "Do you smoke at present?" with several alternatives to the answer (Isohanni *et al.* 2001). A subject's own regular daily smoking was dichotomized as follows: regular smokers [i.e., smoking on 7 days a week] versus occasional [i.e., smoking less than on 7 days per week] and non-smokers (Isohanni *et al.* 2001).

4.3 Statistical methods

In the original study I, a logistic regression analysis was used to examine an association of hospital-treated atopic disorder to depression after adjusting for sex (male/female), father's social class in 1966 (classes I-II/classes III-IV/farmers) (Rantakallio 1979), and the dwelling place in 1980 (urban/rural) (Rantakallio *et al.* 1992).

In the original study II, the proportions of prick test positive cases were compared, separately for males and females, with those of prick test negative ones. Unadjusted odds ratios (OR) and their 95% confidence interval (CI) were calculated for those who were atopic to estimate the increased risk of being depressed sometime in their lifetime. Logistic regression analysis was used to examine the association between atopy and depression, adjusting for confounding variables presented in Table 1. In clinical practice, the presence of atopy requires both positive skin prick tests and clinical symptoms. Therefore, a logistic regression analysis was used to investigate the association between allergic disorders ascertained by skin prick test responses and depression adjusting for confounding variables.

In the original study III, the continuation ratio model was used to estimate the association between depression and allergic symptoms verified by skin prick test responses. This model partitions the analysis of the outcome variable into three different logistic regression models (doctor-diagnosed depression in three different HSCL-25 depression subscale cut-off points (>1.54, >1.74 and >2.00)) for dichotomous responses

(Agresti 1990). Non-depressive subjects in the outcome variable consisted of those cohort members who had neither self-reported doctor-diagnosed lifetime depression nor depressive symptoms in the HSCL-25 depression subscale (mean score=1.0). The final models used odds ratios (OR) and 95% confidence intervals (95%CI) after controlling for confounders presented in Table 1.

In the original study IV, associations of independent variables (cohort member's atopy verified by positive skin prick test response, parental atopy and sibling atopy) and potential confounding factors with self-reported and hospital-treated depression of a cohort member were analyzed separately for both genders with the Chi-Squared Automatic Interaction Detector (CHAID) technique (Moles & Bedi 1997). CHAID divides a population into a series of groups, based on their ability to predict a dependent variable (i.e., depression in this study). The result is a tree diagram. At each stage in the generation of the tree, multiple chi-square-tests are performed in order to select the current most significant predictor of the dependent variable. When there are no more statistically significant predictors (i.e., p-value<0.05), the generation of the tree stops. Due to the small number of hospital-treated depressions among the cohort members, Fisher's Exact test was also used alongside with the chi-square test. In addition, multivariate logistic regression analysis was used to examine the association between exposure variables (cohort member's atopy, parental atopy and siblings' atopy) and self-reported depression of a cohort member when potential/possible confounding factors (presented in Table 1) were adjusted. In order to estimate whether an individual atopic disorder in combination with maternal, paternal or a sibling's atopy were risks with regard to a proband's depression, odds ratios with 95% confidence intervals were calculated for male and female cohort members, characterized by several combinations of family atopy variables. A group with no own/family member's atopy was used as a reference group in the logistic regression analyses.

Statistical analyses were performed using the SPSS version 9.0 for Windows in the original publication I (SPSS Inc. 2001), and by using the SAS software (version 8e) for Windows in the original publications II-IV (SAS Institute Inc. 1999)

4.4 Ethical considerations

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 under review by the Ethics Committee of the Faculty of Medicine, University of Oulu on 17th of June 1996. During the 31-year follow-up, after having been given a complete description of the study, the cohort members have had an opportunity to refuse the use of their data at any point of the data collection.

This study has been approved by the Dean of the Faculty of Medicine, University of Oulu, on 30th of August 2000 as one part of the Northern Finland Health and Well-being Study. Thus, the permission by the Ethics Committee of the Faculty of Medicine on the 17th of June, 1996, covers also the present study. In addition, on the 28th of January 2003,

this study has been approved by the Postgraduate Research Committee of the Faculty of Medicine, University of Oulu.

5 Results

5.1 Atopy and self-reported lifetime depression

While assessing whether depression, in general, is associated with atopy, each cohort member was asked if he/she had ever been treated or diagnosed by a doctor for depression. The likelihood of depression among skin prick test positive cohort members when compared with skin-test negative ones is presented in Table 2 (II: Table 1). The result showed that 6.9% of all females with positive prick tests had been suffering from depression sometime during their lifetime, while the corresponding percentage for females with negative prick test was 4.3%. When in addition to a positive skin test response, also self-reported allergic symptoms were taken into account in defining the presence of atopy, the probability of depression in females increased from 1.8 (95% CI 1.2-2.6) to 2.7-fold (95% CI 1.6-4.6). Among males, there were no statistically significant differences in the proportions of depression (3.0% and 2.9%) in atopic and non-atopic males, respectively (Table 2; II: Table 1).

Table 2. Associations between prick tested atopies and self-administered information of doctor-diagnosed lifetime depression in the Northern Finland 1966 Birth Cohort. (II: Table 1).

Gender and atopy	n	Depressed n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Men				
Prick test positive	904	27 (3.0)	1.0 (0.6–1.6)	0.9* (0.5–1.6)
Prick test negative	1817	53 (2.9)	Reference	Reference
Women				
Prick test positive	750	52 (6.9)	1.6 (1.1–2.3)	1.8** (1.2–2.6)
Prick test negative	1957	85 (4.3)	Reference	Reference

*Adjusting variables were father's social class, mother's parity, and place of residence in 1966, and cohort member's hospital-diagnosed psychiatric disease.

**Adjusting variables were father's social class, mother's parity, and place of residence in 1966, and cohort member's hospital-diagnosed psychiatric disease, use of oral contraceptives, and at least one pregnancy before the age of 32.

5.2 Atopy and the severity of current depression verified by HSCL-depression subscale

In the original publication III, it was investigated whether the strength of the association between atopic disorders and depression was dependent on the severity of the depression. The results (Table 3) showed that the probability of depression – defined by self-reported doctor-diagnosed lifetime depression and with the help of the HSCL-25 depression subscale – increased in line with the increased severity of depressive symptoms in atopic but not in non-atopic females ranging from 3.0 to 4.7-fold (III: Table 2). Among males a corresponding statistically significant association was seen only in the highest depression scores (mean HSCL-25 score over 2.0), adjusted OR being even 6.3-fold (Table 3; III: Table 2).

