



UPPSALA  
UNIVERSITET

*Digital Comprehensive Summaries of Uppsala Dissertations  
from the Faculty of Medicine 809*

# Adolescents with Depression Followed up

*Prognostic Significance of Somatic Symptoms  
and Their Need of In-Patient Care*

HANNES BOHMAN



ACTA  
UNIVERSITATIS  
UPSALIENSIS  
UPPSALA  
2012

ISSN 1651-6206  
ISBN 978-91-554-8461-3  
urn:nbn:se:uu:diva-180328

Dissertation presented at Uppsala University to be publicly examined in Universitetshuset, Sal IX, S:t Olofsgatan, Uppsala, Saturday, October 20, 2012 at 09:00 for the degree of Doctor of Philosophy. The examination will be conducted in Swedish.

### **Abstract**

Bohman, H. 2012. Adolescents with Depression Followed up: *Prognostic Significance of Somatic Symptoms and Their Need of In-Patient Care*. Acta Universitatis Upsaliensis. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 809. 40 pp. Uppsala. ISBN 978-91-554-8461-3.

A dualist approach that distinguishes between mind and body is still the norm in Western medicine. Although we now know that physical and mental health are related in adults, little is known about if, or with what mechanisms, mental illnesses or depression early in life, will affect future physical and psychological health. In-between mental and somatic disorders there are somatic symptoms without medical explanation. These are symptoms that cause much suffering and impairment which are costly for society. Still little is known what they are, how they should be treated and what consequences they have for adolescents when they grow up. This study aims to investigate the long-term relationship between mental and somatic disease and the outcome of adolescents with functional somatic symptoms.

The thesis is based on a 15-year follow-up study of a population-based investigation of adolescent depression. In 1991–1993 first year students in upper secondary school (age 16–17) in Uppsala, Sweden, were screened for depression (n=2300). Adolescents with positive screening and selected peers with negative screening (n=631) were assessed regarding mental health and somatic symptoms. At around age 31, the participants were followed-up in personal interviews (n=369) and national registers (n=609). Outcomes regarding mental DSM-IV diagnosis, in-patient ICD-10 disease diagnosis from the patient register, and blood vessel wall thickness were assessed.

The most important finding is the unexpected poor short and long-term outcome in adolescents with somatic symptoms. The result proves the need for better treatment. The strong prediction of functional somatic symptoms for mental disorder, independent of adolescent depression, suggests that somatic symptoms and depression symptoms are different expressions of a common disorder. Female adolescents with depression need more psychiatric and somatic in-patient care but the males do not. Instead, they have considerably more in-patient stays due to alcohol and drug abuse. The males might be taken care of outside the health care system and seem to need special attention. In women with adolescent and recurrent adult depression there is an association with premature aging of the carotid wall. These women are at risk of developing early cardio-vascular disease and need early interventions.

*Hannes Bohman, Uppsala University, Department of Neuroscience, Child and Adolescent Psychiatry, Akademiska sjukhuset, SE-751 85 Uppsala, Sweden.*

© Hannes Bohman 2012

ISSN 1651-6206

ISBN 978-91-554-8461-3

urn:nbn:se:uu:diva-180328 (<http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-180328>)

# List of papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. **Bohman H**, Jonsson U, von Knorring A-L, von Knorring L, Päären A, Olsson G. Somatic symptoms as a marker for severity in adolescent depression. *Acta Paediatrica* 2010;99:1724-30

II. **Bohman H**, Jonsson U, von Knorring L, Päären A, von Knorring A-L. Prognostic significance of somatic symptoms in adolescence: A 15 years community-based follow-up study of adolescence with depression compared with healthy peers. *BMC Psychiatry* 2012;12:90. doi:10.1186/1471-244X-12-90

III. **Bohman H**, Jonsson U, Päären A, von Knorring A-L, Olsson IG, von Knorring L. Long term follow up of adolescent depression. A population based study. *Upsala Journal of Medical Sciences*, 2010;115:21-9

IV. **Bohman H**, Jonsson U, von Knorring A-L, von Knorring L, Olsson G, Päären A, Larsson M, Naessen T. Thicker carotid intima layer, thinner media layer and higher intima/media ratio in women with recurrent depressive disorders: A pilot study using non-invasive high frequency ultrasound. *The World Journal of Biological Psychiatry* 2010;11:71-5

Reprints were made with permission from the publishers.



# Contents

Introduction.....	9
Adolescent depression.....	11
Somatic symptoms in adolescence.....	11
The relationship between adolescent depression and functional somatic symptoms.....	12
The relationship between adolescent depression and physical illness .....	13
Aim and scope of this thesis .....	14
Methods .....	15
Subjects and procedure.....	15
The original investigation.....	17
The register data.....	17
The follow-up interview.....	18
The ultrasound investigation .....	18
Subjects and measures in papers I-IV .....	19
Paper I (Adolescent somatic symptoms) .....	19
Paper II (Somatic symptoms followed-up).....	19
Paper III (In-patient care) .....	20
Paper IV (Intima/media ratio).....	20
Statistics .....	20
Ethics.....	20
Summary of results .....	21
Paper I .....	21
Paper II.....	22
Paper III.....	23
Paper IV .....	24
Discussion.....	25
Paper I .....	27
Paper II.....	27
Paper III.....	28
Paper IV .....	29
Implications and future research .....	30
Conclusions.....	31

Sammanfattning på svenska.....	32
Bakgrund och frågeställning .....	32
Metod .....	32
Resultat.....	32
Slutsats .....	33
Acknowledgement .....	34
References.....	36

# Abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
BDI	Beck Depression Inventory
BMI	Body Mass Index
CBT	Cognitive Behavioral Therapy
CES-DC	Centre for Epidemiological Studies-Depression Scale for Children
CI	Confidence Interval
CFS	Cerebrospinal Fluid
DD	Double depression
DICA-R-A	Diagnostic Interview for Children and Adolescents in the Revised form according to DSM-III for Adolescents
DSM	Diagnostic and Statistical Manual of Mental Disorders
I/M	Intima/Media Ratio
IL-6	Interleukin-6
MADRS	Montgomery-Åsberg Depression Rating Scale
MD	Major Depression
MINI	Mini International Neuropsychiatric Interview
OR	Odds Ratio
SCI	Somatic symptom Check-list Inventory
SD	Standard Deviation
SSRI	Selective Serotonin Reuptake Inhibitor
TNF	Tumor Necrosis Factor



# Introduction

Although it has long been known that there is a correlation between physical and mental illness, a dualist approach that distinguishes between mind and body is still the norm in Western medicine. Somatic disorders are seen to have a medical explanation. The disease is due to pathological changes found in organs or tissues. For example, cardiovascular disease is due to calcification found in blood vessels. The medical approach is to investigate the disease with X-rays, laboratory or other tests, then confirm or exclude the disease. Mental illnesses, on the other hand, have no known medical explanation. They are based on different theories of mental pathology that cannot be found in body tissues. For example, previous psychological trauma or suppression of psychological problems might create a distorted way of relating to others and behaving. Although the disruption of various physiological mechanisms has been associated with mental illness, such as disturbances in serotonin metabolism and deviant function in certain areas of the brain in the depressed, there is still no definite biological explanation for mental illness that can be tested with laboratory tests, X-rays or MRI scans. Therefore, dualism remains. It is noticeable in the ICD-10 manual for medical illnesses in which physical and mental illnesses are reported in separate sections. But mental and somatic disorders are strongly connected. This relationship is evident in, for example, patients with heart disease. Depressive disorder predicts cardio-vascular disease even after controlling for important confounders (1). In people with cardio-vascular disease, concomitant depression disorder is important for the prognosis of cardiovascular disease (2). For this reason, the American Heart Association has, since 2008, recommended that somatic doctors to look for depression in relation to cardio-vascular disease. Although we now know that physical and mental health are related in adults, little is known about if, or with what mechanisms, mental illnesses or depression early in life, will affect future physical and psychological health.

