CHILDHOOD PREDICTORS OF LATER PSYCHOTROPIC MEDICATION USE AND PSYCHIATRIC HOSPITAL TREATMENT
FINDINGS FROM THE FINNISH NATIONWIDE 1981 BIRTH COHORT STUDY

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ACADEMIC DISSERTATION
To be presented, with the permission of the Faculty of Medicine of the University of Helsinki, for public examination in the Niilo Hallman Auditorium, the Hospital for Children and Adolescents, on April 13, 2012, at 12 noon.

Helsinki 2012
To my family
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ABSTRACT

Adolescence and young adulthood are periods when several mental disorders, such as mood, anxiety, psychotic and substance use disorders, are diagnosed for the first time. In the treatment of these disorders among young people, the use psychotropic medications has become more common during the last two decades, but rather little is known about who uses these medications. There is also a lack of population-based studies from childhood to adulthood that have studied the psychopathology predictors of psychiatric hospital treatment. The scarcity of studies is mainly explained by the fact that psychiatric hospital treatment is a rare event. However, psychiatric hospital treatment is an indicator of severe psychiatric disorder and knowing its predictors is therefore important.

It has previously been shown that, among individuals with mental problems, the first psychiatric treatment contact often occurs in late adolescence or young adulthood. However, the onset of symptoms has often occurred several years before, in childhood. Early identification of individuals who later develop psychiatric problems requiring psychotropic medication and psychiatric hospital treatment has implications for prevention. The aims of this thesis are to describe the cumulative incidence of psychotropic medication use from age 12 to age 25, and to study factors at age eight that predict psychotropic medication use and psychiatric hospital treatment between age 12 and 25.

The thesis is part of the multicentre Finnish Nationwide 1981 Birth Cohort Study, which has been conducted at all five university departments of child psychiatry in Finland. A representative random sample of all children born in 1981 and alive at age eight in 1989 was primarily selected in 1989 (6,017 of 60,007; 10%). At age eight, 5,813 children were assessed using questionnaires (97% of 6,017). The parents and the teacher completed questionnaires with items concerning family structure, parental education level, conduct problems, hyperactive problems, emotional symptoms, bullying, and victimization of bullying behavior. The children themselves completed the Children’s Depression Inventory with questions regarding depressive symptoms, and extra questions regarding bullying, and victimization of bullying behavior. Between 1994 and 2005, when the participants were 12-13 to 24-25 years old, the personal identification numbers of 5,525 subjects (92% of 6,017) were linked to the nationwide Drug Prescription Register and the nationwide Finnish Hospital Discharge Register. Information about psychotropic medication use and psychiatric hospital treatment between age 12 and 25 was collected from these registers.

The main results in the thesis are that more than every seventh subject had used psychotropic medications by age 25, and that psychotropic medication use and psychiatric hospital treatment are strongly associated.
Abstract

with psychiatric symptoms at age eight. Some of the associations between childhood and adulthood were very similar among males and females, such as depressive symptoms predicting treatment of depressive disorders and non-intact family structure predicting a wide range of different psychiatric treatments. However, the predictive value of several characteristics at age eight were different among males and females. Among males, particularly acting-out behaviors, while among females, especially depressive and anxiety symptoms and being a victim of bullying behavior predicted antipsychotic use, antidepressant use, and psychiatric hospital treatment by age 25.

The findings that 15% had purchased any psychotropic medication and 12% had purchased antidepressants between age 12 and 25 extend previous reports of one-year prevalence. The study shows that a considerable proportion of the population has used psychotropic medication at some point by age 25. The results of strong predictive associations between psychiatric problems at age eight and psychotropic medication use and psychiatric hospital treatment by age 25 are in line with prior population-based prospective studies. However, the novel result that the psychiatric outcomes are partly predicted differently among males versus females, should be further studied using large population-based cohorts. If the results are replicated and screening of mental health problems is implemented in primary schools, sex-specific screening strategies might be warranted.
Monet mielenterveyden häiriöt, kuten mielialahäiriö, ahdistuneisuushäiriö, psykoottinen häiriö ja päihdehäiriö, todetaan usein ensimmäistä kertaa nuoruudessa tai varhaisaikuisuudessa. Kahden viimeisen vuosikymmenen aikana nuorten mielenterveyshäiriöiden hoidossa on käytetty lisääntyvästi psykelääkkeitä, mutta tietoa siitä, ketkä lääkkeitä käytävät, on varsin vähän. Lisäksi vain harvoissa väestöpohjaisissa, lapsuudesta aikuisuuteen ulottuvissa tutkimuksissa on selvitetty psykiatrista sairaalahoitoa ennustavia mielenterveyteen liittyviä tekijöitä. Tutkimusten vähäisyys selittyy pääosin psykiatristen sairaalahoitojaksojen harvinaisuudella. Koska psykiatrin sairaalahoito on merkki vakavasta psykiatrisesta häiriöstä, on sen ennustetekijöiden tunteminen kuitenkin tärkeää.


LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications that are referred to in the text by their roman numerals.


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* I made the following contributions to publication V: gathering of the follow-up data; design and coding of the outcome variables; drafting parts of the methods section; participation in the writing of the manuscript after the first version of the draft
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADHD</td>
<td>Attention-deficit hyperactivity disorder</td>
</tr>
<tr>
<td>CDI</td>
<td>Children's Depression Inventory</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>df</td>
<td>degrees of freedom</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>F</td>
<td>females</td>
</tr>
<tr>
<td>FN1981BCS</td>
<td>Finnish Nationwide 1981 Birth Cohort Study</td>
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<tr>
<td>HR</td>
<td>hazard ratio</td>
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<tr>
<td>IQR</td>
<td>inter-quartile range</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>IQ</td>
<td>intelligence quotient</td>
</tr>
<tr>
<td>M</td>
<td>males</td>
</tr>
<tr>
<td>MDD</td>
<td>Major Depressive Disorder</td>
</tr>
<tr>
<td>ML</td>
<td>maximum likelihood</td>
</tr>
<tr>
<td>NFBC</td>
<td>Northern Finland Birth Cohort</td>
</tr>
<tr>
<td>PHT</td>
<td>psychiatric hospital treatment</td>
</tr>
<tr>
<td>PIN</td>
<td>personal identification number</td>
</tr>
<tr>
<td>PPV</td>
<td>positive predictive value</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SE</td>
<td>standard error</td>
</tr>
<tr>
<td>SII</td>
<td>Social Insurance Institution of Finland</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>UKNCDS</td>
<td>United Kingdom National Child Development Study</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>κ</td>
<td>Kappa</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>Chi square</td>
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1 INTRODUCTION

Mental health refers to mental or psychological well-being and is more than the absence of mental disorders, according to the definition by the World Health Organization (WHO) (241). Mental disorders are behavioral or psychological syndromes that are associated with distress or disability (14). Among persons with mental disorders, adolescence and young adulthood are the periods when several mental disorders are treated for the first time (129). Common mental disorders during adolescence and young adulthood include mood, anxiety, psychotic and substance use disorders (61, 66). Treatment of mental disorders during adolescence and young adulthood can be pharmacological and non-pharmacological, including, e.g. psychosocial interventions, supportive therapy, and psychotherapy. The treatment is often provided as outpatient treatment, but in some cases also as inpatient treatment, i.e. as psychiatric hospital treatment (PHT). Still, the majority of children and young people with mental health problems do not have a treatment contact (10, 99, 129, 213, 219).

There have been certain changes in the treatment of mental disorders among adolescents and young people. For example, since the beginning of the 1990s, the use of psychotropic medication among young people has increased in many high-income countries (170, 234, 250). In Finland, there has also been an increase in the one-year prevalence of psychiatric hospital treatment (PHT) among adolescents (232), which is in contrast to, e.g., the USA (152).

Though the psychiatric treatment often starts in late adolescence or young adulthood (129), mental health problems or deviant behavior can often be found years before, in childhood, among young adults with mental health problems (49, 104, 218). The identification of early symptoms makes targeted early interventions possible, which may in turn reduce and prevent psychiatric disorders and related events (165). The principle of early interventions has also shown utility from an economic point of view. For example, James J. Heckman, who won the Nobel Prize in Economic Sciences in 2000, has demonstrated that the ratio of invested money per later benefited money is highest for young disadvantaged children (101, 102).

The first years of school provide several advantages for identifying children at risk of adverse outcomes. First, in Western countries, almost all children attend school, i.e. the identification program can reach almost every child. Second, patterns of behavior and social interaction of a whole group of children can be observed by the teachers. Third, once the children have learnt to read and write, standardized questionnaires addressed to the children themselves can be implemented. Fourth, the identification occurs before puberty, i.e. before many problems are serious enough to fulfill diagnostic criteria. Thus, it is possible to identify many subclinical symptoms
in an age group that is rather homogenous with respect to hormonal factors and other developmental aspects of adolescence.

There is a scarcity of detailed information about which factors in early school years predict different outcomes in adulthood. For example, there is little information about what predicts phenomena that have recently become more common, such as psychotropic medication use, and rare events, such as PHT. Furthermore, does psychopathology in childhood among males versus females predict outcomes in adulthood differently? This scarcity of information is understandable, since longitudinal studies from childhood to adulthood have only recently emerged (55, 61, 82, 86, 132, 194). Most of the cohorts have not included over 1,500 subjects, making rare events and interactions difficult to study. However, such detailed information is of importance when planning large-scaled preventive interventions. It is of note that several ethical criteria also need to be fulfilled when systematic identification or screening of risk symptoms and behaviors among children is applied. These issues are, e.g., the availability of effective and cost-effective treatment and that the screening procedure is acceptable to the population and does not cause labeling (165). In sum, all these issues related to screening and prevention remain highly relevant, because mental disorders cause the highest disability rates among young adults (161), are the major causes of death among young people (217), and contribute to very high costs for the society (64).

This thesis is part of the Finnish Nationwide 1981 Birth Cohort Study (FN1981BCS). The focus is on patterns of psychopharmacological treatment and inpatient treatment, because of the increased use of psychotropic medication (172, 234, 250) and because of the severe disorders associated with psychiatric hospital treatment (37). Because there is a scarcity of longitudinal studies of psychotropic medication use, more emphasis is put on psychotropic medication use than on hospital treatment of psychiatric disorders. The major aim is to study childhood predictors of psychotropic drug use and psychiatric hospital treatment.
2 REVIEW OF THE LITERATURE

2.1 PSYCHIATRIC TREATMENT DURING ADOLESCENCE AND YOUNG ADULTHOOD

The time of onset of most psychiatric disorders is childhood or adolescence (61, 179). However, only a minority of children and young persons with mental problems receive any psychiatric treatment (10, 21, 99, 129, 213, 219). Help-seeking among adolescents is often delayed: the time from the onset of the disorder to the first treatment contact tends to be several years (129).

2.1.1 MEASUREMENT OF PSYCHIATRIC TREATMENT

Information about treatment is obtained by asking the person via a questionnaire or an interview, or from official records, such as medical records or administrative registers. Questionnaires or interviews addressed to the patient are not necessarily reliable concerning the age at which the treatment has been given (33). Administrative registers provide a more exact measurement of the timing of the treatment. However, registers covering the total population regardless of insurance status or place of residence exist only in the Nordic countries (5, 93).

2.1.2 PSYCHOTROPIC MEDICATION USE

The use of psychotropic medication among adolescents and young adults has increased in several western countries during the last two decades (172, 234, 250). In the USA and several European countries especially the use of antidepressants, antipsychotics and stimulants has increased. However, in Finland, the use of stimulants has remained low (251). Therefore, the focus will be on antipsychotics and antidepressants.

2.1.2.1 Antipsychotics

Antipsychotics are a group of psychotropic medications mainly aiming to reduce psychotic symptoms, such as hallucinations, delusions, and paranoid thoughts in schizophrenia and related disorders. However, some antipsychotic medications are also used as mood stabilizers in bipolar disorder (166, 170) and unstable personality disorder (245); as aggression-reducing medication in conduct disorder (4, 12, 111) and autism spectrum disorders (111); as adjunctive medication in psychotic depression; and off-label for anxiety (77) and sleeping problems (242).
Antipsychotics are divided into first-generation or typical antipsychotics and second-generation or atypical antipsychotics, depending on when they were developed. Since the introduction of second-generation antipsychotics, the use of antipsychotics has increased in most Western countries. In Finland, the one-year prevalence of antipsychotic use in 2007 was 0.4% in the age group 11-15, 0.7% in the age group 16-20, and 0.9% in the age group 21-26 (25). Antipsychotic use has increased especially among children and adolescents in many countries (77, 170, 234). The increased prevalence rate has also been affected by the fact that the length of treatment periods with antipsychotics has become longer; not only the number of new users per year has increased (119, 121, 193). In addition, the wide range of conditions for which antipsychotics are used (12, 77, 111, 160, 170, 234, 242) may have affected the increased use of antipsychotics.

Reports based on data from the USA (73, 248), Canada (4) and the Netherlands (119, 248) have reported higher antipsychotic prevalence among males than females, while reports from German (248) and Finnish (25) data have reported similar estimates for the sexes. In Finland, the use of antipsychotics is lower among children than among adults (25). However, in the Netherlands in 2005 (119) and in the USA in 2001 (73, 178), the one-year prevalence of antipsychotic use in the age group 10-14 years was higher or similar to that in the age group 15-19 years. There are only a few studies reporting the annual incidence of antipsychotic use among young people (53, 60, 193, 204, 250), but there are no previous reports of the cumulative incidence using a nationwide cohort from early adolescence to young adulthood.

### 2.1.2.2 Antidepressants

Antidepressants are a group of psychotropic medications aiming to reduce depressive symptoms. In addition, many antidepressants have also been found useful in the treatment of, e.g. panic disorder (15), social phobia (28), post-traumatic stress disorder (28), obsessive-compulsive disorder (17), and eating disorders (16).

The newer antidepressants are mostly well tolerated, which has possibly resulted in a lower threshold for physicians to prescribe antidepressants for a variety of conditions (173). This may be one reason why the use of antidepressants has become common among young people. Other possible explanations for the increased antidepressant use include the possible increase in depression prevalence (58), the lowered threshold of help-seeking (182), and the wide range of disorders for which antidepressants are recommended (15-17, 28). In Finland, from 1997 to 2007, the one-year prevalence of antidepressant use in the age group 21-26 has almost tripled to 6% (25). Antidepressants are the most frequently prescribed psychotropic medication in Finland (122) and in the USA (172, 182).
Females use antidepressants more often than males in late adolescence and young adulthood, according to reports from Finland (25), Germany (249), Denmark (249) and the Netherlands (249), while the prevalence is similar in the sexes in the USA (249). Among children and adolescents younger than 15 years, the use of antidepressants is more common in the USA than in Finland (25), Germany (249), Denmark (249) and the Netherlands (249). Among young adults, the prevalence of antidepressants is rather similar in Finland (25) and the USA (158, 172, 249). Some studies have reported the annual incidence of antidepressant use among young people (24, 53, 60, 204, 250), but currently there is only one other report of the cumulative incidence using a nationwide cohort from early adolescence to young adulthood (24).