Table 3. The associations between self-reported doctor-diagnosed lifetime depression and atopic symptoms, verified by skin prick tests as assessed with three logistic regression models according to different cut-off points for HCSL-25 depression subscale (13-items) scores after adjusting for confounding variables in the Northern Finland 1966 Birth Cohort by gender (III: Table 2).*

The status of atopy	1.55–4.00 (vs. No depression**) OR (95% CI)	1.75–4.00 (vs. No depression**) OR (95% CI)	2.01–4.00 (vs. No depression**) OR (95% CI)
Males			
Allergic symptoms+&Prick+	1.6 (0.8–3.3)	2.1 (1.0–4.8)	6.3 (1.7–22.2)
Allergic symptoms+&Prick-	0.9 (0.4–2.1)	1.3 (0.5–3.1)	3.4 (0.8–14.2)
Allergic symptoms-&Prick+	0.5 (0.1–2.2)	0.7 (0.2–3.3)	3.0 (0.5–18.3)
Allergic symptoms-&Prick-	Reference	Reference	Reference
Females			
Allergic symptoms+&Prick+	3.0 (1.5–6.2)	3.7 (1.7–8.3)	4.7 (1.8–12.5)
Allergic symptoms+&Prick-	2.1 (1.1–4.2)	2.4 (1.1–5.2)	2.1 (0.8–5.8)
Allergic symptoms-&Prick+	1.2 (0.3–4.7)	1.2 (0.2–5.8)	2.1 (0.4–11.6)
Allergic symptoms-&Prick-	Reference	Reference	Reference

*Adjusting variables were father's social class (I and II =highest, III, IV=lowest, V=farmers), mother's parity (1, 2-3, 4-5, 6 or more), and place of residence in 1966 (rural, urban).

** 'No depression' means that subject's HSCL-25 depression subscale score was equal to 1.0 and he/she had no self-reported doctor-diagnosed lifetime depression.

5.3 Hospital-treated atopic disorders and depression

When the most severe manifestation of both atopic and depressive disorders were examined, the results (Table 4) showed that hospital-treated atopic disorders increased the probability of hospital-treated depression up to three-fold (OR 3.0, 95% CI 1.4-6.6) after controlling for gender and sociodemographic characteristics of the cohort members (I: Table 1).

Table 4. The association between hospital-treated atopic disorders and hospital-treated depression among the Northern Finland 1966 Birth Cohort members and their sociodemographic factors (I: Table 1).

Variables	Depression (n=64)		No mental disorders (n=10423)		Adjusted Odds ratio*
	n	%	n	%	OR (95 % CI)
Atopic disease in FHDR					
Yes	7	10.9	412	4.0	3.0 (1.4–6.6)
No (reference)	57	89.1	10011	96.0	
Sociodemographic factors					
Sex					
Male	35	54.7	5262	50.5	1.2 (0.7–1.9)
Female (reference)	29	45.3	5161	49.5	
Paternal social class in 1966					
Lower	51	79.7	7645	73.3	2.5 (0.6–10.2)
Farmers	11	17.2	2020	19.4	1.9 (0.4–8.7)
Upper (reference)	2	3.1	758	7.3	
Dwelling place 1980					
Urban	40	62.5	4467	42.9	1.3 (0.8–2.1)
Rural (reference)	24	37.5	5956	57.1	

*Variables in logistic regression: Sex, father's social class in 1966, dwelling place in 1980, and atopic disease according to the Finnish Hospital Discharge Register (FHDR). Dependent variable: Depression vs. no mental disorders according to the FHDR.

5.4 Atopy of the first degree relatives and depression of the proband

The CHAID technique was used to analyze the effects of maternal, paternal, and siblings' atopies on a proband's depression. As Figure 3 shows, in females the strongest risk factor in predicting self-reported lifetime depression was the presence of parental atopy (chi-square test, $\chi 2=12.3$, df=1, $p<0.001$) (IV: Figure 1). Another statistically significant predictor of depression was a proband's regular daily smoking ($\chi 2= 11.9$, df=1, $p<0.001$): When either mother or father were atopics, the proportion of cohort members with depression was 12.7%. Among non-smokers, whose parents and who themselves were atopics, the corresponding proportion was 9.0%. Interestingly, if there existed no parental history of atopy, then living in an urban area as well as a city dweller's own atopy, were both statistically significant predictors of depression.

Figure 4 presents the results for hospital-treated depression in females (IV: Figure 2). Both sibling's atopy as well as parental atopy were significant predictors for hospital-treated depression.

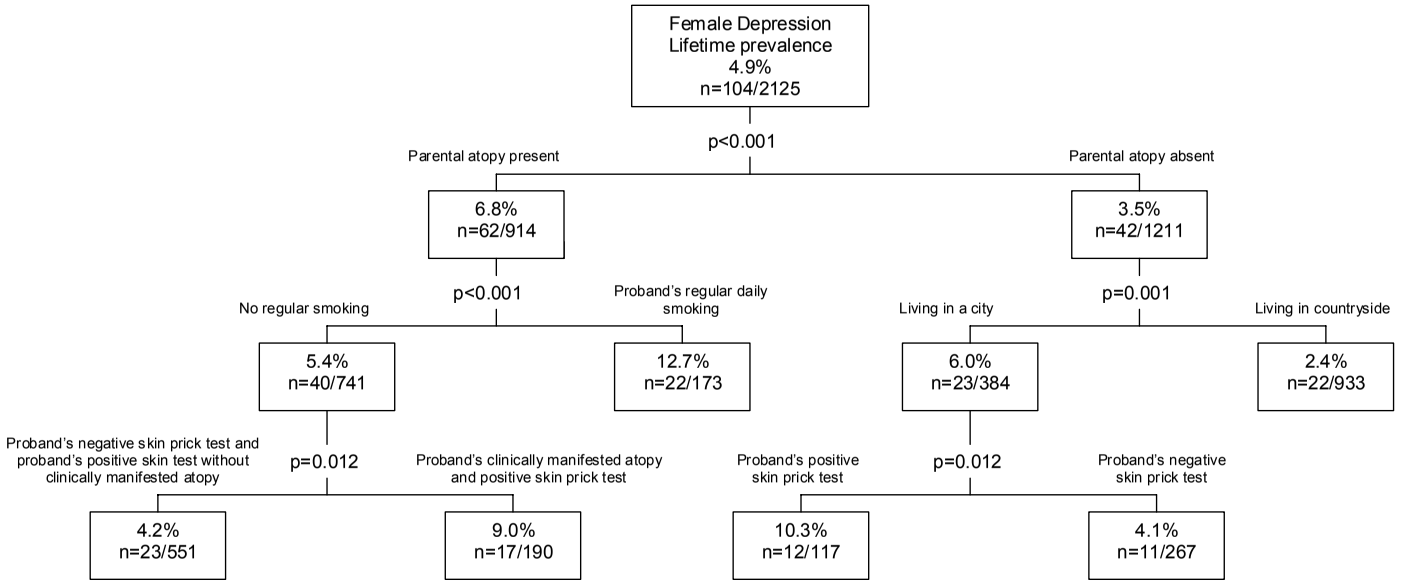

Fig. 3. CHAID flowchart of the statistically significant predictors for self-reported lifetime depression involving female cohort members, the Northern Finland 1966 Birth Cohort study (IV: Figure 1).

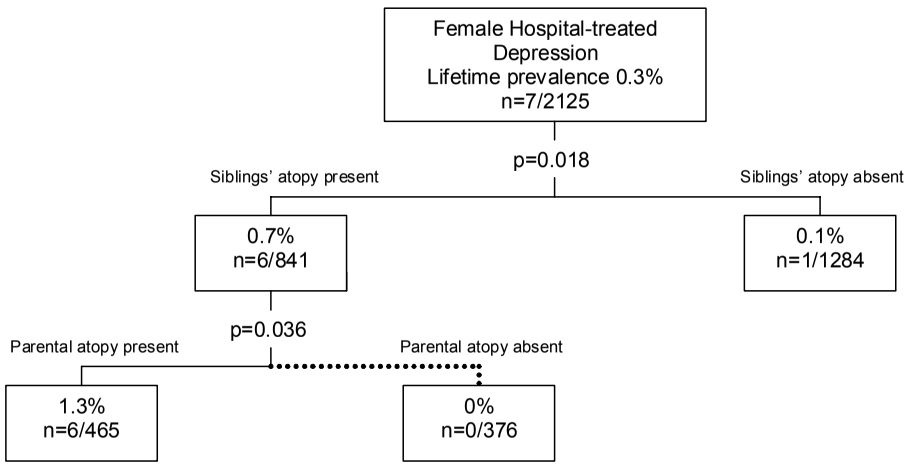

Fig. 4. CHAID flowchart of the statistically significant predictors for hospital-treated depression involving female cohort members, the Northern Finland 1966 Birth Cohort study (IV: Figure 2).