In between physical diseases and mental disorders there are functional somatic symptoms. These are somatic symptoms with no medical explanation. Patients with functional somatic symptoms are investigated primarily within somatic care. When the doctor cannot find a medical explanation for these patients' symptoms confusion often arises. Should the symptoms be treated as a bodily or mental disorder? In physical medicine the patient re-

ceives a reassuring message when potentially serious illness has been excluded according to the normal mode. But, because the patient is still suffering from their bodily problems, he/she may feel disappointed and let down. If the patient is dissatisfied with the result of the investigation, additional costly bodily examinations may ensue, usually without success (3). If no medical explanation is found despite further examinations, the patient might be given a psychological explanation. The psychological explanations have often been based on persistent psychological theories, for example, that the person's physical symptoms are an expression of repressed mental health problems in emotionally immature people who are unable to verbalize their real problems (4). For children and adolescents, the physical symptoms may be interpreted as a way to attract attention to their mental distress or family problems (5). In any case, the somatic symptoms are not interpreted as a separate problem. The patient may feel that he/she does not get the help he/she is looking for. These ambiguous attitudes often create problems for patients, but also for the doctor treating these patients. Patients feel they are not taken seriously and are not satisfied with the assistance they receive. The doctors experience the patients as difficult and demanding (6, 7).

Somatic symptoms with no medical explanation are diagnosed according to DSM-IV somatoform syndrome. These have been criticized for a long time because, among other reasons, they are poorly accepted by patients and doctors and are based on negative criteria (8). This means that when the physical condition is not found, the explanation, by exclusion, is psychological. As the doctor does not find any dangerous cause of the bodily symptoms, it is natural to assume that problems are not severe. The preferred clinical management of somatic symptoms is primarily aimed at minimizing the use of health care and avoiding iatrogenic illness (8). However, the few studies available show that patients with functional somatic symptoms often have more severe problems than patients seeking help for somatic disease with medical explanations and the problems are equal to those suffering from depression (9). Patients with physical symptoms have a lower functional level; they have a higher level of sick leave and consume more health care than patients treated for bodily conditions (10, 11). Besides the high subjective suffering of these patients with somatic symptoms, they are also very costly to society (12). Mental illnesses like depression (conditions that also lack medical explanations that can be verified by studies of body tissues) are often considered to be severe diseases indicating long-term treatment and a close follow up, while functional somatic symptoms are not. Patients with functional somatic symptoms tend, because of insufficient knowledge and research, to be neglected at various levels. There is a lack of long-term follow-up studies (13, 14, 15, 16, 17, 18), and the problem is neglected in large national surveys (19). Although somatic symptoms without medical explanation are common, serious and costly, there is still little knowledge about what functional somatic symptoms are, what distinguishes

them from depression and other mental disorders, and what the long-term outcome is.

## Adolescent depression

From the 1980's depression in children and adolescents has been regarded as resulting from the same affective disorder as in adults (20). A Swedish population-based study, on which the follow-up in the present thesis is based, estimated the lifetime prevalence of major depression in Swedish 16-17-year-olds to 11% (21). Adolescent depression has consistently been reported to be more common among females than among males (22). Population-based studies have revealed that a large proportion of depressed adolescents also have other mental disorders, such as anxiety disorders, disruptive disorders, and substance use disorders (23, 24). In addition, adolescent depression is associated with stressful life events, adverse family environment, and a poor social network (21, 25). Follow-up data from the present study have shown that those with major depression in adolescence were more likely than the former non-depressed adolescents to report virtually all the investigated adult disorders. They were also more likely to report suicidal thoughts and suicide attempts, and all kinds of treatment. Those with adolescent dysthymia were also more likely than the non-depressed adolescents to report depression and anxiety disorders in adulthood, and to report treatment (26).

## Somatic symptoms in adolescence

Research over the two past decades has documented that somatic symptoms without medical explanation are common in community-based samples of children and adolescents (27). One study reported that nearly a quarter of adolescents had at least one functional somatic symptom (28). Another study identified multiple somatic complaints in 11% of girls and 4.5% of boys (29). Somatic symptoms are also common in paediatric samples. Headache and abdominal pain appear to be the most common somatic symptoms (30). Somatic symptoms are more prevalent in girls (4). Several publications have shown that functional somatic symptoms are associated with individual suffering and impairment. This includes poor school performance and attendance as well as interpersonal and social difficulties (30, 31).

There are several theories about the cause of functional somatic symptoms in children and adolescents. The most influential and long-standing theory of functional somatic symptoms is Freud's psychodynamic theory. This theory views functional somatic symptoms as a psychological defence against repressed or unconscious emotions, thoughts, and impulses. In this theory, the child or adolescent expresses the distress through somatic symp-

toms (32). Another long-standing theory is the attachment theory (33). The child's expression of physical distress acts as a care-eliciting function to maintain proximity to the attachment figure. In family system theories, used in family therapy, somatic symptoms are seen to have a communicative function for family members to maintain daily routines and avoid conflicts (34). There are also theories about learned social behaviour. Special attention from parents might reinforce certain behaviour in children when they complain about somatic symptoms (35). Common to all these theories is that the somatic symptoms are not the real problem but are an expression of other psychological problems that cause problematic behaviour and communication.

Other theories acknowledge that somatic symptoms are problems in their own right and link them to CNS dysfunction. The cognitive psychobiological theory (36) believes that somatic symptoms depend on distorted information processing and negative cognition in the CNS. Negative internal monitoring leads to "amplification" or "misinterpretation" of common body sensations. The amplification and misinterpretation of physiological signals may be the process in the development of somatic symptoms.

Lastly, due to high co-morbidity between depression and somatic symptoms, it is believed that somatic symptoms and cognitive and affective depression symptoms are expressions of a common disorder (18). In this case, somatic symptoms and depression would share CNS biological mechanisms and functional somatic symptoms would be an expression of mood disorders.

## The relationship between adolescent depression and functional somatic symptoms

In community samples, adolescents with somatic symptoms are significantly more likely to experience depressive and anxiety symptoms (30). Several studies have shown that a number of somatic symptoms are associated with a greater likelihood of depression. These results suggest a dose-response relationship between somatic symptoms and depression (37). In depressed adolescents the number of somatic symptoms is associated with the severity of depression (38). Abdominal pain seems to be particularly associated with depression. In one large study of 20 000 adolescents, 45% of those with daily abdominal pain experienced depression diagnosed by the screening instrument CES-D (39). Liakopoulo et al reported that 82% of children and adolescents with functional abdominal pain suffered from a psychiatric disorder (40). However, the presence of somatic symptoms is not identical to current depression or other mental disorders. Not all patients with somatic symptoms suffer from depression or mental disorders. According to one

study, a third of patients with five or more somatic symptoms, in primary care, do not have mental disorders (41).

In follow-up studies adolescent somatic symptoms are positively associated with psychiatric disorders later in life (37). However, there are few studies that examine both depression and somatic symptoms at baseline and follow up. An important question is if somatic symptoms are an independent predictor of depression and other mental disorders. If so, there would be no clear borders between depression and somatic symptoms that distinguish the disorders. The few studies available are conflicting (18). Several authors have expressed the need for community based long-term follow-up studies to investigate the relationship between somatic symptoms and mental disorders (13, 14, 15, 16, 17, 18).

## The relationship between adolescent depression and physical illness

The association between somatic illness and psychiatric illness is well established in adults but there are few studies in childhood and adolescence that longitudinally investigate the association. In a large community-based prospective study that investigated a cohort, there was a cross-sectional association between mental and physical illness. Poor physical health predicted mental illness independently of prior depressive episodes. Major depression in adolescence also predicted physical illness. Immune mediating medical disorders were particularly common (42). The relation between adolescent depression and adult somatic immunological disorder was also found by Goodwin et al (43). Asthma and eczema were more common in children followed from 8–23 years of age. Further, in a population-based study of depression, the prescription of drugs during a 15-year follow-up period was analyzed. Increased prescription of drugs for somatic disease related to immune dysfunction, such as eczema, asthma, infection and autoimmune disease was found (44). In subgroups of depressed children, in a long-term population based study, increased inflammatory markers were found in adult age (45). These findings suggest that inflammation is an important link between psychological and somatic disease. Inflammation could also be a possible link between atherosclerosis progression and depression.

# Aim and scope of this thesis

This study aims to investigate the long-term relationship between mental and somatic disease and the outcome of adolescents with functional somatic symptoms.