**2.1.2.3 Polypharmacy**

The term polypharmacy is in many studies defined as the use of two or more medications together (57, 159). However, several other terms have been used to describe similar medication utilization patterns: co-medication (84, 229), multiple use (79, 153, 188), concomitant use (203, 250), and concurrent medication (229). Thus, the classification of polypharmacy has varied considerably across studies (229). First, many define polypharmacy as using two or more medications from different medication classes, e.g. using antidepressants and benzodiazepines together. This has been referred to as across-class polypharmacy (159) or multiclass psychotropic treatment (57). The use of two different medications from the same class, e.g. two antipsychotics, has been referred to as within-class polypharmacy (159). Second, some have measured concomitant use of several medications by reporting point prevalence estimates (247), e.g. surveys of physician visits including several prescriptions (57, 92, 159). Others have measured multiple use of several medications by reporting period prevalence estimates (247), meaning that two different medications have been purchased within a time window of, e.g. one week (84, 153, 248) or one year (151, 204).

There are some widely used combinations of psychotropic medications. For example, the combination of antidepressants and benzodiazepines can be used in the acute phase of depression (19), and in anxiety disorders (103). The combination of antidepressants and antipsychotics has been used in psychotic depression, in comorbid depression, and in borderline personality disorder (245), in bipolar depression (226), to reduce negative symptoms in schizophrenia (246), and to promote sleep in depression (242). There are several challenging drug-drug interactions and limited evidence-based information on many polypharmacy combinations (188). Especially among young people, there is little evidence-based information about the efficacy and safety.

Representative surveys from the USA suggest that polypharmacy use is increasing both among children (57) and among adults (159). In Europe, there are only a few representative studies of polypharmacy use both among young
people (151, 204, 248, 250) and adults (92, 207). On the whole, the comparison of polypharmacy use across populations is very difficult, as most studies have been limited to specific clinical settings (75, 95, 117, 211), and the classification of polypharmacy has varied (229).

A population-based register study from Iceland reported a polypharmacy proportion of 18% among 0- to 17-year-old psychotropic medication users in 2007 (250). In a nationwide survey of physician visits of 6-17-year-olds in the USA, it was reported that polypharmacy was prescribed during 20% of the visits in 2004-2007 (57). In a country comparison of 0- to 19-year-old psychotropic medication users in 2000, the proportion who used medication from different medication classes was 19% in the USA, 9% in the Netherlands, and 6% in Germany (248). In sum, most population-based studies have reported the proportion of polypharmacy use among psychotropic medication users (57, 151, 159, 204, 248, 250). There are no previous reports of the cumulative incidence using a nationwide cohort from early adolescence to young adulthood.

2.1.3 PSYCHIATRIC HOSPITAL TREATMENT

Psychiatric hospital treatment (PHT), i.e. inpatient treatment of psychiatric disorders, indicates a severe psychiatric disorder (37). Adolescent and young adult patients who are treated for psychiatric disorders in hospitals are often diagnosed with psychotic, affective (186), and comorbid disorders, and often have high rates of aggressive behavior (96) or suicidalal behavior (171).

In Finland, approximately 30,000 patients per year were treated for psychiatric disorders in hospitals between 1990 and 2003 (184). This corresponds to a one-year prevalence of 0.6%. The one-year prevalence of PHT is higher among adolescents than children, according to data from both Finland (232) and the USA (186). Among adolescents aged 13 to 17 years in Finland, the use of PHT has increased: the one-year prevalence of treatment in child and adolescent psychiatric inpatient units was 0.29% in 1995-1998, and 0.55% in 2002-2004 (232). This was mainly a result of the political decision in Finland to direct more public funding to adolescence psychiatry beginning from the early 2000s (232). In the USA, the opposite pattern is seen, as there has been a change towards less inpatient treatment among children and adolescents (152).

2.1.4 DIRECT COSTS ASSOCIATED WITH PSYCHIATRIC TREATMENT

The total health care costs in Finland in 2002 were summarized in a report of the National Institute of Health and Welfare (107). Based on information from the report, the health care costs of psychiatric care and other domains are summarized in Table 1 separately for the age groups 7-17 years and 18-40
years. In total, among people aged seven to 40 years, the costs of public psychiatric inpatient and outpatient care were 339 million € in 2002.

Table 1  Nationwide estimates of the yearly health care costs in 2002. Adapted from Hujanen et al. (2004; ref. 107).

<table>
<thead>
<tr>
<th></th>
<th>Age 7-17 years</th>
<th>Age 18-40 years</th>
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<tbody>
<tr>
<td></td>
<td>(n=4172)</td>
<td>(n=10,646)</td>
</tr>
<tr>
<td></td>
<td>Million €</td>
<td>€</td>
</tr>
<tr>
<td>Costs of psychiatric care in public units</td>
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<td></td>
</tr>
<tr>
<td>Psychiatric inpatientb</td>
<td>66</td>
<td>92</td>
</tr>
<tr>
<td>Psychiatric outpatient visits</td>
<td>24</td>
<td>33</td>
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<tr>
<td>Costs of somatic care in public hospitals and wards</td>
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<td></td>
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<tr>
<td>Non-psychiatric inpatientc</td>
<td>68</td>
<td>95</td>
</tr>
<tr>
<td>Non-psychiatric outpatient visits of specialized cared</td>
<td>57</td>
<td>82</td>
</tr>
<tr>
<td>Costs of health centers</td>
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<td></td>
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<tr>
<td>Guidance clinicsd</td>
<td>0</td>
<td>4</td>
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<tr>
<td>School healthe</td>
<td>52</td>
<td>73</td>
</tr>
<tr>
<td>Other costs in health centersf</td>
<td>204</td>
<td>288</td>
</tr>
<tr>
<td>Costs of private physiciansg</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Costs of occupational and student healthh</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Costs of prescription drugsi</td>
<td>44</td>
<td>62</td>
</tr>
<tr>
<td>Other health costsj</td>
<td>89</td>
<td>125</td>
</tr>
<tr>
<td>Totalk</td>
<td>620</td>
<td>872</td>
</tr>
</tbody>
</table>

* Including costs for both males and females. Total costs are estimated by assuming equal proportions of males and females in the population.
* Including costs from all public psychiatric inpatient units and the psychiatric inpatient units of the defense forces. There are no private psychiatric inpatient units in the report.
* Including costs from specialized psychiatric outpatient units in public hospitals and mental health units of the municipalities.
* Including costs from specialized inpatient units in public hospitals and wards in health centers.
* Including costs from specialized non-psychiatric units in public hospitals and specialized units in health centers.
* Including costs from maternity clinics in health centers, well-baby clinics and family planning clinics.
* Including costs related to school and student health organized by the municipalities.
* Including all other costs in public health centers, e.g. general practice, physiotherapy and dental care.
* Including costs reimbursed by the Social Insurance Institution and the costs paid by the patient.
* Including costs of occupational health units and the Finnish Student Health Service.
* Including costs reimbursed by the Social Insurance Institution and the costs paid by the patient.
* Costs which are included in the total health costs, but are not listed above. Includes e.g. rehabilitation, services for patients with mental retardation, inpatient treatment in private hospitals, private dental care, glasses, and pharmacists not requiring a prescription.
* Includes direct costs of health care, except public investments and administration.

As shown in Table 1, the costs of prescription medication were 228 million € in 2002 for people aged seven to 40 years old. However, the report did not separate the costs of psychotropic medication versus other medication (107). In other reimbursement statistics based on all age groups in 2009, the total costs of antipsychotics, benzodiazepines, antidepressants, and stimulants in outpatient care were 165 million €, which corresponds to 9% of the total prescription medication costs (1.77 billion € (122)). Generalizations to
Review of the literature

adolescents and young adults is however difficult to do on the basis of these numbers, because the statistics include all age groups and the old age groups represent higher total costs than the young age groups \(^{(122)}\). The total costs of antidepressants and antipsychotics in all age groups were 50 million € and 89 million €, respectively, in 2009 \(^{(122)}\).

According to a report from the USA, costs from psychotropic medication represent an increasing share of the total health costs of psychiatric disorders among young people \(^{(152)}\). The proportion of psychotropic medication costs of the total outpatient costs of psychiatric disorders ranged between 31% and 52% across disorders, according to a study of privately insured children and adolescents aged 17 or younger in the USA in 2000 \(^{(152)}\). Therefore, the psychotropic medication use is of increasing public health and financial importance \(^{(152)}\).

Though only half a percent of the population are treated in psychiatric inpatient units per year, the proportion of psychiatric inpatient treatment was 10% of the total health costs. One explanation for these high inpatient costs is that the treatment times are often long in psychiatric inpatient care. For example, the mean stay per year in psychiatric inpatient units was over 60 days per treated adolescent \(^{(232)}\). Given that the mean cost per day of psychiatric hospital treatment was 451 € in adolescent inpatient units and 266 € in adult inpatient units in 2006 \(^{(106)}\), the cost of one inpatient treatment period for one patient is often tens of thousands of euros.

2.2 CHILDHOOD PREDICTORS OF PSYCHIATRIC PROBLEMS BY YOUNG ADULTHOOD

First, a methodological overview of how childhood predictors of adult psychiatric problems have been studied is presented. Second, population-based studies on mental health problems in childhood and psychiatric problems are presented. Third, because there is a scarcity of information about the predictors of psychotropic medication use and PHT, a review including a wider outcome, psychiatric problems in adulthood, is presented. The reviewed outcome, adult psychiatric problems, has mainly been measured using diagnostic interviews or register-based information on a specific disorder, such as schizophrenia. A variety of childhood predictors of adult psychiatric problems are presented: prenatal events, neurological development, cognitive abilities, school performance, family-related factors, childhood mental health problems, and bullying and victimization. Throughout these sections, sex-specific differences are brought up. Fourth, the main theme of this thesis, associations between childhood mental health problems and psychotropic medication use and PHT in adulthood, is presented.
2.2.1 CONCEPTS AND METHODOLOGY

In the study of associations between childhood and adult mental health problems, variables of characteristics in childhood and variables of characteristics in adulthood are analyzed. Thereby, the terms predictor and predictive association are often used. These childhood predictors of adult problems can be conceptualized in different ways (223). One possibility is that they are antecedents of adult problems (223), e.g. are childhood depressive symptoms early manifestations of depressive disorders in adulthood? A second possibility is that they are mediating factors between previous factors and adult problems (223), e.g. is genetic susceptibility to depression in adulthood mediated by childhood depressive symptoms? A third possibility is that they are independent risk factors (223), e.g. do depressive symptoms independently predict adult depressive disorders when other possible risk factors are taken into account? Whether the predictive factors are conceptualized as antecedents, mediators, or independent risk factors depends on the study question (223). Because it is not completely clear which developmental risk factors interact and predict mental disorders in adulthood (66), this review will not distinguish between antecedents, mediators, and independent risk factors. The review will focus on main effects between childhood risk factors and adulthood mental health problems.

2.2.1.1 Study designs

The continuity of childhood problems to adult adverse outcomes can be studied using different designs (223). The focus in this literature review is on prospective, i.e. longitudinal, studies, which start by gathering information about predictors and then follow up the sample.

The two most often used prospective study designs to study childhood predictors of psychiatric outcomes in adulthood have been clinical cohort studies and population-based cohort studies. In a clinical cohort study, patients who present with a specific feature (e.g. childhood depression) are chosen from a clinical setting (e.g. a hospital clinic). Controls without the specific feature (e.g. without childhood depression) are usually matched with the patients, meaning that the controls should be as similar as possible to the patients with regard to, e.g. age and sex. Finally, the cohort of patients and controls is followed up and information about the outcome is gathered. Because the patients are chosen from a clinical setting, the major disadvantage of the clinical cohort design is that the results are usually not generalizable to the general population, as only a small proportion of children with, e.g. depression are treated.

In population-based studies, a fraction of the total population is studied regardless of help-seeking or treatment. Because only a minority of children with mental health problems is treated (220), such designs are especially
Review of the literature

valuable in longitudinal child psychiatric studies because the results are representative of the total population and not only of those who receive treatment. Furthermore, if the aim is to analyze a full picture of risk factors and protective factors, population-based studies are needed. Some population-based studies have been named birth-cohort studies. There are several definitions of birth-cohort studies, but the essential factor is that a set of births is followed up (56). Although the first assessment is ideally done already during pregnancy, the timing of the first assessment can vary depending on the study questions (56).

2.2.1.2 Informants of childhood mental health problems
Agreement between parents and children in reporting psychiatric problems is usually low (3). Generally, it is considered that children’s self-reports of psychopathology, especially depressive symptoms, become more important the older the children get (212, 235). On the other hand, a child with disruptive problems might himself or herself not consider them as problems at all. However, there is no “optimal informant” (36). Different informants simply perceive the behavior of the child differently (138). Most disorders, regardless of whether they are obtained from interviews with parents or children, are usually clinically valid and associated with impairment (114).

2.2.2 POPULATION-BASED STUDIES FROM CHILDHOOD TO ADULTHOOD
Prospective population-based studies from childhood to adulthood are summarized in Table 2. First, an overview of the Finnish population-based longitudinal studies from childhood to adulthood is shown. Finnish studies without questionnaire- or interview-based data of childhood psychopathology are also presented, to show the possibilities of longitudinal research in Finland. Second, international population-based cohorts with more than 1,000 subjects and psychopathology measures in both childhood and adulthood are described.