In the CHAID-analysis, none of the family atopy variables predicted depression among males. However, regular daily smoking among males was associated with both self-reported lifetime depression ($\chi 2=4.1$, df=1, p=0.044) and with hospital-treated depression (Fisher's Exact test, p=0.009).

In subsequent analyses, the effects of maternal and paternal atopies to a proband's self-reported lifetime depression were investigated separately (Table 5; IV: Table 2). Logistic regression analyses showed that maternal atopy increased a female proband's risk of lifetime depression up to 1.9-fold (OR=1.9, 95% CI 1.1-3.0), while paternal atopy alone did not associate statistically significantly with a proband's depression. The corresponding risk increased over 4-fold, when a female proband's atopy was combined with parental (OR=4.5, 95% CI 1.6-13.2) or maternal (OR=4.1, 95% CI 1.8-9.4) atopy.

Table 5. Risk of depression associated with family atopy variables and with a cohort member's own atopy for males and females in the Northern Finland 1966 Birth Cohort (IV: Table 2).

The variables for own and familial atopy	Males	Females
	OR (95% CI)	OR (95% CI)
Single risk factor*		
Parental atopy	1.1 (0.2–4.6)	2.1 (1.0–4.1)
Paternal atopy	0.7 (0.3–1.7)	1.6 (0.9–2.9)
Maternal atopy	0.6 (0.3–1.5)	1.9 (1.1–3.0)
Sibling's atopy	1.1 (0.6–2.0)	1.4 (0.9–2.0)
Own atopy	1.0 (0.4–2.0)	1.6 (1.0–2.8)
Combined risk factors**		
Own atopy and parental atopy[a]	Not feasible	4.5 (1.6–13.2)
Own atopy and paternal atopy[b]	Not feasible	2.7 (0.9–7.8)
Own atopy and maternal atopy[c]	1.2 (0.3–4.1)	4.1 (1.8–9.4)
Own atopy and sibling atopyd	1.0 (0.4–2.6)	3.2 (1.7–6.1)

*Adjusted odds ratios (OR). In addition to family atopy variables, the following confounders were used in the logistic regression analyses: The dwelling place in 1966 (urban/rural), father's social class in 1966 (classes I-II/classes III-IV/farmers), maternal smoking during pregnancy (yes/no), cohort member's regular daily smoking at the age of 31 (regular smokers [i.e., smoking on 7 days per week]/occasional smokers [i.e. smoking less than on 7 days per week] and non-smokers), and mother's parity in 1966 (grand multi-parity i.e. ≥6 deliveries/non-grand-multiparity i.e., 1-5 deliveries).

**Reference category: neither own atopy nor parental atopy[a] / paternal atopy[b] / maternal atopy[c] / sibling atopy[d].

6 Discussion

6.1 Overview of the results

The results of this study revealed that at epidemiological level, skin prick test positive females exhibit an up to 1.8-fold greater risk of developing lifetime depression when compared with prick test negative subjects. In addition, the corresponding risk increased up to 2.7-fold among females, who had a positive skin prick test together with self-reported allergic symptoms.

Second, when assessing whether the strength of the association between atopic disorders and depression was dependent on the severity of depression, it was found that the risk of depression – defined with the help of doctor-diagnosed lifetime depression and the HSCL-25 depression subscale – increased in line with the increased severity of depressive symptoms in atopic but not in non-atopic females ranging from 3.0 to 4.7-fold. Among males the corresponding statistically significant association was seen only in the highest depression scores (mean HSCL-25 score over 2.0), adjusted OR being even 6.3-fold.

Third, while investigating the hospital admissions due to both atopic and depressive disorders, the results showed that hospital-treated atopic disorders increased the probability of hospital-treated depression up to three-fold, independently of the subjects' gender and sociodemographic characteristics.

Finally, when examining the association between family atopy variables and depression of the study subjects, the major finding was that maternal atopy or atopies in both parents combined with the subject's own atopy were the most important predictors of a female proband's lifetime depression, the odds ratios being over 4-fold. Maternal atopy alone almost doubled the risk of lifetime depression in female probands when compared with families in which no maternal atopy existed. Neither parental nor siblings' atopies predicted any type of depression in male probands.

6.2 Discussion of the results

6.2.1 The association between atopy and depression

The findings of this thesis, based on extensive birth cohort data, show that there is an association between atopic disorders and depression at epidemiological level: In general, the existence of an atopic disorder increases the risk of both self-reported lifetime and hospital-treated depression about two- to three-fold when compared with an absence of atopic disorders. Thus, the results of this thesis provide firm support to the findings of previous studies concerning the association between these two disorders (Nasr *et al.* 1981, Sugerman *et al.* 1982, Bell *et al.* 1991, Wamboldt *et al.* 1996, 1998, 2000, Hashiro & Okumura 1997, 1998, Cuffel *et al.* 1999, Hurwitz & Morgenstern 1999, Brown *et al.* 2000, Centanni *et al.* 2000, Goethe *et al.* 2001).

The interpretation of the results of different earlier studies concerning the association between atopic disorders and depression is hampered because of several methodological discrepancies in the study designs and case definitions for both depression/depressive symptoms and atopic disorders. The present study was the first general population birth cohort study to demonstrate an association between atopy and depression. Since it is also known that during recent decades the occurrence of atopic disorders has been increasing (Konsensuslausuma 1998, Pekkanen *et al.* 2001a, Savolainen 2001, Hannuksela 2002), while the prevalence of depression has remained rather stable despite the increasing use of antidepressant medication and an upward trend in depression-related disability (Lehtinen & Joukamaa 1994, Salminen *et al.* 1997, Isometsä *et al.* 2000, Herva 2002, Pirkola *et al.* 2002), there are some difficulties between the present and earlier studies with regard to interpreting the results.

However, the results of this thesis are in accordance with the findings of the few earlier studies, which were based on non-clinical samples: In a sample of college students, Bell *et al.* (1991) found that the proportion of self-reported professionally diagnosed allergic disorders was about two times higher among subjects with professionally diagnosed depression than in subjects without depression. Albeit that the occurrence of atopic disorders have been increasing during recent years, the results of the present thesis are in line with the findings of Bell and colleagues (1991). More recently, Cohen *et al.* (1998) followed prospectively a cohort of randomly selected children and found that the preceding atopic disorders increased the probability of subsequent depressive disorders about two-fold from childhood to adulthood. Thus, the results of the present thesis parallel also these findings, which show strong positive associations between atopic disorders and depression. The findings of the present thesis are also on a par with the findings of Cuffel *et al.* (1999), who by using an enormous database of over 600 000 privately insured persons, found that allergic rhinitis was associated with increased, nearly two-fold rates of depression. Finally, in a cross-sectional analysis of a large adult database, Hurwitz and Morgenstern (1999) found that subjects with asthma or hay fever were twice as likely to have been diagnosed with major depression in the past 12 months than those without these illnesses. Thus, the present findings are also consistent with these results. Accordingly, an association between atopic disorders and

depression has now also been confirmed to exist by using a large, genetically homogeneous birth cohort data set.