Four main research questions, one for each paper, were addressed:

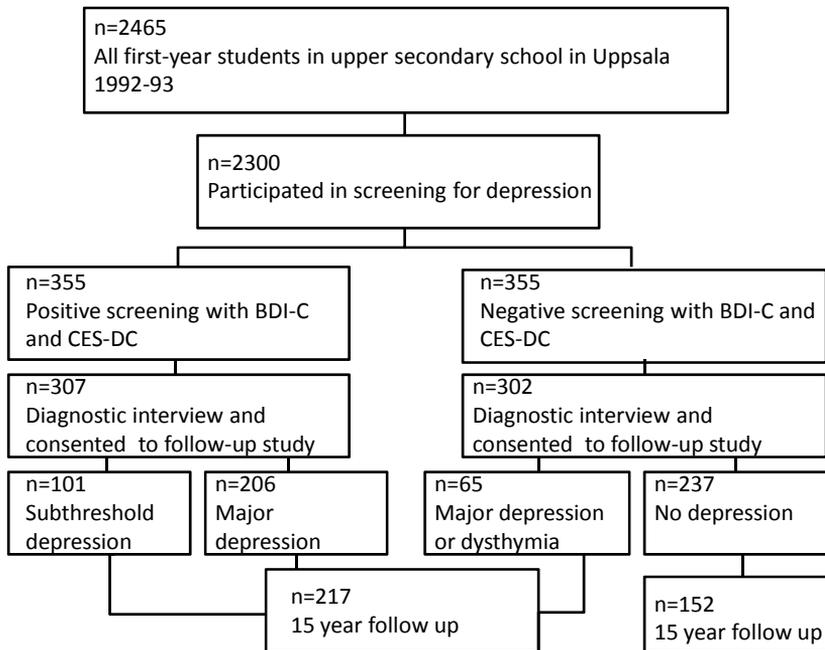
- I Is the number of somatic symptoms in adolescents with depression related to the severity of depression?
- II Is the number of somatic symptoms in adolescence predictive for adult mental disorders?
- III Do adolescents with depression subsequently need more hospital-bound health care?
- IV Do adolescents with depression and repeated recurrence in adulthood subsequently develop less healthy arteries?

# Methods

## Subjects and procedure

The thesis is based on a 15-year follow-up study of a population-based investigation of adolescent depression. In the original investigation (46), carried out in 1991–93 in the Swedish university town of Uppsala, all first-year students in upper secondary school (16–17 years old) during one academic year were asked to participate. Adolescents of the same age group who had dropped out of school were also invited. Out of a total of 2 465 adolescents in the age group, 2 300 (93%) participated in a screening for depression with self-rating scales. Adolescents with positive screening were invited to take part in a more extensive assessment of mental health, social situation, and personality. For each student with positive screening, a same-sex classmate with negative screening was assessed in the same manner in order to create a comparison group. In all, 631 adolescents were interviewed and asked for consent to be contacted for a future follow-up. Of these, 609 participants consented to a future contact and were thereby eligible for the follow-up study.

The follow-up was conducted in 2006–2008, about 15 years after the original investigation, when the participants were 30–33 years old. Two basic sources of information were used. First, data from national registers held by The Swedish National Health and Welfare Board, mainly regarding in-patient care, were obtained for all the 609 eligible participants. Second, the eligible participants were invited to take part in a personal interview about mental health and social situation, and to answer questions about personality. Out of the 609 eligible participants, 409 (67%) took part in the interview, of them 369 had completed the somatic symptom check-list inventory. Figure 1 outlines the procedure.



*Figure 1. Chart illustrating the inclusion of participants, both in adolescence and adulthood.*

## The original investigation

Two self-rating scales of depression, the Beck Depression Inventory-Child (BDI-C) (47, 48) and the Centre for Epidemiological Studies – Depression Scale for Children (CES-DC), were used as screening instruments. Positive screening was defined as  $BDI \geq 16$ , or  $CES-DC \geq 30 + BDI \geq 11$ , or a reported suicide attempt. In the following assessment, mental health was evaluated with the Diagnostic Interview for Children and Adolescents in the revised form according to DSM-III-R for adolescents (DICA-R-A) (49). The DICA-R-A is a structured diagnostic interview that covers a broad spectrum of child and adolescent mental disorders, such as major depression, dysthymic disorder, anxiety disorders and conduct disorders. It also includes questions about social situation and family-related adversities. In addition, the participants completed the Children's Life Events Inventory (50). This self-evaluation mainly covers life events related to social situation and family situation.

## The register data

The Swedish National Health and Welfare Board keeps the official registers concerning health and sickness in Sweden. The national patients register was used. Since 1987, the register includes information concerning episodes of in-patient care in Sweden. Out-patient visits to surgery are available from 1997, and other out-patient visits to specialized physicians have been registered since 2001. Thus, the register data covers only part of the out-patient visits during the 15-year follow-up period. The national registers used do cover in-patient stays and specialized out-patient care. However, visits to general practitioners are not included. The total amount of missing data for somatic short time care for the period 1987–1991 has been estimated to be less than 2%. For all records reported to the national patient register a data control is run. A check is made to ensure that compulsory variables have been reported, e.g. personal identification number, hospital, and main diagnosis. A check is also made to make sure that codes for different variables and dates have valid values. Some obviously incorrect data are corrected in connection with the quality controls. The personal identification number (PIN) makes it possible to follow a patient between different hospitals and over time. The number of in-patient stays in 2003 with missing personal identification numbers was 0.7%. The mother-child register and the medical birth register were also used. By means of these registers, all children belonging to a separate mother can be identified and information can be collected concerning medical complications during pregnancy and delivery. Furthermore, there is information concerning the health of the new-born children.

The register data was obtained divided in groups, in a way so that no single participant could be identified. The participants were grouped into larger groups, depending on their adolescent status regarding depression (no depression; major depression; or subthreshold depressive symptoms).

## The follow-up interview

The participants were interviewed face-to-face at follow-up (or by telephone in the few cases where face-to-face interview were not possible). Mental disorders in adulthood were determined with the Mini International Neuropsychiatric Interview Plus (51), a structured clinical interview. Some disorders (e g MD, hypomania/mania, substance use disorders) were rated from age 19 onwards, while only current status at follow-up was rated for other disorders (e g most anxiety disorders and somatoform disorders). To further enhance the participants' memory of depressive episodes during the investigated period, a life-chart with questions about education, occupation, life-events, depressions, and treatments was used. Further, participants were asked about suicidal ideation and suicide attempts during the period from the age of 19 to follow-up. They were also asked about treatments for mental disorders during the same period, parental mental disorders, demographic data, social situation, and life events. A structured anamnestic interview for these questions was created specifically for this study. The severity of ongoing depressive symptoms was measured using the self-rating version of the Montgomery Asberg Depression Rating Scale (MADRS-S) (52).

## The ultrasound investigation

Carotid total wall thickness and the thickness of the individual artery layers were assessed noninvasively using high-resolution ultrasonography equipment. This new technique makes it possible to investigate the different layers of the carotid artery (intima and media). To follow the process to the development of atherosclerosis, the thickness of the combined carotid artery intima-media layers estimated using ultrasound is the gold standard (53). However, with advancing age and development of atherosclerosis, the intima and media layers change in different directions, i e the intima becomes thicker and the media becomes thinner (54). Thus, separate assessment of carotid artery intima and media thickness using noninvasive high-frequency ultrasound appears to be more valuable, which has previously been shown by a striking difference in intima thickness and the intima/media thickness ratio between subjects with and without cardiovascular disease (55).

## Subjects and measures in papers I-IV

### Paper I (Adolescent somatic symptoms)

The cross-sectional relationship between depression and somatic symptoms was investigated in adolescence. The participants were divided into those with adolescent depression and those without. A case-control design was used with 177 pairs matched for sex, age and school class. Separate analyses were performed on adolescents with depression. Symptoms, signs, or life events that require urgent treatment and/or have a known poor outcome were selected for analyzing their relationship to depression with somatic symptoms. Previous research has suggested that subthreshold depression in adolescence is similar to major depression with respect to functional impairment (56, 57). We therefore used a broad definition of depression in this study. Adolescents meeting the DICA-R-A criteria for lifetime major depression, or either reporting a suicide attempt or scoring high on the self-evaluation (categorized as subthreshold depression), composed a broadly defined group of depressed adolescents. Screening-negative adolescents who turned out to meet the DICA-R-A criteria for lifetime major depression were included in the depression group. The subjects who did not meet any of these criteria were classified as non-depressed and constituted a comparison group.