In Finland, there are a number of longitudinal population-based studies. The oldest cohorts are from Helsinki. Children born between 1924 and 1933 (236) and between 1934 and 1944 (32, 83, 191, 192) in Helsinki University Central Hospital have been followed up to adulthood. These two birth cohorts have focused to a great extent on prenatal and childhood growth patterns and the development of mental (192, 236) and cardiovascular disorders (32, 83). They have utilized manually collected case notes to obtain pregnancy and childhood variables, and register- (236) and questionnaire-based data (192) to obtain information about psychiatric outcomes in adulthood. A third cohort includes children born in Helsinki between 1951 and 1960; it has been followed up with regard to school performance and later mental disorders
according to register-based data (47). A fourth birth cohort from Helsinki consists of children born in 1955 and followed up to age 21 using, e.g. register-based information about hospital admissions, social services and criminal offences, and questionnaire-based information about psychiatric symptoms at age 21 (6, 7, 18). The Jyväskylä Longitudinal Study of Personality and Social Development was started in the 1960’s and has followed up the sample of approximately 350 subjects to age 42 with almost no attrition (185, 190). In Northern Finland, the population-based Northern Finland Birth Cohorts 1966 (NFBC 1966) (110, 150) and 1986 (NFBC 1986) (105, 108, 136, 149), consisting of some 10,000 subjects, have been followed up since birth. The NFBC 1966 has comprehensively utilized case records from childhood and register linkages (110, 150). In the NF 1986, questionnaire-based data on psychopathology at the ages of eight and 16 have also been gathered (149). In addition to the population-based cohorts described in Table 2, a longitudinal study of 1,261 adolescents aged 16 has been followed up in Tampere (109, 180). Also new Finnish cohort studies are being conducted (80, 87, 142). In summary, many Finnish cohort studies have been large and representative, utilizing the personal identification number to link information from several registers and manually collected case notes. Finally, the participation rates in questionnaire-based studies have been rather high.

The methodology of the international studies varies considerably with regard to settings, sampling design, number of subjects, follow-up rates, timing and numbers of assessments, as well as measurements of psychopathology and other variables of interest. Few studies have included over 1,500 subjects. An exception to this is the 1958 British Birth Cohort, which originally included over 17,000 subjects (55, 78, 115). The follow-up rates have mainly varied depending on the methods used. For example, studies with diagnostic interviews have followed up between 66% and 95% of the original study samples (11, 61, 85, 86, 157), while studies utilizing medical records have managed to track virtually all with correctly documented personal information (78). A major strength of some of the studies is the assessment of psychopathology multiple times throughout the development. For example, abnormal behavior was first assessed at the age of three in the Dunedin study, and different measures related to mental health have later been assessed at the ages of 5, 7, 9, 11, 13, 15, 18, 21, 26, and 32 (51, 132, 153, 157, 167). Also in the Zuid-Holland study, psychopathology has been assessed five times between 1985 and 2007 for several age cohorts, i.e. the members were three years old in the youngest age cohort and 17 years old in the oldest cohort at baseline in 1985 (11, 76, 194, 198, 235). A further strength in some studies is the use of diagnostic interviews, which yield more reliable data on psychopathology than do questionnaires. For example, diagnostic interviews were conducted at eleven time points between 1993 and 2005 in the Great Smoky Mountain study (61, 67). In sum, the studies with most detailed information have had smaller sample sizes than, e.g. the 1958 British Birth Cohort (55, 78, 115). Of note, in addition to the cohorts cited above, members of
several cohorts are reaching adulthood currently or in the near future. Examples of some population-based cohorts are the ALSPAC- (26), the TRAILS- (231) and the Generation-R-cohorts (94).

Table 2 Summary of selected population-based studies of childhood predictors of adult psychiatric problems.

<table>
<thead>
<tr>
<th>Study and references</th>
<th>Sample</th>
<th>Measures in childhood</th>
<th>Measures in adulthood</th>
<th>Main strengths</th>
<th>Main limitations</th>
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<tbody>
<tr>
<td><strong>Finnish studies</strong></td>
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<tr>
<td>Helsinki University Central Hospital Cohort (1924-1933) (e.g. ref. 236; Wahlbeck et al., 2001)</td>
<td>- Population: 27,068 born in the public Helsinki University Central Hospital - Selected sample: 8,580 subjects who had birth and school health records in Helsinki - Study sample: 7,086 subjects who were alive in 1971 and whose personal identification number could be traced</td>
<td>- Maternal weight during pregnancy, birth size and childhood growth - (No assessed data on childhood psychopathology with e.g. questionnaires or interviews)</td>
<td>- Finnish Hospital Discharge Register (psychiatric disorders treated in hospitals)</td>
<td>- Large sample - Follow-up extending to age 60-70 - Substantial information about childhood growth</td>
<td>- Childhood psychiatric symptoms not assessed</td>
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<tr>
<td>Helsinki Birth Cohort Study (1934-1944) (e.g. ref. 32, 83, 191, 192; Barker et al., 2005; Eriksson et al., 2001; Räikkönen et al., 2007, 2009)</td>
<td>- Selected sample: born in the public Helsinki University Central Hospital, available birth and child welfare records and living in Finland in 1971: n=8,760 - Invited subsample (e.g. questionnaires) at ages 57-70 and 60-71: n=2,690 and n=1,975, respectively -&gt; participation: n=2,003 and n=1,704, respectively</td>
<td>- Maternal weight during pregnancy, birth size and childhood growth - Neurocognitive functioning of males in military service - (No assessed data on childhood psychopathology with e.g. questionnaires or interviews)</td>
<td>- Finnish Hospital Discharge Register - Beck’s Depression Inventory at age 57-71</td>
<td>- Large sample - Follow-up extending to age 60-70 - Substantial information about childhood growth</td>
<td>- Childhood psychiatric symptoms not assessed</td>
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<tr>
<td>Study and references</td>
<td>Sample</td>
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<td>Helsinki Birth Cohort Study (1951-1960) (e.g. ref 47: Cannon et al., 1999)</td>
<td>- Population: individuals born in the public Helsinki University Central Hospital - Selected cases: schizophrenia in adulthood and available school records - Selected controls: no schizophrenia in adulthood and available school records</td>
<td>- School records - (No assessed data on childhood psychopathology with e.g. questionnaires or interviews)</td>
<td>Nested case-control study using the Finnish Hospital Discharge Register to select the cases</td>
<td>- Large sample - Substantial information about school performance</td>
<td>- Childhood psychiatric symptoms not assessed</td>
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<tr>
<td>Helsinki 1955 Cohort (e.g. ref: 6, 7, 18: Almqvist, 1983, 1986; Amnell, 1974)</td>
<td>- Selected sample: virtually all 6,789 children born in Helsinki in 1955; - by age 21 (1976): 100 untraced, 6,689 followed-up with registers/case notes (99%); 6,346 alive and 343 dead) - age 21: questionnaire, response rate 83%</td>
<td>Case notes from outpatient and inpatient units: e.g. pregnancy and delivery, neonatal data, mortality (4.5% by age 14), malformations, neurological disorders, psychiatric treatment and social care</td>
<td>- Registers and case notes age 15-21: e.g. psychiatric inpatient and outpatient treatment, criminal offences - Cornell Medical Index (questionnaire) at age 21 about psychological health</td>
<td>- Large and representative sample</td>
<td>- Childhood psychiatric symptoms not assessed - No extended follow-up</td>
</tr>
<tr>
<td>Jyväskylä Longitudinal Study of Personality and Social Development (e.g. ref. 185, 190: Pitkänen et al., 2008; Pulkkinen, 1995)</td>
<td>- Selected sample: 12 second-grade classes (age 8) in Jyväskylä were randomly selected in 1968; 100% of the selected subjects participated: n=369 - Assessment at ages 8, 14, 27, 36, and 42 - Between ages 27 and 42, 94% had participated at least once: n=347</td>
<td>Peer nominations and teacher ratings of 33 items, and a personality inventory (Cattell and Coan, 1959) at age 8</td>
<td>Life Situation Questionnaire (LSQ) at ages 27, 36, and 42</td>
<td>- Almost complete follow-up rate - Multiple assessments</td>
<td>- Small sample</td>
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Table 2 continued

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<th>Study and references</th>
<th>Sample</th>
<th>Measures in childhood</th>
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<td><strong>Finnish studies</strong></td>
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| **Northern Finland 1966 Birth Cohort** (e.g. ref. 110, 150; Isokanni et al., 2006; Mäki et al., 2010) | - Selected sample: 96% of all live births in Oulu and Lapland, Finland, in 1966: n=12,058  
- Follow-up data of subjects living and alive at age 16: n=11,017 | - Prenatal events, developmental milestones (learning to walk etc.), and school performance  
- (No assessed data on childhood psychopathology with e.g. questionnaires or interviews) | - Finnish Hospital Discharge Register (psychiatric disorders treated in hospitals) | - Large and representative sample | - Childhood psychiatric symptoms not assessed |
| **Northern Finland 1986 Birth Cohort** (e.g. ref. 105, 108, 136, 149; Honkanen et al., 2011; Hurtig et al., 2011; Koivukangas et al., 2010; Mäki et al., 2011) | - Selected sample: 99% of all live births in Oulu and Lapland, Finland between July 1985 and June 1986: n=9,432  
- Questionnaire and/or clinical examination at ages 7-8 and 16  
- n=6,676 studied both at age 7-8 and 16  
- Participation 74-90% between age 7-8 and 16 | - At age 8 Rutter parent and teacher questionnaire; at age 16 PROD-screen, Youth Self-Report (YSR), Strengths and Weaknesses of ADHD Symptoms and Normal Behaviors (SWAN) completed by parents | - Finnish Hospital Discharge Register (psychiatric disorders treated in hospitals) by age 23 | - Large and representative sample  
- Application of both questionnaires and registers | - No diagnostic interviews in childhood |
<table>
<thead>
<tr>
<th>Study and references</th>
<th>Sample</th>
<th>Measures in childhood</th>
<th>Measures in adulthood</th>
<th>Main strengths</th>
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<tr>
<td>International studies*</td>
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| **The 1958 British Birth Cohort/ The British National Child Development Study** (ref. 55, 78, 115; Clark et al., 2007; Done et al., 1994; Jokela et al., 2009) | - Born during one week in 1958 in England, Scotland and Wales: n=17,416  
- Age 7: n=15,398  
- Age 11: n=15,303  
- Age 7-11: complete data n=11,142 (63%)  
- Age 16-28: all with psychiatric hospital treatment n=154 and random controls n=1914  
- Age 45: n=9,377 (78% of invited to interview) | Teacher-rated Bristol Social Adjustment Guide (questionnaire) at ages 7 and 11 | Diagnostic interview age 45 (Clarke et al., 2007); psychiatric hospital treatment age 16-28 (Done et al., 1994); mortality age 46 (Jokela et al., 2009) | - Large sample  
- Follow-up extending to middle age | - Only teacher reports of psychiatric symptoms at age 7 and 11 |
| **Dunedin Multidisciplinary Health and Development Study** (ref. 51, 132, 155, 157, 167; Caspi et al., 2003; Kim-Cohen et al., 2003; Moffitt et al., 2010, 2011; Ogd et al., 2007) | - 91% of all births between April 1972 and March 1973 in Dunedin, New Zealand, and alive at age 3: n=1,037  
- Assessment at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, and 32.  
- Age 32 (2004-2005) n=962 (95% of 1,015 living cohort members) | Diagnostic interview (Diagnostic Interview Schedule for Children) at ages 11, 13, and 15 | Diagnostic interview (Diagnostic Interview Schedule) at ages 18, 21, 26, and 32 | - Multiple assessments  
- High follow-up rates  
- Diagnostic interviews  
- Wide range of information, including blood samples | - Limited power to study rare events and interactions |
### Table 2 continued

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<tr>
<th>Study and references</th>
<th>Sample</th>
<th>Measures in childhood</th>
<th>Measures in adulthood</th>
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<tr>
<td><strong>International studies</strong></td>
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| **Christchurch Health and Development Study** (ref. 85, 86: e.g. Fergusson et al., 2005, 2007) | - All children born during 4 months in mid-1977 in Christchurch, New Zealand: n=1,310  
- Participation at birth: n=1,265 (97% of source population 1,310); Assessment annually age 1-16, thereafter age 18, 21, and 25  
- Age 25: n=973 with data both in childhood and adulthood (74% of source population 1,310; 77% of original study sample 1,265 at birth) | Rutter and Conner parent and teacher questionnaires at ages 7, 8, and 9 | Diagnostic interview (Composite International Diagnostic Interview, CIPI) at age 25 | - Multiple assessments  
- Diagnostic interview at follow-up | - Limited power to study rare events and interactions |
2.2.3 FAMILY-RELATED GENETIC AND ENVIRONMENTAL FACTORS AS PREDICTORS

Psychiatric disorders tend to run in families (237). Families share both genetic and environmental factors, which in some cases are stressful life events. According to current knowledge, stressful life events and genetic factors combine or interact and thereby increase the risk of psychiatric disorders (51, 125).

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**Table 2 continued**

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<tr>
<th>Study and references</th>
<th>Sample</th>
<th>Measures in childhood</th>
<th>Measures in adulthood</th>
<th>Main strengths</th>
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<tr>
<td><strong>International studies</strong></td>
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<tr>
<td>The Great Smoky Mountain Study (e.g. ref. 61, 67: Copeland et al., 2011; Costello et al., 2003)</td>
<td>- Random sample of children in rural Northern Carolina, USA, aged 9, 11 and 13 in 1993: n=4,067</td>
<td>Diagnostic interview (CAPA, Child and Adolescent Psychiatric Assessment) at ages 9, 10, 11, 12, 13, 14, 15, and 16 (every year 1993-2000)</td>
<td>Diagnostic interview (YAPA, Young Adult Psychiatric Assessment) at ages 19 and 21 (every year 1999-2005)</td>
<td>- Multiple assessments - Diagnostic interviews</td>
<td>- Limited power to study rare events and interactions</td>
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The summary is limited to studies with more than 1,000 subjects and psychopathology measures in both childhood and adulthood.
In addition to the gene-environment interplay (29), the environmental factors tend to cluster. That is, single environmental risk factors, such as family violence and weak parent support (244), often correlate with each other. Different environmental factors act through several pathways. For example, living with a single parent during childhood increases the risk of psychiatric disorders in adulthood (239), but the increased risk can to a large degree be explained by other factors, which are associated with both single parenthood and psychiatric problems among offspring. Such family characteristics or stressful life events include socioeconomic disadvantage (187), financial problems (63), death of parent (123, 124), weak parent support, parent-child discord (244), and childhood abuse (85). Furthermore, it is of note that not all family factors are risk factors; some are protective factors. For example, stimulating activities can reduce the risk of mental health problems (133).

2.2.4 PRE- AND PERINATAL FACTORS AS PREDICTORS
Especially in the research on schizophrenia, a number of risk factors have been found that occur before birth (29, 41). These include, e.g. advanced paternal age (40), maternal infections during pregnancy (42), low birth weight (1, 236), and obstetric complications (48). However, some recent studies indicate that, e.g. smoking during pregnancy (80) and low birth weight (1) predict not only psychotic disorders, but also a wide range of non-psychotic disorders in adulthood.