With the exception of the studies of Wamboldt and colleagues, concerning juvenile (Wamboldt *et al.* 1998) and adult twins (Wamboldt *et al.* 2000), the results of which are discussed in chapter 6.2.3, the other earlier studies have been conducted in connection with selected, relatively small clinical data settings, in which the association between the two disorders has been investigated by studying patients suffering from either depressive or atopic symptoms. Thus, the results of this unbiased large general population database are not comparable with them.

The comparison of the results of the association between atopy and depression (reported in this thesis) with earlier studies addressing the associations between other physical disorders and depression is very difficult due to methodological discrepancies. However, the probability of the presence of depression was shown to be two-fold in patients with diabetes (Anderson *et al.* 2001, Katon 2003), which was similar to that found in atopic cohort members in this study. The proportion of major depression in patients with coronary artery disease have reported to vary between 17% and 27% (Rudisch & Nemeroff 2003), which is in accordance to the proportions of the most severe manifestations of depression found in subjects with atopy in this thesis. Further, similar or even greater prevalences of major depression have been observed in patients with Parkinson's disease (20%-30%) and multiple sclerosis (16%-30%) (Katon 2003). Since congruent or greater risks of developing depression have been noted in connection with many other physical diseases as well, the association between atopic disorders and depression may be non-specific in regard to atopic disorders. To investigate the associations between other physical disorders and depression was, however, beyond the scope of this thesis.

6.2.2 Gender difference and severity of depressive symptoms

This thesis adds some important considerations to the earlier literature, one of them being the gender difference with regard to the association between atopy and self-reported doctor-diagnosed lifetime depression. At epidemiological level, skin prick test positive females exhibited an up to 1.8-fold greater risk of developing self-reported doctor-diagnosed lifetime depression when compared with prick test negative subjects. Further, the corresponding risk increased up to 2.7-fold in females, who had positive skin prick tests together with self-reported allergic symptoms, when compared with skin prick test negative females without self-reported allergic symptoms. The corresponding associations were not found among male cohort members. Thus, the findings of this thesis are consistent with those of Centanni *et al.* (2000), who also found a gender difference while showing increased prevalence of depressive symptoms among asthmatic patients with women having higher depression scores than men.

The severity of the depressive symptoms was assessed in the original publication III with the help of the HSCL-25 depression subscale (Derogatis *et al.* 1973, Winocur *et al.* 1984). In atopic females, the risk of depression increased in line with the increased

severity of depressive symptoms, the odds ratios ranging from 3.0 to 4.7-fold. In the earlier literature, no previous findings were reported with regard to gender differences in the context of different degrees of severity of depression. Putative explanations for the gender differences are discussed in the theoretical discussion of this thesis.

In males the association between atopic disorders and depression was seen only in the most severe manifestations of depression: In the original publication I, it was found that hospital-treated atopic disorders increased the probability of hospital-treated depression up to three-fold, independently of the subject's gender and sociodemographic characteristics. Likewise, in the original publication III, the atopy-depression association was seen only in the highest depression scores, the risk for depression in atopic males being over six-fold.

Whether the strength of the association between atopic disorders and depression is dependent on the severity of the depression is a very sparsely studied area. Previously, Bell *et al.* (1991) found that self-reported frequency of asthma was higher among those, who were most frequently depressed when compared with those, who reported to have had current depressions less often. Thus the results of the original publication III are in line with these findings. However, in contradiction to the findings presented in the original publication III, Bell and colleagues (1991) also found that subjects with differing degrees of self-rated current depression did not differ statistically significantly in the overall presence or absence of allergic disorders (i.e., hay fever, asthma, eczema, and hives (i.e., urticaria)). The definitions of atopic allergies differed, however, to some extent between the present thesis and the study carried out by Bell and colleagues.

In the present thesis the highest odds for the atopy-depression association were to some extent above those of the findings of earlier studies (Bell *et al.* 1991, Cohen *et al.* 1998, Cuffel *et al.* 1999, Hurwitz & Morgenstern 1999). It must be, however, kept in mind that the highest odds in the present thesis reflected the most severe manifestations and symptoms of depression. Thus, these differences between the results can be explained by the differences of the case definitions between the present and the earlier studies.

6.2.3 Atopy in first degree relatives of depressed probands

The major finding of the original publication IV was that maternal atopy or atopies in both parents combined with a subject's own atopy were the most important predictors of a female proband's depression, the odds ratios being over 4-fold. Maternal atopy alone almost doubled the risk of lifetime depression in female probands when compared with families in which no maternal atopy existed. Thus, these findings are on a par with previous studies in which an association between atopic disorders and depression has been noted to exist between first degree relatives (Davis 1977, Wamboldt *et al.* 1996). These earlier studies, however, analysed the prevalence of depression among first degree relatives (Wamboldt *et al.* 1996) or among mothers (Davis 1977) of children with asthma. With regard to the other atopic disorders, corresponding findings are not reported in the

earlier literature. Likewise, there exist no previous studies in which the association between parental atopy and a proband's depression would have been investigated.

Since neither parental nor siblings' atopies predicted any type of depression in male probands, it could be suggested that the putative genetic association (between parental atopic disorders and a child's depression) involves female probands only. Thus, the results of this thesis are in support of recent findings that point to genetic factors playing a greater role in the etiology of depression in women than in men (Bierut *et al.* 1999, Kendler *et al.* 2001a).

In addition, the results of this thesis extend the earlier findings of Wamboldt *et al.* (1998, 2000), who suggested that a common additive genetic effect accounts for the majority of the covariance between atopic and depressive symptoms. Based on the findings of this thesis it could be assumed that regarding heritability, it is specifically the maternal link, which is stronger than the paternal one. Since in the literature reviewed, no earlier findings were reported with regard to the association between maternal or parental atopy and a proband's depression, the putative explanations for these findings are discussed in the theoretical discussion of this thesis. It must, however, be kept in mind that also the findings of this thesis about the familial atopy as a predictor for female proband's depression may be a non- specific finding. It could be speculated that e.g., a mother's other chronic illnesses such as coronary hearth disease, for instance, might also predispose her child to become depressed.

6.2.4 Regular daily smoking and living in a city

According to the CHAID-analysis, a proband's regular daily smoking was the strongest factor associated with both self-reported doctor-diagnosed lifetime and hospital-treated depression in males. Correspondingly, in females with a parental history of atopic conditions, doctor-diagnosed lifetime depression among regular daily smokers (12.7%) was over two times more common than the overall prevalence of depression in females (4.9%). Several previous studies have also indicated an association between smoking/nicotine dependence and depression (Brown *et al.* 1996, Hanna & Grant 1999, Dierker *et al.* 2002), but, as reviewed by Upadhyaya *et al.* (2002), there is more evidence that major depression can be regarded a risk factor of smoking than vice versa.