### Paper II (Somatic symptoms followed-up)

The same definition of depressed and non-depressed adolescents as in paper I was used. Paper II is a 15-year follow-up study focusing on mental health outcome; it used data from the interviews. The outcomes were taken from the MINI plus. The participants were divided into diagnostic subgroups depending on the number of somatic symptoms in adolescence: 1) no somatic symptoms (n=35); 2) 1–2 somatic symptoms (n=73); 3) 3–4 somatic symptoms (n=59); 4)  $\geq 5$  somatic symptoms (n=50); and non-depressed controls (n=152). These groups were defined according to the results of the SCI. Separate analyses were performed in the controls divided into those with or without somatic symptoms. Participants who reported a lifetime hypomanic or manic episode according to the DICA-R-A were excluded from the analyses on the grounds that the trajectories of mental health and personality can be expected to be different in this subgroup. Multivariate analyses of adolescent predictors of adult mental health in adolescents with the somatic and depressive symptoms were conducted and included the following adolescent measures: duration of major depression (episodic or long-term), childhood anxiety disorder (separation anxiety, overanxious disorder, or avoidant disorder), disruptive disorder, conflicts with parents, and family adversities.

### Paper III (In-patient care)

Outcome measures of ICD-10 in patient somatic and psychiatric diagnoses from the national health register were analyzed. The mother–child registers and the medical birth register were also used. 612 adolescents were to be included in the register study, 261 with major depression and 101 with sub-clinical depression. The sample was divided into depressed and non-depressed. Gender differences were investigated.

### Paper IV (Intima/media ratio)

The fourth paper measures early arterial wall changes. 15 women with at least three recurrent depressive episodes with adolescent onset were selected due to availability and willingness to participate in the study. Weight, length, BMI, waist, hip, waist/hip ratio, systolic blood pressure, diastolic blood pressure and pulse were recorded.

The mean age was 31.5 years. The control group included 20 healthy young women with a mean age of 39.6 years. Carotid total wall thickness and the thickness of the individual artery layers were assessed noninvasively using high-resolution ultrasonography equipment. The assessor was blinded to the clinical data of the study subjects.

## Statistics

Univariate comparisons were conducted with the  $\chi^2$ -test for dichotomized variables (Fisher's exact test when applicable). Mann-Whitney tests were also used. Linear by linear were used for linear relationships. Logistic regression models were used to adjust for comorbidity and social characteristics reported in adolescence. P-values below 0.05 in two-tailed tests were considered statistically significant for all statistical analyses. Throughout, SPSS (versions 17.0 and 18.0) was used for the statistical analyses.

## Ethics

Participants reporting current mental disorders or recurrent depressions were informed of available treatment options and where to seek treatment. In some cases, a letter of referral was written to the local psychiatric out-patient clinic after consent from the participant. The register data from Statistics Sweden were obtained in a manner so that no single participant could be identified. The study was approved by the Ethical vetting board in Uppsala, Sweden.

# Summary of results

## Paper I

The adolescents with depressive disorders suffered more often from somatic symptoms than their healthy controls. The most common physical symptom, among all individuals with a depression diagnosis, was headache (42%, OR=6.30). The most pronounced difference between depressed and controls was seen concerning abdominal pain (20%, OR=8.75). There were no significant sex differences among the items of the SCI-questionnaire except for the item “feeling chilly” which was more common in girls. With increasing numbers of somatic symptoms, concurrent severe child and adolescent disorders increased. The linear relationship was significant for suicidal plans/thoughts ( $p < 0.01$ ) (Figure 2), suicide attempts ( $p < 0.01$ ), disruptive behaviour ( $p < 0.001$ ) and stressful relations ( $p < 0.001$ ). In a conditional logistic regression analysis of depressed adolescents, three or more somatic symptoms were used as the dependent variable. Of all the variables tested only one factor was significantly more common as an explanation of more than three symptoms, i.e. multiple stressful relationships; OR=2.35.

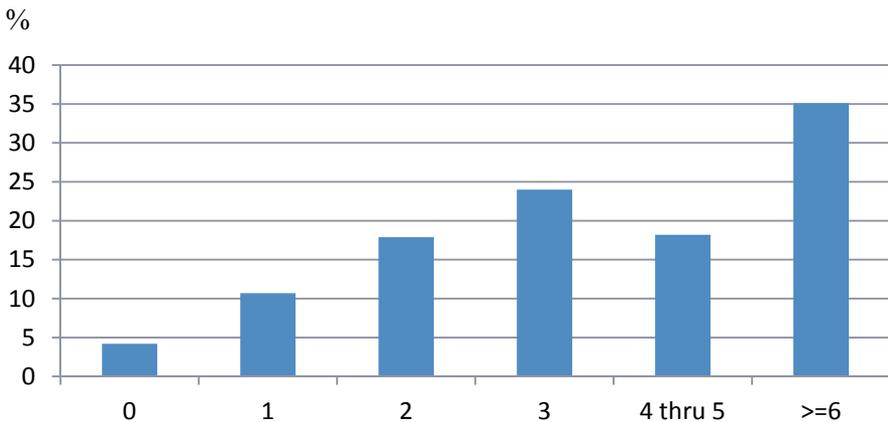


Figure 2. Current suicidal plans and thoughts in adolescents with depression and different numbers of functional somatic symptoms. Numbers expressed in percent of the adolescents in each group. Linear correlation in depression subgroups.  $p < 0.01$ ,  $F=9.9$

## Paper II

There was a linear relationship between the number of somatic symptoms in adolescence with depression and the risk of mental disorders as adults for any disorder ( $p < 0.001$ ), any mood disorder ( $p < 0.001$ ), recurrent depression ( $p < 0.001$ ) (Figure 3), chronic depression ( $p < 0.05$ ), bipolar disorders ( $p < 0.05$ ), any anxiety disorder ( $p < 0.05$ ), panic disorder ( $p < 0.05$ ), and somatoform disorders ( $p < 0.01$ ). Adolescents with depression and  $\geq 5$  somatic symptoms (23% of the depressed) had poor adult mental health outcomes compared to the other groups.

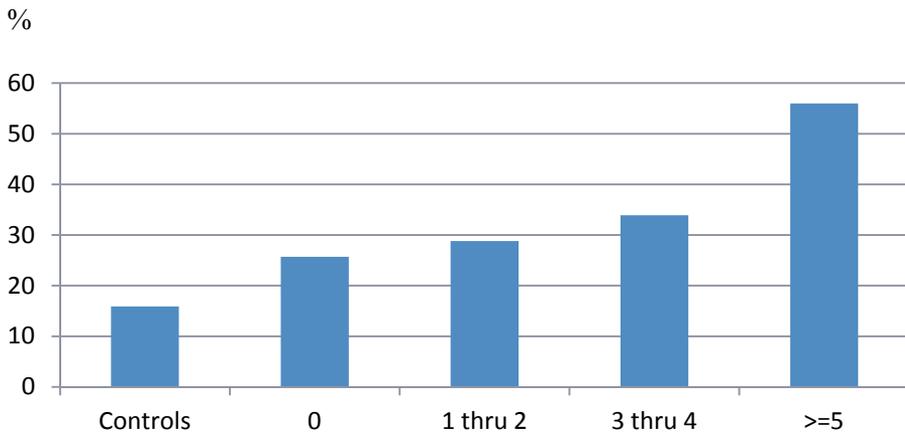


Figure 3. Adult recurrent depression in adolescents with different numbers of functional somatic symptoms. Linear correlation in depression subgroups.  $p < 0.01$

There was a strong overrepresentation of adult suicidal behaviour in adolescents with depression who suffered  $\geq 5$  functional somatic symptoms, compared to the controls ( $p < 0.001$ ).

The controls with somatic symptoms in adolescence were more likely than controls without somatic symptoms to report any disorder, any mood disorder, MDD, any anxiety disorder, and self-harm behaviour ( $p < 0.05$ ).

Abdominal pain, perspiration without exertion and feeling chilly predicted recurrent or extended episodes of depression in adulthood. Abdominal pain remained a significant predictor together with long-term depression when controlling for DSM-IV criteria for MDD, family adversities, and adolescent behaviour problems (suicidal behaviour, disruptive behaviour, and drug abuse) (Table 1). Abdominal pain also predicted anxiety disorders when controlling for DSM-IV criteria for MDD, family adversities and adolescent behaviour problems.