2.2.5 EARLY DEVELOPMENT AND COGNITIVE ABILITIES AS PREDICTORS
Delays in developmental milestones, e.g. learning to walk late, are associated with schizophrenia in adulthood (116). These results have been replicated: delayed early motor development seems to predict specifically schizophrenia, while it is not strongly associated with adult mania, depression, or anxiety (46). Also poor performance in sports and handicrafts in elementary school (47), low educational test scores between age 8 and 15 (116), and low intelligence quotient (IQ) between age 3 and 11 (46) have shown associations with adult schizophrenia.

2.2.6 CHILDHOOD MENTAL HEALTH PROBLEMS AS PREDICTORS
The term problem is used below to describe both symptoms and disorders related to mental health.
2.2.6.1 Externalizing problems

Externalizing problems refer to acting-out behavior. Externalizing disorders include conduct disorders and oppositional defiant disorders. In addition, attention deficits and hyperactivity are also externalizing problems, but are often categorized as a separate entity from other externalizing problems. Conduct disorder constitutes a wide spectrum of “repetitive and persistent patterns of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated” (14). Conduct problems in childhood are strongly linked to conduct problems in adolescence and antisocial personality disorder in adulthood, but some problems do not start until adolescence, while others are limited to childhood (156). There is evidence supporting the view of distinguishing between childhood-onset/life-course persistent, adolescent-onset and childhood-limited conduct problems (156, 167, 168). According to results from the Dunedin study, the group with childhood-onset/life-course persistent problems has poorer mental and physical health in adulthood than the group with adolescent-onset conduct problems (167, 168). Other studies from childhood to adulthood have also shown that childhood conduct problems predict schizophrenia and other psychotic disorders, mood disorders, substance-related disorders, personality disorders, suicidality, and criminality (46, 100, 132, 167, 205). However, some studies have reported that the association between childhood conduct problems and adult emotional problems is different among males and females (2, 76, 244), while others have found no sex differences (55, 86, 132, 194). According to some studies, conduct problems in childhood predict emotional problems in adulthood among males, but not among females (2, 76, 244). Similarly, some studies have shown an association between childhood conduct problems and adult psychotic disorders among males, while the association has been weak among females (78, 174).

Attention-deficit/hyperactivity disorder (ADHD) is characterized by inattention, such as difficulty focusing on a task and distractibility, hyperactivity, and impulsivity, such as restlessness and excessive talking (34). Attention-hyperactivity problems in childhood predict several adverse outcomes in adulthood (81, 146). However, both some clinical (35) and some population-based studies (194) have shown that attention-hyperactivity problems alone do not have such a strong predictive value for adult outcomes. That is to say, the prognosis of ADHD may be poor if ADHD presents together with other disorders, e.g. the frequently present combination of ADHD and oppositional defiant disorder (35). However, “pure” ADHD may have little impact on adversities in adulthood.

2.2.6.2 Internalizing problems

Internalizing problems include emotional problems such as depression and anxiety disorders. Both clinical (183, 238) and population-based (55, 132) studies
have shown a strong association between childhood emotional problems and similar adult problems. Childhood internalizing problems have been reported to predict psychotic disorders in adulthood (46, 132). Some studies suggest that childhood emotional problems are associated with psychotic disorders in adulthood especially among females, while the association is less strong among males (78, 174). Childhood internalizing problems also predict suicidality (88, 217).

### 2.2.6.3 Comorbid externalizing and internalizing problems

Comorbidity refers to the co-occurrence of two or more different conditions (20). In psychiatric research, study groups with and without comorbidity are often compared (113). The subgroups with and without comorbidity have been studied as to whether they differ with regard to, e.g. risk factors, prognosis, treatment response, and neurophysiological characteristics (113). The study of children with combined conduct and emotional disorders provides one example of such a research field. Children with comorbid conduct and emotional problems have shown an increased risk of several adverse outcomes, compared to children with "pure" disorders, that is to say, children without comorbidity (82, 88, 90, 91, 214, 217). During recent years, this “mixed conduct and emotional disorder” among children and adolescents has also been called “dysregulation”, “irritable” and, controversially, “bipolar disorder not otherwise specified” (225). For the term “severe mood dysregulation”, diagnostic criteria for research purposes have been developed (145). Severe mood dysregulation is characterized by high levels in all three domains of mood problems (e.g. sadness), hyperarousal (e.g. agitation) and reactions to negative stimuli (e.g. aggression towards people or property) (145). Using these criteria, it has been shown that the severe mood dysregulation entity in childhood predicts a wide range of disorders in adulthood (11) and shows specific profiles in neuroimaging studies (145). However, to test whether severe mood deregulation can be verified as a distinct clinical syndrome, further observational studies and treatment trials are needed (145).

### 2.2.7 Bullying and Victimization

Bullying has been defined as a repetitive, non-provoked, aggressive act in an interpersonal relationship, where there is an imbalance of power, i.e. the victim cannot defend him- or herself (208). Thus, the phenomenon of bullying is complex and includes aspects of both behavior (bullying) and stressful life events (victimization). Males are more involved in physical bullying, while bullying among females involves more relational forms of bullying such as social exclusion and verbal bullying (134, 164).
In cross-sectional studies, bullying and victimization are shown to be associated with poor family functioning (196), domestic violence (27), and parental maltreatment (206). There are very few prospective studies of childhood bullying behavior and victimization and their impact on later problem behavior and poor health. Kim and colleagues followed bullying, victimization, and psychiatric problems among seventh and eighth grade students for ten months (131). They concluded that bullying and victimization cause psychiatric problems rather than that psychiatric problems cause bullying and victimization (131). Olweus followed up 87 men from grade nine to age 23 and concluded that victimized boys had depression more often as adults than non-victimized boys (175). In previous studies of the males in the Finnish 1981 Nationwide Birth Cohort (the From a Boy to a Man study), bullying predicted outcomes that indicated an antisocial tendency in young adulthood (215, 216). However, these studies did not include the females in the sample, because the follow-up was restricted to males using mainly information from military call-up health examinations (215, 216).

2.2.8 CHILDHOOD MENTAL HEALTH PROBLEMS AS PREDICTORS OF PSYCHOTROPIC MEDICATION USE AND PSYCHIATRIC HOSPITAL TREATMENT BY YOUNG ADULTHOOD

Previous child psychiatric birth cohort studies have not reported on childhood mental health problems as predictors of psychotropic medication use in adulthood. With regard to childhood mental health problems and later PHT, there are some previous studies. Clinical cohort studies have shown that children with a psychiatric diagnosis are at risk of PHT in adulthood (135, 238). The only large-scale prospective birth cohort study examining childhood predictors for later PHT with a follow-up extending to adulthood is the UK National Child Development Study (UKNCDS) (78). The study included all 115 cohort members who had been treated for schizophrenia, affective psychotic disorders, and neurotic disorders in a hospital, and 1191 randomly selected controls from the original cohort of over 15,000 subjects with childhood data. Among males, teacher reports of externalizing and internalizing problems both at age seven and age eleven predicted hospital treatment of psychosis or neurotic disorders before the age of 28. Conversely, among females, internalizing problems at age seven did not substantially increase the likelihood of PHT.

There is a scarcity of gender-specific data on childhood mental health problems as predictors of PHT, since PHT is a rather rare phenomenon in adolescence and young adulthood, and the number of subjects has not exceeded 1,500 participants in most population-based birth cohort studies with information about both childhood psychopathology and adult psychiatric outcomes. Moreover, the impact of comorbid conduct and emotional problems on later PHT is not known, though childhood comorbid conduct and emotional problems increase the risk of several adult adverse
outcomes (82, 88, 135, 214, 217). Lastly, in the UKNCDS, childhood mental health problems were assessed using only teachers as informants. However, information about childhood mental health problems should be based on standardized tools from several informants (65).

2.2.8.1 Childhood predictors of costs associated with health service use

Only a few studies have studied the impact of childhood problems on later acquired health care costs (135, 146, 205). Scott and his colleagues (205) used the population-based Inner London cohort study. Children with and without conduct disorder at the age of ten in 1970 were followed up to age 28. Health care costs were estimated by asking the subjects as adults about the frequency of different medical treatments. The information about the medical treatment was then multiplied with unit costs for general and psychiatric inpatient and outpatient treatment. The study showed that the mean health care costs among children with conduct disorder was almost nine times higher as adults compared to children without conduct disorder.

Leibson and colleagues (146) identified 309 children (mean age 7) with ADHD in 1987 using school and medical records in Minnesota, USA. These were compared with children in the community who did not have ADHD. The cases and the controls in the cohort were followed up to the year 1995 (mean age 15). Medical care costs were derived from databases including inpatient, outpatient, and emergency department care. Information on health costs was almost complete, except for information from a few private practitioners, which could not be included in the study. The study showed that the median medical care costs incurred by children with ADHD were approximately twofold compared to children without ADHD.

Knapp and colleagues (135) studied long-term costs among children and adolescents (mean age 14) treated in the Maudsley clinic in London between 1970 and 1983. The costs of medical care were assessed by asking the subjects as adults about different medical treatments after the age of 17 and then transcribing them to costs in a similar way to that done in the study by Scott et al. (205). Cost comparisons were made between children who had depression versus comorbid conduct disorder and depression. The study showed that the medical care costs in adulthood were approximately twice as high for the comorbid conduct-depression group compared to the pure depression group.

None of these three studies assessed prospectively the predictors of psychotropic medication costs. However, costs from psychotropic medication use represent an increasing share of the total health costs (152). The proportion of psychotropic medication costs of the total outpatient costs ranged between 31% and 52% across psychiatric disorders, according to a study of privately insured children and adolescents aged 17 or younger in the USA in 2000 (152).
3 AIMS OF THE STUDY

1. To study the cumulative incidence of different psychotropic medication classes and polypharmacy use of psychotropic medications by the age of 25 (study I).

2. To study how many of the antipsychotic users have been treated for psychiatric disorders in hospitals (study II).

3. To study family characteristics and psychopathology measures at the age of eight as predictors of antipsychotic use, antidepressant use, and hospital treatment of psychiatric disorders by the age of 25 (studies II-IV).

4. To study whether antidepressant costs can be predicted by family characteristics and psychopathology measures at the age of eight, when predictors of antidepressant use are taken into account (study III).

5. To study whether bullying behavior and victimization at the age of eight predict psychotropic medication use and hospital treatment of psychiatric disorders by the age of 25 (study V).
4 METHODS

4.1 STUDY DESIGN

The thesis is part of the multicentre “Finnish Nationwide 1981 Birth Cohort Study” (8, 221). A history of the cohort is presented in Box 1. As shown in Figure 1, the population of the study was all 60,007 Finnish children born during 1981 and alive in 1989 (8). A representative sample of 6,017 children was invited to take part in the study in 1989, i.e. 10% of the population. This representative sample of 8-9-year-old children came from all five university hospital areas in Finland (Helsinki, Turku, Tampere, Kuopio, and Oulu). To assure representativeness of the general population, the communities in the hospital areas were selected according to their degree of urbanization. In small communities, all children born in 1981 were selected, while in larger cities, a random sample of school classes was selected from all school districts of the city. The sociodemographic characteristics of the sample are representative of the population (8).

Of the 6,017 subjects in the original sample, the study sample in 1989 consisted of 5,813 subjects with questionnaire-based information; these subjects represented 97% of the original sample. As shown in Figure 1, altogether 70 subjects were never reached due to migration or unknown address (1.2%) and 134 refused to participate in the study (2.2%) (8).

The study sample between 1994-2005 included 5,525 subjects whose...
Figure 1  Flow-chart of the study participants. PIN, personal identification number.
personal identification numbers were linked with the National Prescription Register and the Finnish Hospital Discharge Register. Altogether 492 personal identification numbers (PIN) of the original sample had been either lost or inappropriately documented (8.2% of 6,017). The attrition at follow-up was due to random error, such as inappropriately documented PINs. The number of subjects with available data in 1989 and between 1994 and 2005 depended on the used measurements; detailed information is given in the tables in the original publications (II-V).

4.2 ETHICAL CONSIDERATIONS

The Joint Commission on Ethics of all five university hospital units and clinics included in the study (Helsinki, Turku, Tampere, Kuopio, and Oulu) approved the research plan at baseline. At follow-up, Turku University and Turku University Central Hospital approved the research plan. The combined information from questionnaires and registry data was analyzed in such a way that no subject could be identified.

4.3 MEASURES IN 1989 AT AGE EIGHT

Data collection in 1989 was organized through teachers, when the subjects attended the second grade in elementary school. The teacher sent parent questionnaires via the child to the parents, and the parents returned the questionnaire with the informed consent in a sealed envelope to the teacher. The children filled in a questionnaire in the classroom. The teacher sent the parent questionnaires in sealed envelopes, the teacher questionnaires, and the child self-reports to the researcher. Parents and teachers filled in brief questionnaires on a variety of mental health problems and additional questions on bullying and victimization. The children filled in a questionnaire on depressive symptoms and additional questions on bullying and victimization.

4.3.1 PSYCHIATRIC SYMPTOMS

Psychiatric symptoms at age eight were assessed using information collected from three different sources: parents, teachers, and children. The parents and the teachers completed the Rutter’s parent questionnaire (RA2) \(^{202}\) and the teacher-questionnaire (RB2) \(^{200}\), respectively. Both scales are validated in Finland \(^{139}\) and have been widely used in child psychiatric research \(^{89}\). The parent questionnaire consists of 31 and the teacher questionnaire of 26 items on a scale ranging from 0 to 2 points. The correlation between the total score on the parent and teacher scales was \(r=0.36\) among males and \(r=0.26\) among females \(^{141}\). In addition to the total score scale, there are three
subscales. The conduct scale has questions about stealing, lying, aggression, defiance; the hyperactivity scale is concerned with restlessness, distractibility, inattention; and the emotional scale addresses shyness, withdrawal and anxiety.

The children themselves filled in the Children’s Depression Inventory (CDI), which measures depressive symptoms \(^{(137)}\). The original English version of CDI has shown good validity for assessing depressive symptoms among children \(^{(62)}\). According to a Finnish study, the CDI can be used as a measure of overall psychiatric disturbance, but only if it is combined with information from other informants \(^{(139)}\). It has 27 items on a scale ranging from 0 to 2 points. The core research committee excluded the question concerning suicidal ideation from the version used in this study. It was considered to be ethically unreasonable to ask children a question about suicidal ideation at that age in a classroom setting, especially without an opportunity to discuss the issue with an adult. In sum, the version used in this study had a maximum score of 52 points.