Whether the presence of parental atopy would have an explanatory role to play with regard to the association between smoking and depression, was behind the scope of this thesis. Also, this far, little is known about the mechanism of co-morbidity between smoking and depression. It has been suggested that depression may result from neurochemical changes brought on by smoking, or that depression may cause smoking by increasing the likelihood that individuals will self-medicate negative feelings with nicotine. In addition, it has been suggested that there may exist a third factor – either genetic or environmental in nature – which would increase the risk of having both of the earlier conditions, as reviewed by Dierker *et al.* (2002).

With regard to the association between the effect of exposure to tobacco smoke and atopic sensibilization, the existing evidence is also to some extent controversial: In some

recent studies both exposure to tobacco smoke *in utero*, and current own smoking have been shown to be associated with atopic disorders (Backer *et al.* 2002, Devereux *et al.* 2002). On the contrary, the prevalence of allergic asthma and allergic rhino-conjunctivitis has been shown to be decreased with increasing exposure to tobacco smoke (Hjern *et al.* 2001), and children who had been exposed to tobacco smoke in childhood have been noted to have lower risks of atopic disorders (Hjern *et al.* 2001, von Linstow *et al.* 2002).

In females, if there existed no parental history of atopy, then living in an urban area was a significant predictor of depression: doctor-diagnosed lifetime depression for citydwellers (6.0%) was 2.5 times more common than for those living in the countryside (2.4%). This finding is in accordance with the findings of previous Finnish surveys, in which depression has been shown to be most prevalent in the most heavily populated areas of the country/in cities (Väisänen 1975, Lehtinen & Joukamaa 1994). Worthy of note is the fact that among females with no parental history of atopy, a city dweller's own atopy was a significant predictor of depression; Since a cohort female's atopy did not predict depression in those individuals living in the country, it could be speculated that the same etiological factors might play a role behind the pathophysiology of the atopy-depression association, and are the cause of the fact that living in a farm environment during childhood/being a farmer's child is associated with a decreased risk of atopic allergies (Kilpeläinen *et al.* 2000, Pekkanen *et al.* 2001b).

6.3 Theoretical considerations

The findings of this thesis can be explained according to the following biological and psychosocial hypotheses, which might serve as a psycho-neuro-biological link between atopic disorders and depression. In the paragraphs below, each hypothesis, theory, or suggestion will be briefly and critically reviewed.

6.3.1 Biological explanations

6.3.1.1 Cytokines

Cytokines play a crucial role in the pathogenesis of allergic diseases (Kronfol & Remick 2000, Kelley 2001). Besides acting as chemical messengers between immune cells, cytokines can serve as mediators between the immune system and the brain (Kronfol & Remick 2000, Dantzer 2001).

In atopic states, there exists a shift from Th1 to Th2 responses originating from Th lymphocyte precursors (Prescott *et al.* 1998, 1999). Of the anti-inflammatory cytokines produced by Th2 cells (Kronfol & Remick 2000, Kelley 2001), IL-4 is an essential mediator of immediate hypersensitivity, favouring the production of immunoglobulin E

(Abbas *et al.* 2000). Very recently, however, a biphasic response of the Th1/Th2 cell subsets has been noted to exist among atopic patients: An initial Th2 response with elevated levels of IL-4 is shown to be followed by a second shift toward a Th1 secretion pattern as reviewed by Buske-Kirschbaum *et al.* (2002). Thus, it seems that the Th cell response pattern differs during different states of atopic disorders. Indeed, it has been proposed that the chronic inflammatory response in allergic dermatitis is dominated by a Th1 response with corresponding cytokine expression (Leung 2000). Furthermore, in asthmatic patients, bronchoalveolar lavage has been shown to contain large quantities of IL-1β (da Silva *et al.* 2002). After antigen challenge, increased levels of IL-1β and IL-6 have also been noted in nasal secretions of allergic patients (Sim *et al.* 1994, 1995, Marshall *et al.* 2002). On the other hand, depression was also shown to be associated with excessive secretion of proinflammatory cytokines such as IL-1 and IL-6 (Maes *et al.* 1998, Maddock & Pariante 2001).

6.3.1.2 The stress system

During an immune response, the brain and the immune system communicate with each other in order to maintain homeostasis in the body (Elenkov *et al.* 2000, Kronfol & Remick 2000). Two major pathways, the HPA-axis and the SNS are involved in this bidirectional interaction (Mössner & Lesch 1998, Elenkov *et al.* 2000).

During the allergic hypersensitivity reaction (late phase reaction), proinflammatory cytokines such as IL-1β and IL-6 are released by the IgE-mediated stimulation of tissue mast cells and basophils (Abbas *et al.* 2000, Hagaman *et al.* 2001, Hurwitz & Morgenstern 2001). In addition, e.g., IL-1β has been shown to be released by structural cells, such as epithelial cells and fibroblasts as well as by eosinophils as reviewed recently by da Silva *et al.* (2002). These proinflammatory cytokines are capable of activating both the SNS and the HPA axis (Elenkov *et al.* 2000, Hurwitz & Morgenstern 2001). The end products of this "stress system"-glucocorticoids and catecholamines - cause a selective suppression of Th1 responses and a Th2 shift by inhibiting the production of IL-12 and favouring the production of IL-10 (Elenkov & Chrousos 1999, Elenkov *et al.* 2000). Proinflammatory cytokines themselves can cause dysfunction of corticosteroid receptors (Maes & Smith 1998, Musselman *et al.* 2001, Pariante *et al.* 1999), which together with hypercortisolism are usually present in depression (Holsboer 2001, Murphy 1997, Pariante & Miller 2001). In addition, both IL-1β and IL-6 have the capacity to induce a syndrome of "sickness behaviour" that shares many features with major depression, including anhedonia, fatigue, anorexia, reduced activity, and altered sleep patterns (Dantzer 2001, Musselman *et al.* 2001). On the other hand, there is also evidence that psychosocial stress suppresses cellular immunity but boosts humoral immunity, thus causing a Th2 shift via these same stress hormones, i.e., glucocorticoids and catecholamines (Elenkov & Chrousos 1999).

6.3.1.3 IL-4 and 5-HT metabolism

5-HT is an important mediator of bidirectional interactions between the nervous and the immune systems (Mössner & Lesch 1998, Mössner *et al.* 2001). As reviewed by Mössner and Lesch (1998), the CNS can, via the autonomic nervous system, induce the neural release of 5-HT to the immune system. 5-HT receptors and the 5-HTT are distributed widely in immune cells and 5-HT is known to have various immunological effects.

Recent evidence indicates that central serotonergic neurotransmission is altered by cytokines released during peripheral immune responses (Dantzer 2001, Mössner & Lesch 1998, Mössner *et al.* 2001). Furthermore, IL-4 has been shown to have an effect on 5-HT metabolism while having different regulatory effects on different 5-HTT genotypes (Mössner *et al.* 2001). Since 5-HT has both an essential role in the pathophysiology of depression and also functions as an important mediator between the nervous and immune systems (Mössner & Lesch 1998, Mössner *et al.* 2001), and because the genetic polymorphism in the 5-HTT gene promoter has been found to be associated with depression (Lesch 2001), the findings of this thesis might be explained by an altered 5-HT metabolism in the brain due to immunological reactions in atopy.