	<b>Model 1</b>	<b>Model 2</b>	<b>Model 3</b>
	OR	OR	OR
Abdominal pain	3.23	3.25	3.13
Perspiration	3.06	3.38	
Feeling chilly	1.86		
Andedonia		2.52	
Long-term depression (>1 year)			3.47

*Table 1. Prediction of recurrent episodes of depression or the recurrence of an episode longer than 6 months. Logistic regression analyses. Only significant results shown.*

*Model 1. Includes the 15 most common somatic symptoms according to SCI and sex.*

*Model 2. Adds 9 DSM-IV depression criteria.*

*Model 3. Adds long-term depression, family adversities, suicidal behavior, disruptive disorder, drug abuse, and stressful relationships.*

## Paper III

The formerly depressed females had significantly more out-patient hospital visits. A higher proportion of the formerly depressed females had injuries, poisonings, and certain other consequences of external causes including attempted suicide and accidents (16.3% versus 8.2%). They also suffered significantly more often from somatic disorders like infectious and parasitic diseases (4.6% versus 1.0%), diseases of the nervous system (6.4% versus 2.1%) and diseases of the digestive system (9.2% versus 4.1%). The formerly depressed females had significantly more in-patient stays (3.6 versus 2.4), and a significantly higher total number of in-patient days (27.4 versus 10.1). A significantly higher proportion of the formerly depressed females had in-patient days due to mental and behavioural disorders (9.5% versus 4.6%), in particular anxiety disorders (4.9% versus 1.0%). Regarding the males, no significant differences were found between formerly depressed males and the comparison group as concerns out-patient visits. Among the formerly depressed males, a significantly higher proportion had in-patient days due to mental and behavioural disorders (16.5% versus 1.8%), in particular alcohol and drug abuse (7.6% versus 0%). A significantly higher proportion of the formerly depressed females had had maternal disorders predominantly related to pregnancy (8.6% versus 0.6%), complications pre-

dominantly related to the puerperal period (5.3% versus 1.2%), and other complications related to pregnancy or delivery (57.4% versus 45.2%).

## Paper IV

In patients with recurrent depressive disorders, compared to control women, the carotid intima was significantly thicker (0.17 versus 0.12 mm,  $z=4.83$ ,  $p < 0.0001$ ), the carotid media significantly thinner (0.49 versus 0.68 mm,  $z=2.40$ ,  $p < 0.02$ ), and the resulting intima/media ratio was significantly higher (0.38 versus 0.20,  $z=4.40$ ,  $p < 0.0001$ ) as was the intima/media ratio (0.36 versus 0.20,  $z=4.01$ ,  $p < 0.0001$ ). The intima thickness, the media thickness, and the intima/media ratio did not correlate significantly with weight, length, BMI, waist, hip, waist/hip ratio, systolic blood pressure, diastolic blood pressure or pulse in the women with recurrent depressive disorders, except for a significant negative correlation between hip circumference and the carotid intima thickness ( $r=-0.53$ ,  $p < 0.05$ ).

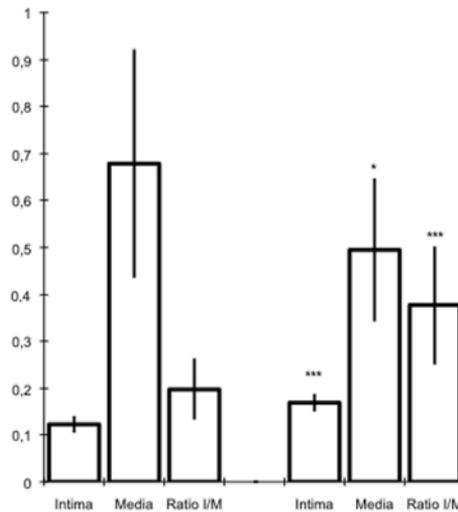


Figure 4. Difference in thickness of the carotid artery wall layer (mm) between 30 year old women with recurrent depression and healthy controls aged 39 years.

\*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$

# Discussion

This study follows up adolescents with depression and matched controls screened from a population-based sample of 2 465 adolescents in which 93% of the entire population participated. The size of the study where almost all of the population participated and the long follow-up period in combination with extensive data from both registers and interviews makes this study unique. The design of the present study makes it well suited for investigating the relationship between adolescent depression and adult somatic and psychiatric disease and functional somatic symptoms.

Somatic symptoms have rarely been studied in population-based studies and several authors have expressed the need of community-based studies of sufficient quality to understand the relationship between somatic symptoms and depression and other mental disorders (14, 15, 16, 17, 18). Such studies could answer questions about whether somatic symptoms and depression are separate disorders or if somatic symptoms are different expressions of depression. This study is particularly well situated to investigate this question for several reasons. The controls were chosen to be as similar as possible compared to the depressed adolescents (matched for age, school class and sex) except that they had never experienced a depressive episode as adolescents. This makes the comparison between adolescents with depression and controls more reliable. Another advantage is that this investigation includes information about the lifetime history at the base line investigation. This information makes it possible to detect new cases of a first episode of depression in the follow-up period. Furthermore, at the 15-year interview, lifetime diagnosis from the age of 19 was investigated. This is of importance since depression and other mental disorders are mostly episodic conditions and not chronic like some somatic conditions, for example high blood pressure. Only cross-sectional data at base-line and follow-up would have been a limitation for the research questions. A limitation with retrospective interview data is however the risk for recall bias.

Furthermore, in the register study (the Swedish Health Register), the diagnoses were investigated throughout the follow-up period. Compared to studies with self rated health or interviews, an experienced clinician diagnosed the conditions objectively and no recall bias by the patient was possible. But a limitation is that the investigation was only possible in large groups, due to ethical reason, so no single individual could be identified.

Thus it was not possible to control for important confounders, e.g. somatic symptoms.

Subsequently the adolescents were interviewed and 367 adolescents consented to participate in register studies. From this group it was now possible to investigate an important research question: how adolescent depression and multiple somatic symptoms ( $\geq 5$ ) predicted subsequent somatic and psychiatric in-patient care in comparison (unpublished data). The results, in a logistic regression analysis, showed that the risk for adolescents with depression to suffer from somatic and psychiatric in-patient care was around the double for both. For adolescents with multiple somatic symptoms there was an even stronger risk for psychiatric in-patient care, but no risk for somatic in-patient care when controlled for adolescent depression and sex. These results further link somatic symptoms to mental disorders, since multiple somatic symptoms independent of adolescent depression predict in-patient care for mental disorders (Figure 5).

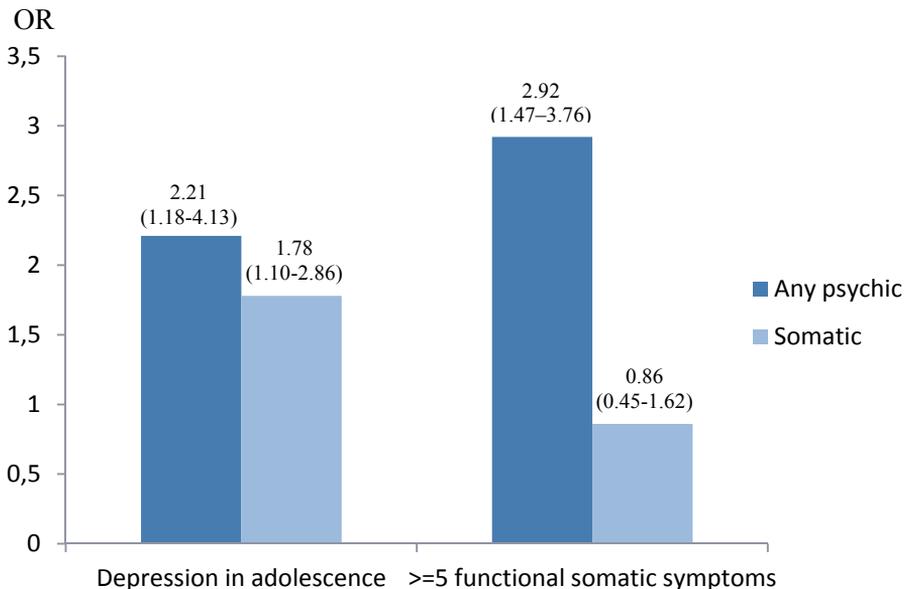


Figure 5. Prediction of adult somatic and psychiatric in-patient care. Logistic regression analyses of adolescents with depression, adolescents with  $\geq 5$  somatic symptoms and sex (not shown in figure). Differences expressed with odds ratios. Confidence interval in brackets.

The mechanisms leading from adolescent psychopathology to adult outcome are not yet well understood. However, it is clear that there is a substantial overlap between depression, somatic symptoms and other mental and somatic disorders. Further studies to examine the mechanisms of these associations are needed.

## Paper I

The study showed a strong relationship between somatic symptoms and depression in adolescence, in line with previous research (37). The study also showed that somatic symptoms were related to the severity of the depression. In further analyses it was shown that the number of somatic symptoms was related to severe child and adolescent disorders and problems in a “dose response relationship”. Previous suicidal attempts and current suicidal plans, as well as conduct disorder and multiple stressful relationships, were all related to the number of somatic symptoms in adolescents with depression. The results from our study diverge from the view that suffering from somatic symptoms is not a severe condition. Nor do the findings support the theories that somatic symptoms function as a way to communicate psychological problems. Rather, this study indicates that concurrent somatic symptoms are core symptoms in severe depression. The findings in this study suggest that patients suffering from multiple somatic symptoms need child and adolescent specialist care.