4.3.1.1 Variable-centered approaches

In studies II-IV, variable-centered approaches were used. Variable-centered approaches are suitable, e.g. to describe the relative importance of predictor variables in explaining the variance of an outcome variable \(^{(143)}\).

**Total scores of the parent and teacher scales:** To study general psychopathology or possible caseness, the total scores of the parent and teacher scales were used. In study IV, the children were divided into screen-positive and screen-negative groups based on the total scores of the parent and teacher reports (males (M): \(n=2638\); females (F): \(n=2554\)). A cut-off point of 13 and 9 was used on the parent and teacher reports, respectively. These cut-off points correspond to the 85th percentile; they are commonly used, and validated to detect mental disorders in Finland \(^{(139)}\). Parent and teacher reports were combined using an “or rule” \(^{(114, 243)}\), i.e. subjects were classified as screen-positive if the points in either the 1) parent report, 2) the teacher report, or 3) both reports were above the cut-off score (M: 29.6%; F: 12.6%). The proportions of screen-positive and screen-negative subjects have been described in detail in a prior report \(^{(9)}\).

In study V, the total scores on the parent and teacher scales were used as possible confounding variables. When used as linear variables, the parent and teacher total scores were summed together. When used as categorical variables, the subjects were classified as screen-positive or -negative in the same manner as described above (study IV).

**Summed subscales and the CDI:** To study specific types of psychopathology, the three subscales of the parent and teacher reports and the CDI were used. In studies II and IV, the scores from the parent and teacher conduct, hyperactivity and emotional subscales were summed
Methods

together to generate the three pooled scales (parent conduct scores + teacher conduct scores = pooled conduct score etc.), while the depressive scale was based on the child self-report alone. These scales were studied as both linear variables to achieve statistical power and as categorical variables to facilitate the interpretation of the results for screening purposes. In line with previous reports using categorical variables \(^{(214, 217)}\), sex-specific cut-off scores at the 90\(^{th}\) percentile based on the distribution in the population-based sample at baseline were used.

**Standardized scales:** In study III, the four scales were standardized, because the range of potential scores on the conduct, hyperactivity and emotional scales were different for parents and teachers. Through standardization, the conduct, hyperactivity, and emotional scales were given equal weight from each informant. All standardization procedures were done separately for males and females. The three subscales of the parent and teacher scales and the CDI were standardized by subtracting the mean value of the scale from the observed value of the subject, and finally by dividing with the standard deviation of the scale (e.g. standardized parent report of conduct symptoms = (observed value - mean value) / standard deviation). The final standardized pooled scales (conduct, hyperactivity and emotional) were generated by taking the average score of the standardized parent subscale and the corresponding teacher subscale (e.g. pooled standardized conduct scale = (standardized parent report of conduct symptoms + standardized teacher report of conduct symptoms) / 2). If information from only the parent or the teacher but not both was available, the pooled scale was not generated for the subject concerned. The standardized pooled scales were studied both as linear variables and as categorical variables. When using categorical variables, sex-specific cut-off scores at the 90\(^{th}\) percentile were used.

**4.3.1.2 Person-centered approach**

In study IV, person-centered approaches were used. Person-centered approaches take into account that the heterogeneity of the population might affect the prediction of an outcome \(^{(143)}\). The predictor “conduct problems” can serve as an example: a group of persons with “pure” conduct problems may be heterogeneous compared to a group with both conduct and emotional problems with regard to an outcome \(^{(214)}\). Likewise, mental health symptoms reported by adults or reported by the children themselves may predict an outcome differently \(^{(214)}\). The four summed psychopathology scales using the sex-specific 90\(^{th}\) percentile cut-off points were combined to form 16 combinations (M: n=2544; F: n=2478). As shown in Figure 2, these 16 groups were a priori collapsed into six clinically meaningful groups in line with previous reports \(^{(214, 217)}\):
1. The Reference group was negative (below the 90th percentile) on all four scales;
2. The Conduct-Emotional group was conduct-positive and emotional-positive or CDI-positive, indicating a high level of symptoms in both conduct and emotional domains;
3. The Conduct-only group was positive on the conduct scale, but negative on both the emotional scale and the CDI
4. The Attention-Hyperactivity group was positive on the hyperactive scale, but negative on the conduct scale
5. The Emotional-only group was positive on the emotional scale and/or the CDI, but negative on conduct and hyperactivity scales
6. The Invisible group had high levels of self-reported depressive symptoms, but was screen-negative on all three scales based on adult reports.

![Screen positive on psychopathology scale](image)

**Figure 2** The criteria of belonging to different groups of childhood psychopathology in the person-centered approach. CDI, Children’s Depression Inventory.
4.3.2 BULLYING AND VICTIMIZATION
In study V, information from all three informants, i.e. the parent, the teacher and the children themselves, was used to assess bullying and victimization. In the Finnish versions of the parent and teacher reports, a question about bullying and another about victimization were included: “The child bullies/is bullied”. The answer alternatives were (1) “doesn't apply”, (2) “applies somewhat”, and (3) “certainly applies”. In the self-report, bullying was assessed by giving the child three alternatives from which to choose: (1) "I bully other children almost every day", (2) "I bully sometimes", and (3) "Usually I do not bully". Victimization was assessed by the alternatives: "Other children (1) bully me almost every day", (2) "bully me sometimes", and (3) "usually do not bully me". Alternatives 1 and 2 were regarded as indicating no or only sometimes bully or victim status, whereas alternative 3 indicated frequent bully or victim status.

The sample was classified into the following groups: (1) those who never or only sometimes bully and are not victimized according to parental, teacher, and self-reports; (2) those who frequently bully (but are not victimized) according to at least one informant; (3) those who are frequently only victimized according to at least one informant; and (4) those who frequently both bully and are victimized using pooled information from all three informants. For example, if a boy frequently bullied according to teachers and was frequently victimized according to self-reports, he was classified into the bully-victim group. Only subjects with complete information about bullying and victimization from all three informants were included in the analysis. Combining the parent, teacher, and child reports of information about bullying/victimization by using the "either-or" rule is justified by the finding that the interrater agreement was low (weighted $\kappa$ in range 0.11–0.22).

4.3.3 FAMILY CHARACTERISTICS
Information about family characteristics at the age of eight was used in studies II-IV and was derived from the parent report. Parental education level was based on information about whether the father or the mother had completed of at least 12 years of education or if both parents had a lower education level (in Finland compulsory education consists of 9-year comprehensive school after which education can be continued in vocational school or in upper secondary school concentrating on theoretical subjects). Family structure was based on information about whether the child lived in a family with two biological parents or if the family had some other constellation.

In Finland, every citizen has a unique personal identification number (PIN), consisting of the date of birth and a four-digit suffix. The PIN is given at birth and stays the same throughout life, regardless of changes of name or place of residence. The PIN codes of the participants were linked to data from the Drug Prescription Register, the Special Reimbursement Register, and the Finnish Hospital Discharge Register between January 1st, 1994, and December 31st, 2005, when the subjects were from 12-13 to 24-25 years old.

4.4.1 PSYCHOTROPIC MEDICATION USE

In studies I, II, III and V, psychotropic medication use was studied. For convenience, the outcome, having at least one purchase of a psychotropic medication, is referred to as psychotropic medication use. Information about the use of psychotropic medication was collected from the nationwide Drug Prescription Register, which is filed by the Social Insurance Institution of Finland (SII). The register contains information about the personal identification number, the purchased medication, the cost of the purchase, and the date of the purchase. The nationwide Drug Prescription Register tracks medication that has been purchased from a pharmacy, and comprises data on 97%-98% of all reimbursed prescriptions (166). The SII reimburses prescription medicines that have been approved for reimbursement as treatment of an illness. The SII also keeps the Special Reimbursement Register, which includes the PINs of subjects who are granted a high level special reimbursement for the continuous medication of some chronic disorders (e.g. epilepsy and psychotic disorders).

The medication is coded according to the Anatomic Therapeutic Chemical (ATC) classification system in the register (166). In study I, the use of psychotropic medication was classified into groups accordingly:

1. antipsychotics (ATC-codes N05A, except N05AB01 “dixyrazine” and N05AN01 “lithium”);
2. antidepressants (N06A and N06CA “antidepressants in combination with psycholeptics”);
3. benzodiazepine derivates including anxiolytics (N05BA) and hypnotics (N05CB and N05CF);
4. mood stabilizers (N03, except N03AE01 clonazepam; and N05CB02 barbiturates in combination with other drugs) included antiepileptics that were not purchased by subjects who had epilepsy according to the Special Reimbursement Register; and,
5. “other psychotropic medications” included medications, which could not be categorized in the above-mentioned groups or have indications for both psychiatric and other types of disorders (N05AB01 “dixyrazine” which is indicated for both psychosis and nausea,
N05AN01 “lithium”, N05BB01 hydroxyzine which is indicated for both anxiety and allergy, N05BE01 buspirone, N06BA04 methylphenidate, N07BB01 disulfiram).

In study V, a very similar classification and terminology was used as in study I, but with the following differences:

- Anxiolytics in study V refers to the same class as benzodiazepines in study I (the benzodiazepine class in study I included both anxiolytics, such as diazepam and lorazepam, and hypnotics, such as zopiclone).
- Antiepileptics in study V refers to the same class as mood stabilizers in study I, but subjects who had epilepsy according to the Special Reimbursement Register were not excluded in study V. In study I, subjects with epilepsy were excluded from the mood stabilizer group.

In the thesis as a whole, special focus was laid on the use of antidepressants, and antipsychotics, because they are medication classes with clear psychiatric indications and had the highest number of users.

**4.4.1.1 Polypharmacy use**

In study I, polypharmacy use was assessed. There is no standard width of the time window within which two purchases can occur to be defined as polypharmacy in register-based research \( ^{153, 247} \). In study I, a time window of one day was primarily chosen, in order to make comparisons with several surveys, which have defined polypharmacy as a physician visit with more than one psychotropic medication prescription \( ^{57, 92, 159} \). The focus was on across-class polypharmacy, i.e. the concomitant use of two medications from different psychotropic medication groups.

**4.4.1.2 Costs of antidepressant medication**

In study III, costs of antidepressant medication were assessed. The costs of all purchases were recorded in the Drug Prescription Register in Finnish Marks (FIM) between 1994 and 2001, and in euros between 2002 and 2005. All prices were adjusted to correspond to 2005 prices in euros, using the official FIM/euro exchange rate for the years between 1994 and 2001 \( ^{30} \), and adjusted for inflation using the Price Consumer Index \( ^{222} \).

**4.4.2 PSYCHIATRIC HOSPITAL TREATMENT**

In studies II, IV and V, psychiatric hospital treatment was studied. Information about psychiatric hospital treatment between 1994 and 2005 was based on the Finnish Hospital Discharge Register in Finland, which is extensively documented in psychiatric research \( ^{126, 181, 217, 228} \). The register covers, e.g. the diagnosis and the day of admission in all general, mental and private hospital inpatient care units in Finland.
The outcome of “psychiatric hospital treatment” was defined as having a primary diagnosis of a psychiatric disorder in the hospital discharge register between 1994 and 2005. All patients treated according to the register were included in the study, i.e. both psychiatric and general hospitals were included. The diagnostic codes were registered according to ICD-9 in the years 1994-1995, and ICD-10 in 1996-2005.

In study II, the hospital discharge register was searched for all psychiatric main diagnoses of subjects who had used antipsychotics during the follow-up. The subjects were classified into the following groups:

1. Non-affective psychoses (ICD-10 codes F20-F29; ICD-9 codes 295 and 297-298)
2. Affective disorders (F30-F39; 296)
3. Other psychiatric disorders (F00-F99, except F20-F39; 290-319 except 295-298)
4. No inpatient treatment of psychiatric disorders (no F00-F29 or 290-319 main diagnosis in the register during the follow-up).

In study II, the same subject could belong to only one group, so that group 1 overruled group 2 etc. (e.g. a subject who had been discharged with both a non-affective psychosis and an affective disorder during the follow-up, belonged to the non-affective psychotic disorder group).

In study IV, diagnostic codes of specific diagnoses and diagnostic groups were classified according to the transcription of ICD-9 and ICD-10 codes to DSM-IV-TR diagnoses (19). The association with childhood variables was analyzed for having any psychiatric diagnosis and, additionally, separately analyzed for the four diagnostic groups with most subjects: psychosis, mood disorders (non-psychotic), anxiety disorders, and substance-related disorders.

In study IV, subjects could belong to several diagnostic groups (some subjects were diagnosed with different diagnoses at different treatment periods). Subjects who had not been treated for a psychiatric disorder according to the register data between 1994 and 2005 were used as a reference group in all statistical analyses in study IV.

4.4.3 POOLED OUTCOME OF PSYCHOTROPIC MEDICATION USE AND/OR PSYCHIATRIC HOSPITAL TREATMENT

In study V, information about psychotropic medication use and psychiatric hospital treatment was pooled as a global index of psychiatric treatment at follow-up.
4.5 STATISTICAL ANALYSIS

4.5.1 DESCRIPTIVE MEASURES
In studies II, III, IV and V, the lifetime prevalence of the received treatment by the end of the follow-up was reported in percentages by dividing the number of users with the total number of subjects in the beginning of the follow-up period. In studies I and II, the cumulative incidence of medication use was also reported in percentages, but the cumulative incidence was calculated using survival analysis.

4.5.2 SURVIVAL ANALYSIS
The age in days of the subjects defined the survival time in all studies (I-V). The event was defined as the first purchase of the studied medication or the first psychiatric hospital treatment period. The time to moving from the country (n=35), death (n=35), or the end of the follow-up on December 31st, 2005, was treated as the censored time observation.

4.5.2.1 Cumulative incidence
In studies I and II, the cumulative incidence and its 95% confidence intervals (CI) were based on survival analysis (120). The cumulative incidence was defined as 1 – the survival probability.

4.5.2.2 Cox regression
Cox proportional hazard regression models were fitted in all studies in this thesis (69). The associations between the predictors and the outcomes were quantified with hazard ratios (HR) and their 95% confidence intervals. P-values were calculated using the Wald $\chi^2$-test. In univariate analyses, each predictor was analyzed separately in a model. In multivariate analyses, all defined predictors were entered at once into the model.