6.3.1.4 The histamine metabolism

The histamine metabolism may also be drawn upon to explain at least some of the results of this thesis. During an immediate hypersensitivity reaction histamine is released from the cytoplasmic granules of activated mast cells. As a biogenic amine, histamine is mediating a variety of biological effects (Abbas *et al.* 2000). Via stimulation of H2-receptors, histamine has been shown to be capable of suppressing IL-12 and stimulating IL-10 secretion (Elenkov *et al.* 1998), thereby causing the shift of Th1/Th2 balance toward Th2-dominance (Elenkov *et al.* 1999, 2000). It is also known that histamine has various physiological roles as a neurotransmitter in the brain (Ito 2000). Histamine turnover in the diencephalon has been suggested to be related to the pathology of the depressive state (Ito *et al.* 1999), and it is known that histamine H3 receptor antagonists have antidepressive effects (Ito 2000). Furthermore, H1 receptor antagonists - commonly called antihistamines – have immunological effects by inhibiting the immediate wheal and flare response to intradermal allergens (Abbas *et al.* 2000), but they also have psychological effects by decreasing the anxiety state of a person (Ito 2000).

6.3.1.5 The PUFA metabolism

Changes in PUFA intake or metabolism can also be linked to the findings. Because PUFAs are either precursors of eicosanoids, such as prostaglandins, or affect eicosanoid and cytokine formation, they have important effects on immune and inflammatory processes (Maes & Smith 1998, Kelley 2001). An increased ratio of omega-6 to omega-3

PUFAs may lead to an overproduction of inflammatory cytokines and eicosanoids, which are responsible for the allergic inflammation, and which are also associated with major depression (Maes & Smith 1998, Kelley 2001). Evidence has been accumulating that diminished omega-3 fatty acid intake or concentrations are associated with depressive disorders (Hibbeln 1998, Maes *et al.* 1999, Peet *et al.* 1998, Tanskanen *et al.* 2001a, 2001b), and persons with atopic disorders have also been noted to have low levels of omega-3 fatty acids in their plasma and red cell membranes (Duchen 2001). On the other hand, fatty acids of the omega-3 type have anti-inflammatory effects by reducing the production of inflammatory cytokines/eicosanoids, which forms the basis for their use in the management of inflammatory diseases (Kelley 2001). Correspondingly, highly purified ethyl eicosapentaenoic acid, an omega-3 fatty acid, has also been shown to be effective in improving major depression even in two randomised, placebo-controlled studies (Peet & Horrobin 2002, Nemets *et al.* 2002).

6.3.1.6 Gender difference

There are some explanations for the gender difference, i.e., the fact that in females the association between the disorders is evident independently of the severity of the depression and that among males it is only seen in the presence of the most severe manifestations. It has been suggested that atopic disorders and depression share a common genetic etiology (Wamboldt *et al.* 1998, 2000). Since there is evidence that in women genetic factors play a greater role in the etiology of depression than in men (Bierut *et al.* 1999, Kendler *et al.* 2001a), it could be speculated that also the pathophysiology of the atopy-depression association would arise from different origins in females and males. For example, with respect to the serotonin metabolism, Enoch *et al.* (2001) have recently established that the 5-HT(2A) promoter polymorphism is associated with affective disorders in women but not in men. Because IL-4 has been shown to have an effect on the 5-HT metabolism (Mössner *et al.* 2001), it can be hypothesized that there might be an association between immediate hypersensitivity reactions with serotonin-related mental disorders and the female gender.

On the other hand, there is evidence that subtypes of depression may differ with respect to some immune parameters (Miller *et al.* 1999). Thus, it could be possible that in men minor depression could have different immuno-pathophysiological roots than those of major depression, which could explain the lack of the atopy-association among less depressive men.

In addition, it is also possible that men have underreported depression and/or were unable to recognize their symptoms correctly and this could have caused a bias in our results. In this same set of birth cohort data, it has previously been possible to show that the prevalence of alexithymia was higher in men (9.4%) than in women (5.2%) (Kokkonen *et al.* 2001). Further, since alcohol abuse and violent behaviour, for example, can be signs of psychosocial distress in men (Epperly & Moore 2000), it can be postulated that “masked depression” might be a manifestation of minor depression in predominantly men rather than in women.

6.3.1.7 The "parent-of origin" effect

Based on the findings of the original publication IV, it could be assumed that regarding heritability, it is specifically the maternal link, which is stronger than the paternal one. If true that atopic disorders and depression share a common genetic etiology (Wamboldt *et al.* 2000), the characteristic mode of inheritance for these disorders could be a gender-related pattern of inheritance, i.e., "parent-of-origin" effect. McMahon *et al.* (1995) first proposed that this "parent-of-origin" effect might involve mitochondrial inheritance. On the basis of recent genetic studies, Kato (2001) suggested that maternal inheritance could be one possible etiological factor in bipolar disorders via an association with mitochondrial DNA mutations. Since mitochondrial DNA mutations have also been found in persons with atopic and other skin-disorders (Karvonen *et al.* 1999), it could be hypothesised that mitochondrial DNA could have a role in the pathophysiology of unipolar depression as well. There exist also other possible explanatory genetic mechanisms for the "parent-of origin" effect, such as the phenomenon of genomic imprinting (Davies *et al.* 2001, Strauch *et al.* 2001).

6.3.2 Psychosocial explanations

Psychosocial explanations are also possible. The roots of atopic disorders exist already during pregnancy and in the first years of a person's life (Björksten 1999). On the other hand, childhood psychosocial experiences (Veijola *et al.* 1998) together with genetic vulnerabilities (Kendler *et al.* 2001a) have been reported to be more highly predisposing factors to depression in women than in men. Psychosocial factors can have an effect on biochemical and metabolic functions, as well as on the immune system, due to the complex interactions between body and mind. Severe stress early in life can, for example, result in long-term alterations of the function of the HPA-axis (Heim *et al.* 2001). It could therefore be speculated that women may be more sensitive to changes in their body due to the symptoms of atopic disorders, which could at least partly explain the findings about the gender differences in this thesis.

For example, with regard to atopic dermatitis, psychosocial stress and skin condition appear to be bidirectionally related. Stressful situations are often accompanied by an exacerbation of symptoms of atopic dermatitis; however, worsening of skin condition may also lower the stress threshold as reviewed by Buske-Kirschbaum *et al.* (2001). Consequently, a vicious cycle of emotional stress and skin condition can be initiated (Buske-Kirschbaum *et al.* 2001). It has also been shown that preceding or concomitant stressful life-events may promote the manifestation of asthma and allergic rhino-conjunctivitis (Kilpeläinen *et al.* 2002).

There exist a growing body of evidence on stress-induced alterations in immune-mediated diseases and in the immune function (Olff 1999, Kilpeläinen *et al.* 2002). However, there seems to be considerable individual variability in the immune response to stress. Once the stressor has been perceived, interpreted and evaluated, the subsequent emotional and behavioural response is determined by the subject's specific defense and

coping strategies. Prolonged exposure to stressors may outweigh the person's coping resources, ultimately leading to depression (Olff 1999). On the other hand, inadequate coping skills described in patients suffering from atopic disorders (Scheich *et al.* 1993), can make atopic patients liable to be stressed by the various normative life-cycle events and other stressful situations they have to face (Buske-Kirschbaum *et al.* 2001).