## Paper II

This paper found that somatic symptoms predicted depression and other mental illnesses independent of depression in adolescence. Two out of the investigated somatic symptoms (abdominal pain and perspiration) predicted adult depression and anxiety stronger than all of the 9 DSM-IV depression criteria. These results show that there are no clear boundaries between functional somatic symptoms and depression. Somatic symptoms and affective and cognitive depression symptoms seem to be different expressions of a common condition. The present study is consistent with a previous long-term community based study (58) but not with another study, demonstrating that physical symptoms do not predict depression or mental illness if controlled for depression in adolescence (37). Although our study and the study of Dhossche et al (37) are quite similar, these studies differ in two important aspects. Our study investigates mental illnesses during a 15-year follow-up period, compared to one-year prevalence in the study of Dhossche et al. Our study also has information about the life-time history of depression in ado-

lescents. This enables better comparison between depressed and non-depressed adolescents in the follow-up investigation.

The present study also demonstrated that the number of somatic symptoms reported by adolescents with depression was closely related to the severity of adult psychiatric diagnoses in a progressive manner. This finding showed that somatic symptoms in adolescent depression do not reflect transient problems. Mental health problems remain with increasing severity for each somatic symptom experienced during adolescence. The strong prediction of poor mental health indicated by somatic symptoms is of great importance in health care. The prognosis for mental disorders is as poor for adolescents with depression and several somatic symptoms as for those with long-term adolescent depression. Considering the poor prognosis for mental health, the need for patient health care should not be underestimated for adolescents. The clinical implication of this study is that adequate treatment guidelines are needed for patients with somatic symptoms.

The finding that somatic symptoms in adolescence predict future suicidal attempts several years later has, to our knowledge, not been described previously. The link between suicidal behaviour and somatic symptoms needs further study.

The 15-year follow-up study and our previous cross-sectional study suggest that a depression diagnosis would benefit from including a number of somatic symptoms as a marker of the severity of current depression and as a prognostic marker of future mental disorders and suicidal behaviour.

## Paper III

In previously published follow-up studies, there has been a tendency indicating the same course in males and females with adolescent depression (59). In the present study the females with depressive disorders during adolescence had a higher hospital bound health care consumption for somatic and psychiatric disease during the 15-year follow-up period. But males with former depressive episodes in adolescence did not have more in-patient care due to mental or somatic disorders. Instead, they had considerably more in-patient stays due to alcohol and drug abuse. We know that the male adolescents included in the present study had more behavioural disturbances and drug abuse (60). Thus, the males might be taken care of outside the health care system, e.g. in prisons or in treatment homes for alcohol and drug abusers.

The subjects with adolescent major depressive disorders had very similar long-term outcomes to the subjects with adolescent subsyndromal disorders or dysthymia as concerns general ill-health and somatic comorbidity, in line with the results from earlier studies (61). This finding indicates that there is no natural cut off for depression.

The increased frequency of certain infectious and parasitic diseases in former depressed females at as early an age as 30 is of interest as it has been demonstrated that depressed patients in long term follow-ups have an almost ten times increased risk of death from infectious disorders (62).

Apart from the differences found between the former depressed patients and the comparison group, it is also of interest that there is no increased risk of diseases of the circulatory system at young adult age.

## Paper IV

The most remarkable finding in the present pilot study is that young women, around 30 years old, with recurrent depressive disorders with adolescent onset without any clinical signs of cardio-vascular disease have significantly thicker carotid intima, significantly thinner carotid media and significantly higher intima/media ratio than about 10 years older healthy women. The findings indicate a less healthy carotid artery wall, according to previous documentation (55). Risky behaviour and life style factors have been suggested as one possible mechanism to explain the increased risk of cardio-vascular disease in patients with recurrent depressive disorders (63). In the present study, the changes in carotid intima and media thickness do not seem to be related to life style factors, at least not to smoking.

The findings indicate the importance to control patients with recurrent depressive disorders for early signs of cardio-vascular disease, even when there are no clinical signs of such diseases.

## Implications and future research

The unexpected poor short and long-term outcome in adolescents with somatic symptoms proves the need for better developed treatment for this group. The strong prediction of functional somatic symptoms for mental disorder, independent of adolescent depression, suggests that somatic symptoms and cognitive and affective depression symptoms are different expressions of a common disorder. Treatment, sick-leave and follow-up of somatic symptoms should not differ considerably to that of depression and other mental disorders.

The subjects with adolescent major depressive disorders did have similar long-term outcomes as the subjects with adolescent subsyndromal disorders or dysthymia as concerns general ill-health and somatic comorbidity. This finding indicates that there is no natural cut off for depression, in line with several other reports (64). The number of depression symptoms, as well as the number of concurrent somatic symptoms, seems to be more important in choosing the level of treatment.

Males with adolescent depression are likely to be taken care of outside the health care system. They seem to need special attention concerning mental and somatic disease.

The ultrasound pilot study indicates that sub-groups of depression might develop early cardio-vascular disease. Early interventions might be needed.

The first three articles in this thesis investigated the epidemiological relationship between depression, functional somatic symptoms and somatic and mental disease. The final study goes one step further. It investigated the mechanisms linking depression and somatic disease. Studies that investigate biomarkers in population based studies are sparse but are needed to answer important questions. This is partly shown by the fourth study. Our next aim is to continue investigating the mechanisms linking mental disorders and somatic disease and functional somatic symptoms with different biomarkers. Currently the population is being reinvestigated with physical measures, ultrasound of the carotid artery, and other laboratory biomarkers for immunology, coagulation and stress. These additional data from the population-based study might give unique possibilities to answer several important research questions, such as: With what mechanisms are mental disorders related to somatic disorders? With what mechanisms are functional somatic symptoms related to mental disorders? Through what mechanism is suicidal behaviour related to somatic symptoms?

# Conclusions

- Functional somatic symptoms in adolescence are strongly related to depression.
- The number of somatic symptoms is correlated to the severity of adolescent depression and the long-term mental health outcome.
- Somatic symptoms predict adult mental disorders independent of adolescent depression.
- Multiple somatic symptoms in adolescence are a powerful predictor of continued poor mental health in adulthood, as evidenced by recurrent depression, multiple mental disorders, and suicidal ideation.
- Female adolescents with depression have more in- and out-patient care with psychiatric and somatic diagnoses in the Swedish patient registers. The males do not. Instead, they have considerably more in-patient stays due to alcohol and drug abuse.
- In women with adolescent depression and recurrent depression in adulthood there is an association with premature aging of the blood vessel wall compared to healthy controls, but not for other risk factors of cardio-vascular disease.

# Sammanfattning på svenska

## Bakgrund och frågeställning

Kroppsliga symtom utan medicinsk förklaring, som magont och huvudvärk, är vanliga bland både ungdomar och vuxna. Sådana symtom orsakar lidande, funktionsnedsättning, sjukskrivningar och är kostsamma för samhället. Trots att problemen är vanliga och allvarliga finns det förvånansvärt lite forskning på området. Man vet fortfarande lite om vad de här symtomen är, hur de ska behandlas och vilken betydelse de har för ungdomars vuxna hälsa. Syftet med avhandlingen är att undersöka hur det går för ungdomar som har kroppsliga symtom. Avhandlingen undersöker också om ungdomar med depression i framtiden behöver vårdas oftare på sjukhus för både psykiska och kroppsliga orsaker.

## Metod

Avhandlingen bygger på en studie av ungdomar i årskurs 1 i gymnasiet som följdes upp efter 15 år. Under 1991 till 1993 undersöktes i stort sett alla första års studerande i gymnasieskolan (16-17 år) i Uppsala (n=2300). De screenades för depression. Cirka 600 ungdomar med positiv screening och utvalda kontroller med negativ screening intervjuades. Psykisk hälsa, social situation och somatiska symtom undersöktes. Runt 31 års ålder följdes deltagarna upp med personliga intervjuer och i nationella register. Psykisk och kroppslig hälsa undersöktes också.