4.5.3 COST ANALYSES

4.5.3.1 Choice of analytical method
In study III, the aim of the study was to predict antidepressant costs in a population-based sample. Thus, information on subjects who had acquired zero costs should also be taken into consideration. The statistical challenge with analyzing predictors of antidepressant costs in the total sample, is that
health costs, such as antidepressant costs, are extremely right-skewed \(^{(45)}\). Hypothetically, the following strategies could be considered:

1. Predicting arithmetic mean costs using a regular test, such as the t-test, cannot be used, because the test requires a normal distribution.
2. Predicting median costs does not require a normal distribution, but in this case the median equals zero.
3. Predicting mean costs using a logarithmic transformation of the costs is not in line with the aim to include the total sample, i.e. also the subjects with zero costs (the logarithm of zero is not defined).
4. Predicting mean costs using the bootstrap technique \(^{(31, 227)}\) would enable the calculation of standard errors and confidence intervals of the arithmetic mean costs, even when the distribution is skewed. This strategy has been used in some studies \(^{(112, 135, 148, 205)}\). However, the bootstrap technique does not take into account that a big proportion of the study population has zero costs.
5. Predicting mean costs using sample selection models \(^{(45, 189)}\) takes into account that a proportion of the study population has zero costs \(^{(45)}\). Once this is taken into account, a logarithmic transformation of the costs can be performed \(^{(45)}\).

### 4.5.3.2 Sample selection models

In study III, Heckman sample selection models were used to analyze predictors of antidepressant costs. It can be hypothesized that once the predictors of antidepressant use (binary variable) have been analyzed, it is unlikely that any further predictive value of predictors of antidepressant costs (linear variable) would be found.

Sample selection models have been widely used in, e.g. econometric analyses \(^{(189)}\) and to correct for drop-out in longitudinal criminological research \(^{(44)}\). Among sample selection models, the most often used models are the two-step model and the maximum likelihood model \(^{(45)}\). The two-step model is mainly used for explanatory analyses, while the more efficient maximum likelihood should be primarily chosen \(^{(189)}\). In this thesis, both models were used for comparison of the results, as suggested \(^{(44)}\).

In step one of the two-step model, the inverse Mills ratio is estimated by predicting a binary outcome (yes/no), and in step two, the linear outcome is estimated, by adjusting with the inverse Mills ratio. In the maximum likelihood model, all parameters in the model are estimated using maximum likelihood estimation relying on the Newton-Raphson algorithm \(^{(230)}\).

To define a good sample selection model, exclusion restrictions are required \(^{(44)}\). This means that some of the variables that have been used to predict antidepressant use (binary variable), cannot be used to predict antidepressant costs (linear variable). In study III, the hyperactivity and
emotional scales were excluded, because they had the lowest HR:s and the highest p-values in the Cox models.

4.5.4 STATISTICAL SOFTWARE
Survival analyses in studies II, III, IV and V were done with SAS System for Windows, release 9.1 (studies IV and V) and 9.2 (studies II and III). Survival analyses in study I and cost analyses in study III were done with R software, release 2.10.1. The cost analyses were done using the sampleSelection-package in R \(^{(230)}\).
5 RESULTS

5.1 USE OF PSYCHOTROPIC MEDICATION (AIMS 1 AND 2; STUDIES I AND II)

Box 2  The main findings of psychotropic medication use.

- 15% of this sample of Finnish people born in 1981 had used psychotropic medications by age 25. With regard to drug class, 2.5%, 12%, and 5% had used antipsychotics, antidepressants, and benzodiazepines, respectively, by age 25 (study I).
- 4% had used polypharmacy combinations, i.e. two or more psychotropic medications concomitantly. Among psychotropic medication users, the proportion of polypharmacy use was 27%. The majority of antipsychotic and benzodiazepine users had used polypharmacy combinations, while a minority of antidepressant users had used polypharmacy combinations (study I).
- Psychotropic medication use remained uncommon until late adolescence (study I).
- More females than males had used antidepressants, the antidepressant-benzodiazepine combination, and the antidepressant-mood stabilizer combination (study I).
- Three-fourths of antipsychotic users had been treated for a psychiatric disorder in a hospital. The diagnostic groups of hospital treatment among antipsychotic users varied by sex: non-affective psychoses were common among males, while affective disorders were common among females (study II).

5.1.1 CUMULATIVE INCIDENCE OF PSYCHOTROPIC MEDICATION USE BY AGE 25 (AIM 1; STUDY I)

The cumulative incidences of psychotropic medication use by age 25 are shown in Figure 3A: the cumulative incidence of having purchased at least one psychotropic medication was 15.2% (n=780). The most common medication groups were antidepressants and benzodiazepines with cumulative incidences of 12.2% and 5.2%, respectively. The users of benzodiazepines (n=265) had used anxiolytics (n=193; cumulative incidence 3.8%) and/or hypnotics (n=127; cumulative incidence 2.4%). More females than males had used any psychotropic medication (female:male HR 1.4) and antidepressants (female:male HR 1.6).
**Figure 3**  The cumulative incidence by age 25 of all psychotropic medication use (A) and of polypharmacy use (B, next page). Summary of Table 1 in study I. Abbreviations in A: Any, any psychotropic medication use; Dep., antidepressant use; Bnz., benzodiazepine use; Ps., antipsychotic use; Mstab., mood stabilizer use; Other, use of other psychotropic medications. Abbreviations in B: Any, use of any polypharmacy combination; Dep+Bnz, antidepressant-benzodiazepine use; Ps+Dep, antipsychotic-antidepressant use, Ps+Bnz, antipsychotic-benzodiazepine use; Dep+Mstab, antidepressant-mood stabilizer use; Ps+Mstab, antipsychotic-mood stabilizer use.
5.1.2 CUMULATIVE INCIDENCE OF POLYPHARMACY USE OF PSYCHOTROPIC MEDICATIONS BY AGE 25 (AIM 1; STUDY I)

Polypharmacy use was defined as having purchased medications from different psychotropic medication classes during the same day. As shown in Figure 3B, the cumulative incidence of any polypharmacy use by age 25 was 4.1% (n=210). The most common combination was the antidepressant-benzodiazepine combination with a cumulative incidence of 2.9%. More females than males had used the antidepressant-benzodiazepine combination: the cumulative incidence was 3.5% among females and 2.3% among males, and the female:male HR was 1.5. The cumulative incidence of the antidepressant-mood stabilizer combination was higher among females
than among males: the cumulative incidences were 0.9% for females (n=19) and 0.1% for males (n=6).

### 5.1.3 TIMING OF PSYCHOTROPIC AND POLYPHARMACY MEDICATION USE (AIM 1; STUDY I)

The cumulative incidence of both any psychotropic medication use and any polypharmacy medication use started to peak in late adolescence. To describe this, the cumulative incidences for any psychotropic medication use by ages 15, 20, and 25 were 1.3%, 6.1%, and 15.2%, respectively. The cumulative incidences of polypharmacy medication use by ages 15, 20, and 25 were 0.2%, 1.1%, and 4.4%, respectively. As shown in Table 3, the median age in years of the first purchase of different medication classes ranged between 20 and 22 years across medication classes.

### 5.1.4 POLYPHARMACY USE AMONG ALL PSYCHOTROPIC MEDICATION USERS (AIM 1; STUDY I)

As shown in Table 3, the proportion of any antidepressant polypharmacy during the same day was 33%. Among benzodiazepine and antipsychotic users, the proportions of any polypharmacy use were 61% and 72%, respectively.

<table>
<thead>
<tr>
<th>Users of any psychotropic medication (n=710)</th>
<th>Age in years at first purchase (median (IQR))</th>
<th>Proportion of users with polypharmacy use (IQR) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Users of antidepressants (n=623)</td>
<td>21.2 (19.1, 22.9)</td>
<td>33</td>
</tr>
<tr>
<td>Users of benzodiazepines (n=265)</td>
<td>21.8 (19.5, 23.2)</td>
<td>61</td>
</tr>
<tr>
<td>Users of antipsychotics (n=124)</td>
<td>21.2 (18.7, 23.1)</td>
<td>72</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, inter-quartile range
* At least two medications from different medication classes purchased during the same day.

### 5.1.5 REIMBURSEMENT DUE TO PSYCHOTIC DISORDERS AMONG PSYCHOTROPIC MEDICATION USERS (STUDY I)

Psychotic disorders (e.g. documented schizophrenia, psychotic bipolar disorder or psychotic depression) according to the Special reimbursement Registers were documented among 8% of users of any psychotropic medication (n=62/780), 47% of antipsychotic users (n=58/124), 8% of antidepressant users (n=50/623), 7% of benzodiazepine users (n=19/265),
40% of mood stabilizer users (n=21/52), and 22% of users of psychotropic polypharmacy combinations (n=47/210).

5.1.6 PSYCHIATRIC HOSPITAL TREATMENT AMONG ANTIPSYCHOTIC USERS (AIM 2; STUDY II)

Among subjects with antipsychotic use, inpatient treatment of psychiatric disorders during the follow-up was studied. In both sexes, three-fourths of the antipsychotic users had been treated for psychiatric disorders in a hospital (76.8% among males and 74.5% among females with antipsychotic use). However, the diagnostic groups differed among males and females with antipsychotic use. Among males with antipsychotic use, 43.5% had been treated for non-affective psychotic disorders and 13.0% had been treated for affective disorders. Among females with antipsychotic use, non-affective psychoses were less common than affective disorders: 23.6% had been treated for non-affective psychotic disorders and 38.2% for affective disorders.

5.2 USE OF PSYCHIATRIC HOSPITAL TREATMENT (STUDY IV)

In Figure 4 it is shown that 6.2% (n=168) of the males and 4.1% (n=108) of the females had been discharged from psychiatric treatment. The most common psychiatric reason (diagnostic group) for being treated in hospitals among males was substance-related disorders (1.8%, n=48), while among females it was non-psychotic mood disorders (1.9%, n=50).

The number of subjects who had been treated for specific psychiatric diagnoses, is shown in Table 4. Males (1.5%) were more often than females (0.8%) treated for psychotic disorders. More males than females were treated for non-affective psychoses (1.3% vs. 0.5%), and two of its six sub-diagnoses: schizophrenia (0.6% vs. 0.2%) and psychotic disorder not otherwise specified (0.8% vs. 0.2%). As shown in Table 5, some subjects had several inpatient treatment periods with different primary diagnoses.

The mean age at the first treatment period for any psychiatric diagnosis was 19.1 years (SD 2.4) among males and 18.8 years (SD 3.7) among females.
### Results

#### Table 4  Number of subjects with and without hospital treatment of psychiatric disorders. Summary of partly unpublished results related to study IV. $^{a, b, c}$

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Males</th>
<th>Females</th>
<th>Sex-difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any psychiatric diagnosis</td>
<td>6.2 (168)</td>
<td>4.1 (108)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychotic disorders</td>
<td>1.5 (40)</td>
<td>0.8 (22)</td>
<td>0.03</td>
</tr>
<tr>
<td>Non-affective psychoses</td>
<td>1.3 (35)</td>
<td>0.5 (13)</td>
<td>0.002</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>0.6 (15)</td>
<td>0.2 (4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>0.1 (2)</td>
<td>0.04 (1)</td>
<td>≈1</td>
</tr>
<tr>
<td>Schizophreniform disorder</td>
<td>-</td>
<td>-</td>
<td>NA</td>
</tr>
<tr>
<td>Delusional disorder</td>
<td>0.1 (2)</td>
<td>-</td>
<td>0.50</td>
</tr>
<tr>
<td>Brief psychotic disorder</td>
<td>0.1 (3)</td>
<td>0.2 (6)</td>
<td>0.34</td>
</tr>
<tr>
<td>Psychotic disorder NOS</td>
<td>0.8 (22)</td>
<td>0.2 (5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Affective psychoses</td>
<td>0.4 (10)</td>
<td>0.4 (11)</td>
<td>0.83</td>
</tr>
<tr>
<td>Bipolar disorder with psychotic features</td>
<td>0.04 (1)</td>
<td>0.04 (1)</td>
<td>≈1</td>
</tr>
<tr>
<td>MDD with psychotic features</td>
<td>0.3 (9)</td>
<td>0.4 (10)</td>
<td>0.82</td>
</tr>
<tr>
<td>Mood disorders, non-psychotic</td>
<td>1.5 (40)</td>
<td>1.9 (50)</td>
<td>0.24</td>
</tr>
<tr>
<td>Bipolar disorder, non-psychotic</td>
<td>0.04 (1)</td>
<td>0.2 (5)</td>
<td>0.12</td>
</tr>
<tr>
<td>Depressive disorders, non-psychotic</td>
<td>1.4 (39)</td>
<td>1.8 (47)</td>
<td>0.33</td>
</tr>
<tr>
<td>Substance-related disorders</td>
<td>1.8 (48)</td>
<td>0.9 (24)</td>
<td>0.006</td>
</tr>
<tr>
<td>Alcohol-related disorders</td>
<td>0.7 (19)</td>
<td>0.3 (7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Cannabis-related disorders</td>
<td>0.3 (8)</td>
<td>-</td>
<td>0.008</td>
</tr>
<tr>
<td>Opioid-related disorders</td>
<td>0.3 (8)</td>
<td>0.3 (7)</td>
<td>≈1</td>
</tr>
<tr>
<td>Other substance-related disorders</td>
<td>0.7 (18)</td>
<td>0.5 (12)</td>
<td>0.36</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>1.4 (37)</td>
<td>0.5 (14)</td>
<td>0.002</td>
</tr>
<tr>
<td>Social phobia</td>
<td>0.1 (2)</td>
<td>0.04 (1)</td>
<td>≈1</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>0.2 (4)</td>
<td>-</td>
<td>0.13</td>
</tr>
<tr>
<td>Generalized anxiety</td>
<td>0.1 (3)</td>
<td>0.04 (1)</td>
<td>0.63</td>
</tr>
<tr>
<td>Obsessive compulsive disorder</td>
<td>0.1 (2)</td>
<td>0.04 (1)</td>
<td>≈1</td>
</tr>
<tr>
<td>Acute stress disorder</td>
<td>0.6 (16)</td>
<td>0.1 (3)</td>
<td>0.004</td>
</tr>
<tr>
<td>Posttraumatic stress disorder</td>
<td>-</td>
<td>0.1 (2)</td>
<td>0.24</td>
</tr>
<tr>
<td>Other anxiety disorders</td>
<td>0.5 (14)</td>
<td>0.2 (6)</td>
<td>0.12</td>
</tr>
<tr>
<td>Adjustment disorders</td>
<td>1.4 (37)</td>
<td>0.3 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Eating disorders</td>
<td>-</td>
<td>0.5 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Personality disorders</td>
<td>0.4 (10)</td>
<td>0.2 (6)</td>
<td>0.46</td>
</tr>
<tr>
<td>Cluster A</td>
<td>0.1 (3)</td>
<td>0.04 (1)</td>
<td>0.63</td>
</tr>
<tr>
<td>Cluster B</td>
<td>0.2 (5)</td>
<td>0.2 (6)</td>
<td>0.77</td>
</tr>
<tr>
<td>Cluster C</td>
<td>0.1 (2)</td>
<td>-</td>
<td>0.50</td>
</tr>
<tr>
<td>Other</td>
<td>0.8 (21)</td>
<td>0.6 (15)</td>
<td>0.41</td>
</tr>
<tr>
<td>No hospital treatment</td>
<td>93.8 (2542)</td>
<td>95.9 (2528)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NOS, not otherwise specified; NA, not applicable.