6.4 Methodological considerations

6.4.1 Strengths of the study

The major strengths of this study was that it was based on a large, unbiased and genetically homogenous Northern Finland 1966 Birth Cohort database: In the provinces of Oulu and Lapland, 96% of all women (n= 12068), with an expected date of delivery falling between 1st January and 31st December, were evaluated. These women gave birth to 12058 liveborn infants. A variety of biological, socioeconomic and health conditions as well as living habits and family characteristics of the cohort members have been collected prospectively from pre-natal stages up to the age of 31 (Rantakallio 1969, 1988; Rantakallio *et al.* 1995, 1997).

Hospital diagnoses, with regard to atopic disorders and depression, were obtained from the national hospital discharge registers, which cover all treatment episodes in general, mental, military, prison, and private hospitals as well as the inpatient wards of local health centers nation-wide. These register data have been shown to be a reliable tool for epidemiological research (Poikolainen 1983, Keskimäki & Aro 1991).

In addition, the diagnostic accuracy concerning hospital-treated depression is good due to the validation process. All cohort members, having been admitted to a hospital during 1982-1997 for reasons of a psychiatric disorder, were identified from the FHDR and their hospital case notes were collected and scrutinised; The FHDR diagnoses were carefully validated by re-checking them against DSM-III-R criteria (Isohanni *et al.* 1997, Moilanen *et al.* 2003).

Skin prick tests are known to be one of the best objective assessments for demonstrating an IgE-mediated mechanism underlying clinical atopic symptoms (The European Academy of Allergology and Clinical Immunology 1993). In the original publications II-IV, the detection of a cohort member's atopic disorder was based on positive responses from skin prick tests, and in this respect only a very small number of false positive cases may have been included in the analyses.

Finally, the HSCL-25 has been proved to be an acceptable screening scale in obtaining information on symptoms of depression in the normal population (Sandanger *et al.* 1998). In addition, the HSCL-25 was found to be a valid instrument in a Nordic multicentre investigation (Fink *et al.* 1995) as well as a Finnish one (Veijola *et al.* 2003).

6.4.2 Limitations of the study

There were several limitations that need to be commented on in this thesis. As in any large population sample, only part of the potential exposure or confounding variables could be taken into account. First, it was not explored whether the association between atopic disorders and depression is specific to atopic disorders, or more generally to virtually any chronic physical disorder (for a review, see Katon 2003). Among the major weaknesses in this study were also that solid data on immunoglobulin-E or cytokine and other immunomediator profiles were lacking.

Further, the overall number of the subjects suffering from hospital-treated atopic disorders was rather low. Likewise, the number of hospitalisations due to depression was also rather low in both genders and this imposes restrictions on statistical analyses. In general, in the database of the FHDR a small amount of missing or erroneous personal identification numbers are known to exist, involving the treatment periods from the 70s to the early 80s and amounting to 15% and 10%, respectively (Näyhä 1992). Since then, thanks to computerized hospital registers and automatic checking systems for the personal identification number, there are practically no erroneous data in the FHDR any longer (Mähönen *et al.* 2000). In any case, there is no reason to assume that the missing and erroneous data in the FHDR would have been unevenly distributed in the study populations of this thesis.

With regard to self-reported lifetime doctor-diagnosed depression, the definition was based on a single question obtained from postal questionnaires. However, treatment-seeking had earlier been found to be a good predictor of lifetime depression (Kendler *et al.* 2001b). Further, the findings of this thesis about the gender differences can be biased due to the fact that cases of depression are more common among females and that the validity of diagnoses through questionnaires are inferior to those of structured diagnostic rating scales; it is also possible that men have underreported their depressive disorders.

Self-report rating scales such as the HSCL-25 conducted at one time point (in this study at the age of 31) give a very limited approximation of lifetime depression of all cohort members. However, in the original publication III, in addition to HSCL-scores, the data on self-reported doctor-diagnosed lifetime depression could also be used. In spite of the fact that the exact diagnosis of the self-reported depression was not available and that further it was also not known when exactly a cohort member had been treated by a doctor for depression, the findings of the original publication III about the highly symptomatic cohort members (i.e., having HSCL-25 depression subscale scores in excess of 2.0), together with the doctor-diagnosed depression, mean that those cohort members have very likely had, before the age of 32, a major depression – either a single episode or a recurrent one. It must also be remembered that self-filled rating scales may include items such as “crying easily” and “lost interest in sex”, which have recently been suggested to give too high a score of depressiveness in females when screening depression (Salokangas *et al.* 2002).

It was unfortunate that the temporal sequence could not be taken into account in the statistical analyses of the original publications. The variables for “symptoms of allergies” and for “self- reported doctor-diagnosed clinical histories of allergic disorders” did not include the information on the onset age of allergic symptoms or disorders.

Finally, the definitions of parental atopy and a sibling's atopy were also based upon postal questionnaires and objective measurements, such as skin prick tests, were not available. This can lead to a biased definition of familial atopic disorders. In general, using self-administered questionnaires may easily lead to an underestimation rather than overestimation of the phenomenon studied. However, the procedure does facilitate comparisons with earlier epidemiological studies of atopic disorders, for most of them have also used written questionnaires (Burr 1992, Remes 1998).

7 Conclusions

7.1 Main conclusions of the results

An association between atopic disorders and depression has now been confirmed with the help of a large, genetically homogeneous birth cohort database. Generally, the existence of atopic disorders increases the risk of both self-reported and hospital-treated lifetime depression about two- to three-fold when compared with an absence of atopic disorders.

This thesis adds some important considerations to the earlier literature, one of them being the observed gender difference with regard to the association between atopy and depression: In atopic females, the association between atopic disorders and depression was present in connection with every level of the depressive symptoms, but the likelihood of depression increased in line with the increased severity of the depressive symptoms. On the other hand, in males an association between atopic disorders and depression was seen only in the most severe manifestations of depression.

Establishing an argument for causation is very difficult in epidemiological research, because of the many potential confounding factors. Due to the study design, the causal hypothesis could not be tested: One can not know whether suffering from atopic disorders is causing a person to suffer also from depression, or vice versa. It is also possible that both atopic and depressive disorders were caused by some third factor, which differs from those that were able to be taken into account as confounding factors. Since it is well established that the roots of atopic disorders exist already during pregnancy and in the first years of a person's life (Björksten 1999), the finding of this thesis that maternal atopy or atopies in both parents combined with a subject's own atopy were the most important predictors of a female proband's depression is worthy of note: Inevitably, the presence of parental atopy precedes the presence of a proband's depression, and, thus some evidence for the temporal sequence between atopy and depression could be provided. Earlier twin-studies have preferred to assume a common genetic rather than environmental etiology to exist behind these two disorders (Wamboldt *et al.* 1998, 2000). Since neither parental nor siblings' atopies predicted any type of depression in male probands, it could be suggested that the putative genetic association (between parental atopic disorders and a child's depression) involves female probands only. Thus, the

results of this thesis are in support of recent findings that genetic factors might play a greater role in the etiology of depression in women than in men (Bierut *et al.* 1999, Kendler *et al.* 2001a). It must, however, be reminded that psychosocial familial factors might also explain at least part of the findings of this thesis.

Previous psycho-neuroimmunological studies have deepened our understanding about the body-mind connection. Inevitably one's feelings have their biological/physiological correspondences, and vice versa. Dysfunction at biological or psychosocial level can cause an atopic disorder or depression of a person, and in the end, genes are involved with all of the functions of the body. Once the homeostasis of the body has been disturbed, the adaptive systems of the human body are starting their work in order to return to the homeostasis. There exist many psycho-neuroimmunological links, which could serve as reasonable explanations for the association between atopy and depression even though the exact mechanisms (or possible dysfunctions of them) are so far incompletely understood in this context.