## Resultat

Det viktigaste fyndet i avhandlingen är att kroppsliga symtom har ett oväntat starkt samband med psykiska problem i tonåren men även med fortsatta psykiska problem i vuxen ålder. Resultaten visar att för varje kroppsligt symtom som ungdomen led av ökade risken att ha försökt begå självmord och ha ett normbrytande beteende eller drogmissbruk i tonåren. Risken ökade också att som vuxen drabbas av allvarlig psykisk sjukdom, t ex manodepressiv sjukdom, självmordsförsök och kroniska depressioner. Det visade sig att kroppsliga symtom oberoende av depression och andra problem i tonåren

kunde förutse psykisk sjukdom. Detta samband var speciellt tydligt för mag-smärta. Om ungdomen angav att han/hon hade haft ont i magen flera gånger i veckan senaste månaden förutspådde detta framtida depressioner lika starkt som om han/hon hade lidit av depression mesta tiden av senaste året. Även enstaka kroppsliga symtom hos friska ungdomar som aldrig hade varit deprimerade fördubblade risken för depression, ångest och självskadande beteende i vuxen ålder. Resultaten av de här fynden går tvärtemot uppfattningen att enstaka kroppsliga symtom är lätta problem som inte behöver följas upp.

Avhandlingen visar också att ungdomsdepression inte är ett övergående problem. Ungdomar som var deprimerade i tonåren har en dubbelt så stor risk att behöva sjukhusvård för psykisk sjukdom, men de hade också en fördubblad risk att vårdas på sjukhus för kroppsliga sjukdomar. Kvinnor som var deprimerade i tonåren och fortsatte att vara deprimerade i vuxen ålder har förändringar i blodkärlen som om de vore 20–30 år äldre. Dessa förändringarna skulle kunna innebära insjuknande i hjärt- och kärlsjukdomar i framtid. De är i sådana fall i behov av preventiva åtgärder.

## Slutsats

Avhandlingen visar att ungdomar med kroppsliga symtom inte tas tillräckligt på allvar. Effektiva behandlingsmetoder samt uppföljning behövs. Ungdomar med många kroppsliga symtom och depression ser ut att behöva barnpsykiatrisk specialistkompetens, med tanke på de allvarliga problem som de ofta har, t ex självmordstankar och normbrytande beteende. Depression hos ungdomar är inte något som bara hör ungdomen till. Risken för fortsatt både psykisk och kroppslig sjukdom är stor. Resultaten från den här avhandlingen talar för att ungdomar med depression behöver en riktad aktiv behandling mot depression. Så är fallet inte idag då mindre än 10 % av ungdomar med depression behandlas med terapi eller medicin, jämfört med ca 40–50 % av vuxna. Detta trots att tidigare studier visar att de flesta som insjuknar i depression för första gången gör det som vuxna och att de då har ett betydligt mildare och kortvarigare förlopp jämfört med de som insjuknar i tonåren.

# Acknowledgement

This study was carried out at the Department of Neuroscience, Child and Adolescent Psychiatry, Uppsala University. Financial support was received from the Swedish Council for Working Life and Social Research (FAS), the Märta and Nicke Nasvell Foundation, and the Foundation in Memory of Professor Bror Gadelius.

I would like to express my gratitude to all who have contributed to this work, especially:

Anne-Liis von Knorring, principal supervisor, who once was my father's PhD candidate and who I have known and very much liked already since I was a child. Thanks for believing in me, helping me get started and for supporting my ideas and work throughout.

Lars von Knorring, supervisor, for your support throughout the work, and for having shared your excellent scientific knowledge, writing and creative ideas. I am especially grateful for the help I received to do research on my own areas of interest: the relationship between somatic and mental disorders.

Gunilla Olsson, supervisor, for your impressive work with the first part of the study, in the early 1990's. Each day of research, I feel happiness for working with an outstanding material. Thanks for the interest and the support of my work.

Hans Arinell, statistician, for your invaluable statistical support and always interesting discussions over a cup of coffee.

Ulf Jonsson, Med doctor and fellow PhD-student, for your impressive work with the second part of the study. Thanks for excellent collaborations throughout and many good laughs during the way.

Aivar Päären, fellow PhD-student, thanks for excellent cooperation and always insightful scientific discussions that stem from your vast clinical experience.

Tord Naessen, Professor and co-author, for sharing and educating me in your novel imaging methods, and contributing with offices, equipment and staff for research.

Marita Larsson, for teaching me how to use the ultrasound equipment.

Agneta Siegbahn, Professor, for the interest in our work and for the sharing of storage of our blood samples.

Sara Brolin Låftman, my wife, for the support, proof reading, for insightful comments. Since we do research in the same area we hopefully someday will do research together.

Peter Engelsöy, Head of Unit, Child and Adolescent Psychiatric Clinic Stockholm, for supporting my studies economically with a paid day a week.

Berit Hård-Wallenqvist, for all help with practical things and for saving my funds.

Frank Lindblad, Professor, for always being supportive and for the interest in my work.

# References

1. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med* 2004;66:802–13.
2. van Melle JP, de Jonge P, Spijkerman TA, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med* 2004;66:814–22.
3. Jackson JL, Kroenke K. Difficult patient encounters in the ambulatory clinic: clinical predictors and outcomes. *Arch Intern Med* 1999;159:1069–75.
4. Campo JV. Somatization disorder. Ammerman, RT and Hersen, M (Eds.) *Handbook of child behavior therapy in the psychiatric setting*. Wiley series on personality processes. (pp. 442–51). New York: Wiley; 1995.
5. Aro H. Life stress and psychosomatic symptoms among 14 to 16-year old Finnish adolescents. *Psychol Med* 1987;17:191–201.
6. Dirkwager AJ, Verhaak PF. Patients with persistent medically unexplained symptoms in general practice: characteristics and quality of care. *BMC Fam Pract* 2007;31:33–42.
7. Lin EH, Katon W, von Korff M, Bush T, Lipscomb P, Russo J, Wagner E. Frustrating patients: physician and patient perspectives among distressed high users of medical services. *J Gen Intern Med* 1991;6:241–6.
8. Mayou R, Kirmayer LJ, Simon G, Kroenke K, Sharpe M. Somatoform disorders: time for a new approach in DSM-V. *Am J Psychiatry* 2005;162:847–55.
9. Koch H, van Bokhoven MA, ter Riet G, van der Weijden T, Dinant GJ, Bindels PJ. Demographic characteristics and quality of life of patients with unexplained complaints: a descriptive study in general practice. *Qual Life Res* 2007;16:1483–89.
10. Hoedeman R, Blankenstein AH, Krol B, Koopmans PC, Groothoff JW. The contribution of high levels of somatic symptom severity to sickness absence duration, disability and discharge. *J Occup Rehabil* 2010;20:264–73.
11. Smith GR, Monson RA, Ray DC. Patients with multiple unexplained symptoms. Their Characteristics, functional health, and health care utilization. *Arch Intern Med* 1986;146:60–72.

12. Meerding WJ, Bonneux L, Polder JJ, Koopmanschap MA, van der Maas PJ. Demographic and epidemiological determinants of health-care costs in Netherlands: cost of illness study. *BMJ* 1998;317:111-5.
13. Beck, JE. A developmental perspective on functional somatic symptoms. *J Pediatr Psychol* 2008;33:547-62.
14. Lieb R, Zimmermann P, Friis RH, et al. The natural course of DSM-IV somatoform disorders and syndromes among adolescents and young adults: a prospective-longitudinal community study. *Eur Psychiatry* 2002;17:321-31.
15. olde Hartman TC, Borghuis MS, Lucassen PL, van de Laar FA, Speckens AE, van Weel C. Medically unexplained symptoms, somatisation disorder and hypochondriasis: course and prognosis. A systematic review. *J World Psychiatry* 2006;5:146-50.
16. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Arch Intern Med* 2003;163:2433-45.
17. Creed F. Should general psychiatry ignore somatization and hypochondriasis? *Psychosom Res* 2009;66:363-77.
18. Campo JV. Annual Research Review: Functional somatic symptoms and associated anxiety and depression – developmental psychopathology in pediatric practice. *J Child Psychol Psychiatry* 2012;53:575-92.
19. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Survey replication. *Arch Gen Psychiatry* 2005;62:593-602
20. Angold A. Childhood and adolescent depression. I. Epidemiological and aetiological aspects. *Br J Psychiatry* 1988;152:601-17.
21. Olsson GI, Nordstrom ML, Arinell H, von Knorring AL. Adolescent depression: social network and family climate – a case-control study. *J Child Psychol Psychiatry* 1999;40:227-37.
22. Sheeber L, Hops H, Davis B. Family processes in adolescent depression. *Clin Child Fam Psychol Rev* 2001;4:19-35.
23. Lewinsohn PM, Rohde P, Klein DN, Seeley JR. Natural course of adolescent major depressive disorder: I. Continuity into young adulthood. *J Am Acad Child Adolesc Psychiatry* 1999;38:56-63.
24. Fergusson DM, Woodward LJ. Mental health, educational, and social role outcomes of adolescents with depression. *Arch Gen Psychiatry* 2002;59:225-31.
25. Bond L, Toumbourou JW, Thomas L, Catalano RF, Patton G. Individual, family, school, and community risk and protective factors for depressive symptoms in adolescents: a comparison of risk profiles for substance use and depressive symptoms. *Prev Sci* 2005;6:73-88.