$^a$ Only the primary diagnosis is taken into account. The ICD-9 and ICD-10 diagnoses are classified according to the DSM-IV-TR transcription of ICD-codes. Please see methods for references.

$^b$ Bold face indicates statistically significant differences between the sexes at $p<.05$.

$^c$ The totals of the group percentages are > 100%, because some subjects had several treatment periods with different primary diagnoses. Overlapping between diagnostic groups is shown in Table 5.

$^d$ Differences between the sexes of the proportions of treated subjects were analyzed with Fisher’s exact test, two-sided $p$-values are given. ≈1 indicates $p$-values very close to 1.000 in the performed Fisher exact test. Subjects without the studied diagnosis were used as reference group.
Figure 4  The percentage of the females (n=2,637) and males (n=2,710), who had been treated for psychiatric disorders in a hospital during the follow-up period between 1994 and 2005 (aged 12-13 to 24-25 years). Summary of results in study IV.

Table 5  Overlapping between diagnostic groups among subjects with psychiatric hospital treatment.

<table>
<thead>
<tr>
<th></th>
<th>Psychosis</th>
<th>Mood</th>
<th>Anxiety</th>
<th>Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%a</td>
<td>%a</td>
<td>%a</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td>40</td>
<td>-</td>
<td>30.0</td>
<td>7.5</td>
</tr>
<tr>
<td>Mood disorders, non-psychotic</td>
<td>40</td>
<td>30.0</td>
<td>-</td>
<td>12.5</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>37</td>
<td>8.1</td>
<td>13.5</td>
<td>-</td>
</tr>
<tr>
<td>Substance-related disorders</td>
<td>48</td>
<td>16.7</td>
<td>16.7</td>
<td>4.2</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td>22</td>
<td>-</td>
<td>40.9</td>
<td>18.2</td>
</tr>
<tr>
<td>Mood disorders, non-psychotic</td>
<td>50</td>
<td>18.0</td>
<td>-</td>
<td>8.0</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>14</td>
<td>28.6</td>
<td>28.6</td>
<td>-</td>
</tr>
<tr>
<td>Substance-related disorders</td>
<td>24</td>
<td>16.7</td>
<td>37.5</td>
<td>12.5</td>
</tr>
</tbody>
</table>

*a Percentage (No.) of the subjects in the rows who had also been discharged for a disorder in the columns
5.3 CHILDHOOD PREDICTORS OF PSYCHOTROPIC MEDICATION USE AND PSYCHIATRIC HOSPITAL TREATMENT (AIMS 3-5; STUDIES II-V)

Box 3  The main findings of childhood predictors of psychotropic medication use and psychiatric hospital treatment.

- Both externalizing and internalizing problems, and reports by both parents and teachers and by the children themselves predicted a wide range of outcomes (studies II-V). When the linear psychopathology scales were studied in univariate analyses, 88% of the tested psychopathology variables among males and 61% among females was associated with the studied outcomes.

- Some predictive associations were very similar in both sexes.
  - Self-reported depressive symptoms at age eight predicted hospital treatment of mood disorders (study IV) and antidepressant use (study III) in both sexes.
  - The combination of externalizing and internalizing problems at age eight was associated with the highest risk of later psychiatric hospital treatment in both sexes (study IV).
  - Living in a family with other than two biological parents predicted almost all studied outcomes in both sexes (studies II-IV).

- Some predictive associations were different among males and females.
  - Externalizing problems predicted a wide range of outcomes especially among males (studies II-V). Also when adjusted for other psychiatric symptoms, conduct problems among males predicted independently several outcomes. Among females, conduct problems predicted independently hospital treatment of substance-related disorders.
  - Internalizing problems predicted many outcomes, especially among females (studies II-V). The self-reported depressive scale predicted independently hospital treatment of mood disorders and antidepressant use in both sexes, but among females, in addition a wider spectrum of outcomes, namely, PHT and antipsychotic use.
  - Being a frequent bully or a frequent bully-victim at age eight was more common among males than females and predicted several outcomes among males (study V).
  - Being a frequent victim of bullying behavior at age eight predicted a wide range of outcomes among females, even when the psychopathology scores at age eight were taken into account (study V). Among males, being a frequent victim modestly predicted some outcomes, but the associations did not remain statistically significant when psychopathology at age eight was adjusted for.

5.3.1 PREDICTORS OF ANTIPSYCHOTIC USE (AIM 3; STUDY II)

When the sex-interactions of the childhood variables on the outcome, antipsychotic use, were studied, the CDI showed a statistically significant interaction both as a linear variable (p=0.01) and as a categorical variable (p=0.03). Thus, the childhood predictors were reported separately for males and females.
Living in a family with other than two biological parents predicted antipsychotic use among both males and females. Parental education level did not predict antipsychotic use among either males or females. The results for family characteristics as predictors of antipsychotic use and other outcomes in the thesis are summarized in Table 8. Figure 5 shows the results from the univariate analysis of categorical childhood predictors and later antipsychotic use. The same associations remained statistically significant when the psychopathology variables were analyzed as linear variables (Table 8). Among males, antipsychotic use was predicted by conduct, hyperactivity and emotional problems. Among females, the outcome was predicted by emotional and self-reported depressive symptoms.

In multivariate analyses, the two family variables and the four categorical psychopathology scales were included in the model. Among males, family structure and conduct problems at age eight independently predicted use of antipsychotics. Among females, family structure, a high level of parent- and teacher-reported emotional and self-reported depressive symptoms independently predicted antipsychotic use. The results of the multivariate models of antipsychotic use and other outcomes in the thesis are summarized in Figure 12.

5.3.2 PREDICTORS OF ANTIDEPRESSANT USE (AIM 3; STUDY III)
The sex interactions between childhood psychopathology scales and antidepressant use were studied. Significant sex interactions were found for the conduct X sex interaction (p=0.03 for the categorical variable; p=0.004 for the linear variable) and the hyperactivity X sex interaction (p=0.003; p=0.004). Thus, analyses were done separately for the sexes.

Living in a family with other than two biological parents predicted antidepressant use among both males and females. Parental education level did not predict antidepressant use among either males or females. The results for family characteristics as predictors of antidepressant use and other outcomes in the thesis are summarized in Table 8. In Figure 6, the association between categorical psychopathology variables and antidepressant use is shown; family structure was included as a covariate in the analyses. It is shown that, among both males and females, the emotional and self-reported depressive scales predicted antidepressant use. The conduct and hyperactivity scales predicted the outcome among males, but not among females. Among males, the highest risk was associated with conduct problems, as 17.5% of the screen-positive males had used antidepressants, while 8.4% of the screen-negative group had done so. Among females, the self-reported depressive scale had the strongest predictive association with later antidepressant use (20.4% vs. 13.0%). The results for linear psychopathology variables as predictors of
**Results**

**Figure 5**  Associations between categorical psychopathology variables at age 8 and antipsychotic use between age 12 and 25. Hazard ratios (HR) and 95% confidence intervals (CI) are based on univariate Cox regression analysis. The association is significant at $p<0.05$ if the 95%CI of the HR does not include 1 (the dotted line). Summary of Table 2 in study II. A, the conduct scale; B, the hyperactivity scale; C, the emotional scale; D, the self-reported depression scale, i.e. the Children’s Depression Inventory (CDI).

Antidepressant use and other outcomes in the thesis are summarized in Table 8.

In the final multivariate models, the family and standardized linear psychopathology variables that were associated with antidepressant use in the univariate analysis were included in the model. In both sexes, family
structure, the emotional scale and the self-reported depressive scale independently predicted antidepressant use. Among males, the conduct scale predicted the outcome. The results of various multivariate models of antidepressant use and other outcomes in the thesis are summarized in Figure 12.

**Figure 6**  Associations between categorical psychopathology variables at age 8 and antidepressant use between age 12 and 25. Hazard ratios (HR) and 95% confidence intervals (CI) are based on Cox regression analysis when family structure was used a covariate. The association is significant at p<0.05 if the 95%CI of the HR does not include 1 (the dotted line). Summary of figures A-C and text in the results section in study III. A, the conduct scale; B, the hyperactivity scale; C, the emotional scale; D, the self-reported depression scale, i.e. the Children’s Depression Inventory (CDI).
5.3.2.1 Predictors of antidepressant costs (Aim 4; study III)

Table 6 shows descriptive information on lifetime antidepressant costs stratified by predictors at the age of eight. First, the ratio of mean costs between screen-positive and screen-negative subjects ranges between 1.2 (the hyperactivity scale) and 2.0 (the conduct scale). Females had 1.5 times higher lifetime antidepressant costs than males. In summary, these ratios are similar to the hazard ratios found in the Cox regression analysis of antidepressant use (binary outcome; Figure 6). Second, Table 6 shows that the mean costs equal costs between the 90th and 94th percentiles, indicating a highly right-skewed distribution of antidepressant cost. The skewness of the costs in the total sample (n=5,525) is further described in Figure 7A. Even among subjects with antidepressant purchases (n=623), the costs were right-skewed (Figure 7B).

To test whether the lifetime antidepressant costs (linear variable) could be predicted by variables at age eight, when predictors of antidepressant use (binary variable) are taken into account, Heckman selection models were fitted. The outcome was lifetime antidepressant use (binary variable) in the selection equation, and lifetime antidepressant costs (linear variable) in the outcome equation. As suggested for health care cost data (45), a logarithmic transformation of the lifetime costs was done (Figure 7C). In the outcome equations of the models, exclusion restrictions were applied, i.e. the hyperactivity and emotional scales were excluded from the outcome equations to improve the models (see section 4.5.3.2 for a more detailed rationale for exclusion restrictions). Both a two-step selection model and a maximum likelihood model were fitted to the data. The parameters of the models appeared well chosen, because the estimates from the two-step and maximum likelihood models did not vary dramatically and there were only seven iterations in the maximum likelihood model (under the recommended maximum of 15 iterations (230)).

The main results of the maximum likelihood (ML) model are shown in Table 7. In the selection equation of the ML model, the conduct, emotional and self-reported depressive scales and sex predicted antidepressant use, and the standard errors (SE) were small. Table 7 shows that the SE:s in the outcome equation are much higher than the SE:s in the selection equation. The conduct scale was inversely associated with antidepressant costs, when the effect of having any antidepressant use was taken into account. However, the latter result should be interpreted with caution, because the standard errors were large, the level of censoring was high (4,444 censored of 5,022), and the two-step model did not reach statistical significance (estimate -0.41, SE 0.35, p=0.24).
Table 6  Descriptive information about the lifetime antidepressant costs in the sample.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Lifetime antidepressant costs (euro)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Total sample (n=5,525)</td>
<td>60</td>
</tr>
<tr>
<td>Conduct scale at age 8</td>
<td></td>
</tr>
<tr>
<td>Screen negative (n=4,636)</td>
<td>55</td>
</tr>
<tr>
<td>Screen positive (n=594)</td>
<td>112</td>
</tr>
<tr>
<td>Hyperactivity scale at age 8</td>
<td></td>
</tr>
<tr>
<td>Screen negative (n=4,601)</td>
<td>60</td>
</tr>
<tr>
<td>Screen positive (n=516)</td>
<td>71</td>
</tr>
<tr>
<td>Emotional scale at age 8</td>
<td></td>
</tr>
<tr>
<td>Screen negative (n=4,557)</td>
<td>58</td>
</tr>
<tr>
<td>Screen positive (n=573)</td>
<td>88</td>
</tr>
<tr>
<td>Self-reported depressive scale at age 8</td>
<td></td>
</tr>
<tr>
<td>Screen negative (n=4,636)</td>
<td>55</td>
</tr>
<tr>
<td>Screen positive (n=594)</td>
<td>99</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Males (n=2,834)</td>
<td>48</td>
</tr>
<tr>
<td>Females (n=2,691)</td>
<td>74</td>
</tr>
</tbody>
</table>

Note: Screen negative and positive refers to screening under and above, respectively, the cutoff score at the sex-specific 90\(^{\text{th}}\) percentile on the studied psychopathology scales at the age of 8.

\(^{a}\) The costs are adjusted for inflation and correspond to year 2005 euros.

Table 7  Regression coefficients of the Heckman selection model, which uses maximum likelihood estimation (summary of the maximum likelihood selection model in Table 3 in study III; n=5,022).

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Probit selection equation (antidepressant use yes/no)</th>
<th>Outcome equation (antidepressant costs(^a))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
</tr>
<tr>
<td>Conduct(^c)</td>
<td>0.25</td>
<td>0.07</td>
</tr>
<tr>
<td>Hyperactivity(^d)</td>
<td>-0.04</td>
<td>0.07</td>
</tr>
<tr>
<td>Emotional(^e)</td>
<td>0.15</td>
<td>0.06</td>
</tr>
<tr>
<td>CDI(^f)</td>
<td>0.27</td>
<td>0.07</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>-0.24</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Abbreviations: CDI, Children’s Depression Inventory; SE, standard error

\(^a\) The natural logarithm if the lifetime antidepressant costs on an individual level. The costs are adjusted for inflation and correspond to year 2005 euros.

\(^b\) Bold face indicates a statistically significant association at \(p<0.05\).

\(^c\) The psychopathology scales were dichotomized at the sex-specific 90\(^{\text{th}}\) percentile cutoff point.

\(^d\) Exclusion restrictions are applied to the hyperkinetic and emotional scales in the outcome equation.
Results

A. All subjects (n=5,525)

B. Close-up of subjects with purchases (n=623)
5.3.3 PREDICTORS OF PSYCHIATRIC HOSPITAL TREATMENT (AIM 3; STUDY IV)

In both sexes, living in a family with other than two biological parents predicted hospital treatment of any psychiatric diagnosis. Low parental education level predicted hospital treatment of any psychiatric diagnosis in both sexes. The results for family characteristics as predictors of PHT and other outcomes in the thesis are summarized in Table 9.