7.2 Research implications

Due to the fact that in females, the association between atopy and depression was apparent independently of the severity of the depressive symptoms, and that in males, the association was seen only in the most severe manifestations of depression, it can strongly be suggested that in future studies the gender difference and the level of depression should be taken into account while investigating the association between these two disorders. Whether the occurrence of depression is more prevalent during the allergy seasons of atopic patients should also be taken into account in further studies, since it was very recently shown that subjects with allergic rhinitis reported to have had higher levels of general and mental fatigue during ragweed seasons (Marshall *et al.* 2002).

The finding of this thesis that maternal atopy increases the likelihood of a female proband's depression needs to be replicated and further investigated by using other databases. Given that genetic factors might play a greater role in the etiology of depression in women than in men (Bierut *et al.* 1999, Kendler *et al.* 2001a), and that earlier twin-studies have preferred to accept that a common genetic rather than an environmental etiology exists behind these two disorders (Wamboldt *et al.* 1998, 2000), genetic investigations are recommended. Since maternal inheritance has been postulated to be one possible etiological factor in bipolar disorders via an association with mitochondrial DNA mutations, and because mitochondrial DNA mutations have also been found in persons with atopic disorders (Karvonen *et al.* 1999), it could be recommended that mitochondrial DNA would be worth an investigation to determine whether it has a role in the pathophysiology of unipolar depression as well. The other possible explanatory genetic mechanisms for the "parent-of origin" effect, such as the phenomenon of genomic imprinting (Davies *et al.* 2001, Strauch *et al.* 2001), should also not be overlooked while studying the genetic etiology behind the atopy-depression association.

The association of stress with stress hormones and cytokine secretion, in general, is complex and not fully understood (Kronfol & Remic 2000). There is, however, some evidence that stress is not uniform and non-specific reaction (Elenkov & Chrousos 1999); Stress has various dimensions (e.g., psychological vs. biological) and it may be considered in terms of its duration, quantity and quality as reviewed by Maddock and Pariante (2001). Different types of stressors might also have different effects on the immune response (Elenkov & Chrousos 1999). In addition, stress systems have different regulatory effects at systemic level than at local level in the body (Elenkov & Chrousos 1999). Thus, further investigations have been called for to clarify these complex interactions between the neuroendocrine and the immune body systems (Elenkov & Chrousos 1999, Kronfol & Remic 2000).

With regard to cytokine secretion, particularly during allergic inflammation, there is also a need for further investigations to deepen our understanding about the underlining profound immunological patterns and their putative associations with immunopathological changes in depression. Since there is evidence that the Th cell response pattern differs during different states of atopic disorders, it should be investigated in forthcoming studies, whether or not these Th response differences have an influence on the association between atopy and depression. As proposed by Schwarz *et al.* (2001), it is premature in major depression to formulate either a Th1- or a Th2- related hypothesis for all patients suffering from this disorder: There is some evidence that Th1 cytokines are associated with the pathophysiology of suicidality in major depression, whereas the cytokine profile might be towards Th2 dominance among non-suicidal depressive patients (Schwarz *et al.* 2001). Thus, the possibility that different types of depression might have different immunological features should also not be overlooked in any future studies.

The HPA-axis activation and the resultant hypercortisolemia could be, in general, seen as a negative feedback mechanism to suppress an otherwise exaggerated inflammatory response. Most probably, the HPA axis is also involved with the body-mind interactions between atopic disorders and depression. Since it is still unknown, what the exact mechanisms of altered HPA axis activity in the association between atopic disorders and depression might entail, additional investigations are needed. In addition to immunomediators of the HPA axis and the SNS, also several other hormones, e.g., sex steroids, growth hormones, and opioid peptides have been implicated in immunomodulatory processes (Buske-Kirschbaum *et al.* 2001). This should be kept in mind in further investigations.

In its entirety, the association between atopy and depression is in all likelihood multifactorial in its origin. Most probably this phenomenon is caused by complex associations between biological, psychological, environmental, and social processes during human development. In order to gain a deeper understanding about the association between these two disorders, controlled experimental studies using multidisciplinary research strategies are needed. In addition, large epidemiological studies are called for when the goal is to investigate, whether the association between atopic disorders and depression is specific to atopic disorders, or whether depression is related to other physical disorders as well. In addition, the strength of the association between atopic disorders and depression compared with that between other physical disorders and depression should also be assessed.

Finally, it has also been suggested that the association between various physical diseases – such as coronary artery disease, diabetes mellitus, and some immune-mediated illness – and depression might be explained by disturbed fatty acid and phospholipid metabolisms (Horrobin & Bennet 1999). Further studies are, however, needed to ascertain the pathophysiological mechanisms behind the association of atopic disorders and depression as well as behind the association of other physical disorders and depression. This would facilitate the search of whether there exist fundamental differences in relation to the mechanisms that govern the associations between different types of physical disorders and depression.

7.3 Clinical implications

Both atopic disorders and depression are illnesses of major public health concerns and are therefore of considerable importance in most Western countries. Since about one million Finnish people (20% of all Finns) are suffering from atopic disorders, and because they are shown to have an increased likelihood of suffering from depression, also the co-morbidity between these two disorders is worth being taken note of from the viewpoint of public health. Co-morbidity, thus, should be taken seriously and monitored in clinical practice.

Based on the findings of this thesis and earlier studies, there seems to be at least a subset of patients for which the interrelationship between atopic allergies and depressive symptoms may be very salient (Wamboldt *et al.* 2000). This is noteworthy at clinical work while treating atopic and/or depressive patients. Due to psycho-neuroimmunological interactions, it could be hypothesized that the adequate treatment of co-morbid depression in atopic patients would be beneficial for the successful management of atopic symptoms, and vice versa. Untreated atopy should also be kept in mind as one possible etiological factor behind the treatment-resistant depression. On the other hand, the possibility of an underlining depression has to be remembered when treating persistent atopic symptoms, and as a potential cause for the exacerbation of an atopic condition. When conducting randomized follow-up studies in atopic patients, the procedure should also include repeated screenings with regard to depressive symptoms. This would help to establish, whether a medication for atopy is successful in the treatment of depression as well, or may even prevent the development of depressive disorders.

Given that there exists an inflammatory stage in the human body during allergic reactions, an untreated atopy most probably exposes at least some persons to depression. Thus, early detection and treatment of atopic disorders might promote mental health by preventing the development of depressive disorders. On the other hand, since many other physical disorders have been shown to be associated with depression, diverse approaches involving basic, clinical, epidemiologic, and services-related research efforts are being called for to understand how depression eventually arises and can best be prevented and treated in the context of physical disorders (Stover *et al.* 2003).

Once a deeper understanding about the pathophysiology behind the body-mind interactions has been obtained, new treatment strategies for both disorders can apparently evolve. In the case of co-morbid atopy and depression, the drug of choice would be a preparation, which has been developed to have an effect on the pathophysiology, which is common for both disorders. For example, if the HPA axis activation turned out to be causally linked with co-morbid atopy and depression, the therapy should then be focused on the corresponding or accompanying neurobiological abnormalities (Holsboer 2001).

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