26. Jonsson U, Bohman H, von Knorring L, Olsson G, Päären A, von Knorring A-L. Mental health outcome of a long-term and episodic adolescent depression: 15-year follow-up of a community sample. *J Affect Disord* 2011;130:395–404.
27. Steinhausen HC, Winkler Metzke C. Continuity of functional-somatic symptoms from late childhood to young adulthood in a community sample. *J Child Psychol Psychiatry* 2007;48:508-13.
28. Berntsson LT, Kohler L. Long-term illness and psychosomatic complaints in children aged 2–17 years in the five Nordic countries: Comparison between 1984 and 1996. *Eur J Public Health* 2001;11:35–42.
29. Offord DR, Boyle MH, Szatmari P, et al. Ontario Child Health Study. II. Six-month prevalence of disorder and rates of service utilization. *Arch Gen Psychiatry* 1987;44:832–6.
30. Campo JV, Fritsch SL. Somatization in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 1994;33:1223–35.
31. Bernstein GA, et al. Somatic symptoms in anxious-depressed school refusers. *J Am Acad Child Adolesc Psychiatry*. 1997;36:661–8.
32. Lask B, Fosson A. Childhood illness: The psychosomatic approach: Children talking with their bodies. New York: Wiley; 1989.
33. Bowlby J. Attachment and loss: Attachment. New York: Basic Books; 1973.
34. Aro H, Paronen O, Aro S. Psychosomatic symptoms among 14–26 year old Finnish adolescents. *Soc Psychiatry* 1987;22:171–6.
35. Craig T, Cox A, Klein K. Intergenerational transmission of somatization behaviour: A study of chronic somatizers and their children. *Psychol Med* 2002;32:805–16.
36. Boyer MC, Compas BE, Stanger C, Colletti RB, Konik BS, Morrow SB, et al. Attentional biases to pain and social threat in children with recurrent abdominal pain. *J Pediatr Psychol* 2006;31:209–20.
37. Dhossche D, Ferdinand R, van der Ende J, Verhulst F. Outcome of self-reported functional-somatic symptoms in a community sample of adolescents. *Ann Clin Psychiatry* 2001;13:191–99.
38. McCauley E, Carlson GA, Calderon R. The role of somatic complaints in the diagnosis of depression in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 1991;30:631–5.
39. Youssef NN, Atienza K, Langseder AL, Strauss RS. Chronic abdominal pain and depressive symptoms: analysis of the national longitudinal study of adolescent health. *Clin Gastroenterol Hepatol* 2008;6:329–32.
40. Liakopoulou M, Alifieraki T, Protagora D, et al. Recurrent abdominal pain and headaches. *Eur Child Adolesc Psychiatry* 2002;11:115–22.
41. Kisely S, Goldberg D, Simon G. A comparison between somatic symptoms with and without clear organic cause: results of an international study. *Psychol Med* 1997;27:1011–9.

42. Cohen P, Pine DS, Must A, Kasen S, Brook J. Prospective associations between somatic illness and mental illness from childhood to adulthood. *Am J Epidemiol* 1998;147:232–9.
43. Goodwin RD, Sourander A, Duarte CS, Niemelä S, Multimäki P, Nikolakaros G, Almqvist F. Do mental health problems in childhood predict chronic physical conditions among males in early adulthood? Evidence from a community-based prospective study. *Psychol Med* 2009; 39:301–11.
44. Päären A, von Knorring L, Jonsson U, Bohman H, Olsson G, von Knorring AL. Drug prescriptions of adults with adolescent depression in a community sample. *Pharmacoepidemiol Drug Saf* 2012; 21:130–6.
45. Danese A, Moffitt TE, Pariante CM, Ambler A, Poulton R, Caspi A. Elevated inflammation levels in depressed adults with a history of childhood maltreatment. *Arch Gen Psychiatry* 2008;65:409–15.
46. Olsson GI, von Knorring AL. Adolescent depression: prevalence in Swedish high-school students. *Acta Psychiatr Scand* 1999;99:324–31.
47. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561–71.
48. Schoenbach VJ, Kaplan BH, Grimson RC, Wagner EH. Use of a symptom scale to study the prevalence of a depressive syndrome in young adolescents. *Am J Epidemiol* 1982;116:791–800.
49. Reich W, Herjanic B, Welner Z, Gandhi PR. Development of a structured psychiatric interview for children: agreement on diagnosis comparing child and parent interviews. *J Abnorm Child Psychol* 1982;10:325–36.
50. Coddington RD. The significance of life events as etiologic factors in disease of children. I. A survey of professional workers. *J Psychosom Res* 1972;16:7–18.
51. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59 Suppl 20:22–33.
52. Svanborg P, Asberg M. A comparison between the Beck Depression Inventory (BDI) and the self-rating version of the Montgomery Asberg Depression Rating Scale (MADRS). *J Affect Disord* 2001;64:203–16.
53. Wendelhag I, Gustavsson T, Suurkula M, Berglund G, Wikstrand J. Ultrasound measurement of wall thickness in the carotid artery: fundamental principles and description of a computerized analysing system. *Clin Physiol* 1991;11: 565–577.

54. Gussenhoven EJ, Frietman PA, The SH, van Suylen RJ, van Egmond FC, Lancée CT, et al. Assessment of medial thinning in atherosclerosis by intravascular ultrasound. *Am J Cardiol* 1991;68:1625–32.
55. Rodriguez-Macias KA, Lind L, Naessen T. Thicker carotid intima layer and thinner media layer in subjects with cardiovascular diseases. An investigation using noninvasive high-frequency ultrasound. *Atherosclerosis* 2006;189:393–400.
56. Gonzalez-Tejera G, Canino G, Ramirez R, Chavez L, Shrout P, Bird H, et al. Examining minor and major depression in adolescents. *J Child Psychol Psychiatry* 2005;46:888–9.
57. Fergusson DM, Horwood LJ, Ridder EM, Beautrais AL. Subthreshold depression in adolescence and mental health outcomes in adulthood. *Arch Gen Psychiatry* 2005;62:66–72.
58. Zwaigenbaum L, Szatmari P, Boyle MH, Offord DR. Highly somatizing young adolescents and the risk of depression. *Pediatrics* 1999;103:1203–9.
59. Kovacs M, Feinberg TL, Crouse-Novack MA, Paulauskas SL, Finkelstein R. Depressive disorders in childhood, I: a longitudinal prospective study of characteristics and recovery. *Arch Gen Psychiatry* 1984;41:229–37.
60. Olsson G. Epidemiology, nosology, life stress and social network. Mini-review based on a doctoral thesis. *Ups J Med Sci* 1998;77–145.
61. Shankman SA, Lewinsohn PM, Klein DN, Small JW, Seeley JR, Altman SE. Subthreshold conditions as precursors for full syndrome disorders: a 15-year longitudinal study of multiple diagnostic classes. *J Child Psychol Psychiatry* 2009;50:1485–94.
62. Harris EC, Barraclough B. Excess mortality of mental disorder. *Br J Psychiatry* 1998;173:11–53.
63. Lespérance F, Frasurre-Smith N. Depression and heart disease. *Cleve Clin J Med* 2007;74:(Suppl 1):S63–6.
64. Andrews G, Brugha T, Thase ME, Duffy FF, Rucci P, Slade T. Dimensionality and the category of major depressive disorder. *Int J Methods Psychiatric Res* 2007;16:(Suppl 1):S41–S51.



# Acta Universitatis Upsaliensis

*Digital Comprehensive Summaries of Uppsala Dissertations  
from the Faculty of Medicine 809*

Editor: The Dean of the Faculty of Medicine

A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine.



ACTA  
UNIVERSITATIS  
UPSALIENSIS  
UPPSALA  
2012

Distribution: [publications.uu.se](http://publications.uu.se)  
urn:nbn:se:uu:diva-180328