To study the impact of possible psychiatric caseness at age eight, the screening status on the parent and/or teacher report of the total score was studied with regard to later PHT. The sensitivity of screening positive at age eight on later PHT was 51.5% among males (n=84/163 with childhood data), while the positive predictive value (PPV) was 10.7% (HR 2.6; 95%CI 1.9-3.5; p<0.001). The corresponding sensitivity and PPV among females were 27.1% (n=29/107) and 9.0%, respectively (HR 2.7; 95%CI 1.8-4.1; p<0.001).
Results

Figure 8  Cumulative incidences (A, males; B, females) and hazard ratios (HR; C, males; D, females) of psychiatric hospital treatment between age 12 and 25 by psychopathology groups at age 8. The cumulative incidences and their 95% confidence intervals (CI) are calculated using survival analysis. HR:s and 95% and their CI:s are based on univariate Cox regression analysis. The association is significant at p<0.05 if the 95%CI of the HR does not include 1 (the dotted line). Abbreviations: Cond-Emot, conduct-emotional; Cond-only, conduct-only; Attent, attention/hyperactivity; Emot-only, emotional-only; Invis, invisible; Ref, reference.
In both sexes, the categorical conduct, emotional and self-reported depressive scales predicted psychiatric hospital treatment of any psychiatric diagnosis. Among males, the categorical hyperactivity scale also predicted hospital treatment of any psychiatric diagnosis. When the four psychopathology scales were analyzed as linear variables, all scales predicted PHT in both sexes, as summarized in Table 8.

In multivariate analyses, the two family variables and the four categorical psychopathology scales were included in the models. Among males, family structure, parent- and teacher-reported conduct and emotional problems independently predicted PHT. Among females, only the self-reported depressive scale independently predicted PHT. The results regarding the psychopathology variables in the multivariate models of PHT and other outcomes in the thesis are summarized in Figure 12.

In a person-centered approach, the conduct, hyperactivity, emotional and self-reported depressive psychopathology scales were combined to disentangle the predictive value of pure versus comorbid problems and of parent- and teacher-reports versus self-reports. Figures 8A and 8B show the cumulative incidences and Figures 8C and 8D show the hazard ratios of PHT among the studied groups. In both sexes, the strongest predictive association for PHT was found for the comorbid conduct-emotional groups: the cumulative incidence of PHT was 21.1% among males, and 11.4% among females belonging to this group, while it was 3.9% and 3.2%, respectively, among the reference groups of males and females. Among males, also the conduct-only group, the attention-hyperactivity group, and the emotional group predicted PHT. In an additional analysis, when the effects of the interactions between the psychopathology types, family structure, and parental education level were analyzed on the main outcome PHT, no significant interactions were found.

5.3.3.1 Hospital treatment of specific diagnostic groups (Aim 3; study IV)

In both sexes, living in a family with other than two biological parents predicted hospital treatment of substance-related disorders. Among males, living in a family with other than two biological parents also predicted treatment of psychotic and mood disorders. The results for family characteristics as predictors of hospital treatment of a specific diagnostic group are summarized in Table 8.

Figure 9 shows the hazard ratios of being treated for psychotic disorders (including both affective and non-affective psychoses) when the linear psychopathology scales at age eight were used as predictors. Among the 40 males who had been treated for psychotic disorders, 32.5% scored above the sex-specific 90th percentile on the categorical conduct scale at age eight, 28.2% on the emotional scale, and 22.5% on the hyperactivity scale. Among
**Results**

**Figure 9**  Associations between linear psychopathology variables at age 8 and treatment of psychotic disorders between age 12 and 25. Hazard ratios (HR) and 95% confidence intervals (CI) are based on univariate Cox regression analysis and represent one standard deviation change. The association is significant at $p<0.05$ if the 95%CI of the HR does not include 1 (the dotted line). A, the conduct scale; B, the hyperactivity scale; C, the emotional scale; D, the self-reported depression scale, i.e. the Children’s Depression Inventory (CDI).

The 22 females who had been treated for psychotic disorders, 27.3% scored above the 90th percentile on the categorical emotional scale. In sex-stratified multivariate models including the two family variables and the four linear psychopathology scales, the conduct scale independently predicted treatment of psychotic disorders among males.
The results from univariate analyses of other specific diagnostic groups are summarized in Table 8. The multivariate models of specific diagnostic groups included the two family variables and the four linear psychopathology scales as predictors. In both sexes, treatment of mood disorders was independently predicted by the emotional scale and the self-reported depressive scale. Among males, treatment of anxiety disorders was independently predicted by the emotional scale. In both sexes, treatment of substance-related disorders was independently predicted by non-intact family structure and the conduct scale. The results regarding the psychopathology variables in the multivariate models of hospital treatment of psychotic, mood, anxiety, and substance-related disorders and other outcomes in the thesis are summarized in Figure 12.

![Graph showing prevalence of frequent bully-victim, frequent bully, and frequent victim statuses at age 8 among females and males.]

**Figure 10** The prevalence of frequent bully-victim, frequent bully, and frequent victim statuses at age 8 among females and males.

### 5.3.4 BULLYING AND VICTIMIZATION AS PREDICTORS OF LATER PSYCHIATRIC TREATMENT (AIM 5; STUDY V)

As shown in Figure 10, 6.4%, 6.0% and 2.8% of the males were classified as frequent victims (but not bullies), frequent bullies (but not victims), and frequent bully-victims, respectively. Among females, 3.6% were classified as frequent victims, while only 0.6% and 0.2% were classified as frequent bullies and frequent bully-victims, respectively (Figure 10).

In Figure 11, the univariate hazard ratios and 95% confidence intervals are shown for having psychotropic medication use and/or psychiatric hospital
Results

Figure 11  Associations between frequent bully-victim (A), frequent bully (B) and frequent victim (C) statuses at age 8 and having psychotropic medication use and/or psychiatric hospital treatment between age 12 and 25. Hazard ratios (HR) and 95% confidence intervals (CI) are based on univariate Cox regression analysis. Children without frequent bullying or victimization were used as reference in the analyses. The association is significant at p<0.05 if the 95%CI of the HR does not include 1 (the dotted line). Summary of the figure in study V.

Treatment during the follow-up. Among males, the outcome was predicted in the univariate analyses by frequent bully-victim status (HR 3.8), frequent bully status (HR 1.6), and frequent victim status (HR 1.6) at age eight, when compared to males who were neither frequent bullies nor victims at age eight. When the total psychopathology score from the parent and teacher
reports was included as a covariate in the analysis, none of the bully or victim statuses predicted the outcome at a statistically significant level among males (p<0.05). Among females, the outcome in the univariate analyses was predicted by frequent bully status (HR 2.6) and frequent victim status (HR 2.2) at age eight (Figure 11). Frequent victim status predicted the outcome even after adjustment with the total psychopathology score (HR 1.7, 95%CI 1.1-2.5).

The univariate results of frequent victim, frequent bully and frequent bully-victim status predicting antipsychotic, antidepressant, and hospital treatment of any psychiatric disorder are summarized in Table 8 (specific diagnoses were not analyzed due to the small number of subjects). When the total psychopathology score was included as a covariate in the analyses, no statistically significant associations could be found for antipsychotic use, antidepressant use, or PHT, among males. Among females, frequent victim status predicted antipsychotic use, antidepressant use, and PHT, when the total psychopathology score was included as a covariate in the analyses.

5.3.5 SUMMARY OF UNIVARIATE RESULTS (AIMS 3 AND 5; STUDIES II-V)

A summary of the univariate results of the family variables, the linear psychopathology scales, and the bullying and victim groups predicting antipsychotic use, antidepressant use, and hospital treatment of any psychiatric disorder, psychotic disorders, mood disorders, anxiety disorders and substance-related disorders are shown in Table 8. Altogether 99 analyses are described in Table 8, and of these, 49 associations (49.5%) reached a significance level lower than 0.05.

Non-intact family structure predicted all outcomes in both sexes, except anxiety disorders in both sexes and psychotic disorders and mood disorders among females (Table 8). With regard to psychopathology scales, there were 28 analyses per sex. Among males, 85.7% (n=24) of the tested psychopathology scales were statistically significantly associated with the studied outcomes, while the corresponding figure among females was 60.7% (n=17). Most notably, among males, the conduct scale predicted all outcomes. Also the hyperactivity scale predicted all outcomes, except mood disorders, among males. Among males, frequent bully-victim status predicted antipsychotic use, antidepressant use, and PHT, while frequent-bully status predicted antidepressant use (specific diagnostic groups of PHT were not analyzed). Among females, the self-reported depressive scale predicted all outcomes, except hospital treatment of psychotic and substance-related disorders. Also the emotional scale predicted all outcomes, except treatment of anxiety and substance-related disorders, among females. Among females, frequent victim status predicted antipsychotic use, antidepressant use, and PHT, while frequent bully-victim and frequent bully
status did not predict these outcomes or were not analyzed due to the small number of subjects in these groups.

**Table 8** Summary of results from univariate Cox regression analyses.

<table>
<thead>
<tr>
<th>Variable at age 8</th>
<th>Antipsychotic use</th>
<th>Antidepressant use</th>
<th>Psychiatric hospital treatment</th>
<th>Psychotic disorders*</th>
<th>Mood disorders*</th>
<th>Anxiety disorders*</th>
<th>Substance-related disorders*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family characteristics (categorical)</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>Non-intact family structure*</td>
<td>3.0***</td>
<td>2.4**</td>
<td>1.8***</td>
<td>1.6***</td>
<td>2.7***</td>
<td>1.8**</td>
<td>2.9**</td>
</tr>
<tr>
<td>Lower parental education level*</td>
<td>1.1</td>
<td>0.9</td>
<td>1.0</td>
<td>1.1</td>
<td>1.4*</td>
<td>1.6*</td>
<td>0.8</td>
</tr>
<tr>
<td>Psychopathology scales (linear)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conduct</td>
<td>1.6***</td>
<td>1.2</td>
<td>1.5***</td>
<td>1.2**</td>
<td>1.6***</td>
<td>1.2**</td>
<td>1.7***</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>1.4***</td>
<td>1.0</td>
<td>1.4***</td>
<td>1.0</td>
<td>1.5***</td>
<td>1.2**</td>
<td>1.5**</td>
</tr>
<tr>
<td>Emotional</td>
<td>1.6***</td>
<td>1.3*</td>
<td>1.3**</td>
<td>1.4***</td>
<td>1.5**</td>
<td>1.3**</td>
<td>1.5**</td>
</tr>
<tr>
<td>Self-reported depressive scale</td>
<td>1.0</td>
<td>1.6***</td>
<td>1.3***</td>
<td>1.3**</td>
<td>1.4***</td>
<td>1.4**</td>
<td>1.1</td>
</tr>
<tr>
<td>Bullying behavior (categorical)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent victim</td>
<td>1.0</td>
<td>4.3***</td>
<td>1.5</td>
<td>2.0**</td>
<td>1.9**</td>
<td>3.6***</td>
<td>-</td>
</tr>
<tr>
<td>Frequent bully</td>
<td>1.8</td>
<td>-</td>
<td>1.9**</td>
<td>2.4</td>
<td>1.6</td>
<td>1.8</td>
<td>-</td>
</tr>
<tr>
<td>Frequent bully-victim</td>
<td>2.9*</td>
<td>-</td>
<td>2.8***</td>
<td>1.2</td>
<td>3.3***</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: Bold face indicates statistically significant association at p<0.05.
+ Abbreviations: HR, hazard ratio; M, Males; F, Females; CDI, Children's Depression Inventory; -, not analyzed due to small number of subjects.
* p<0.05; ** p<0.01; *** p<0.001
* Family structure including two biological parents versus other family structure.
* Parental education level lower than upper secondary school versus higher.
* HR given for one standard deviation change of all outcomes, except of antidepressant use, where one score on the standardized scales defined the HR. See text for details.
+ Children who were not frequent bullies and frequent victims were used as reference.
+ Disorders treated in hospitals. Subjects without any psychiatric hospital treatment were used as a reference group.

**5.3.6 SUMMARY OF MULTIVARIATE RESULTS OF PSYCHOPATHOLOGY VARIABLES (AIM 3; STUDIES II-IV)**

Figure 12 presents a summary of the independent associations of the psychopathology variables in predicting various outcomes.

Definition of the models: The multivariate models did not include the same variables in studies II, III, and IV. Therefore, to compare the results, the multivariate models were re-analyzed including the same predictor variables in each model. The multivariate models in Figures 12A and 12B include family structure, parental education level, and the four linear psychopathology scales. The multivariate models in Figures 12C and 12D include family structure, parental education level, and the four categorical
Figure 12  Summary of Cox regression multivariate models. Each outcome was studied in a separate model. Multivariate models in A (males) and B (females) included the two family variables and the four linear psychopathology scales. Multivariate models in C (males) and D (females) included the two family variables and the four categorical psychopathology scales. Arrows indicate independent associations of psychopathology variables (associations of the family variables are not shown).
Results

psychopathology scales. For descriptive purposes, the predictors are classified into variables that are mainly related to externalizing problems (black) or internalizing problems (light gray). The outcomes are depicted according to the childhood variables that are statistically associated: associated with externalizing problems (black), internalizing problems (light gray), or both externalizing and internalizing problems (medium gray).

Results: The conduct scales independently predicted several outcomes among males (Figure 12A and 12C), but very few outcomes among females (Figure 12B and 12D). The emotional and self-reported depressive scale independently predicted mainly internalizing or mixed outcomes among both males (Figure 12A and 12C) and females (Figure 12B and 12D), but some differences were found: the self-reported depressive scale independently predicted antipsychotic use among females (Figure 12B and 12D), but not among males (Figure 12A and 12C). The hyperactivity scale did not predict any of the studied outcomes independently in the multivariate analyses among males (Figure 12A and 12C), though the hyperactive scale predicted a wide range of outcomes in the univariate analyses (Table 8).

Some methodological issues can also be seen. Since the number of subjects with each outcome differs, it is seen that the associations more easily reach a significant level if a large number of subjects are affected by the outcome. This is most obvious with the independent association seen for antidepressant use (230 males and 335 females) versus hospital treatment of mood disorders (37 males and 46 females): several highly significant associations are found for antidepressant use, whereas few associations are seen for treatment of mood disorders, though both outcomes deal with theoretically similar problems. It is also of note that the models including linear psychopathology scales (Figure 12A and 12B) show more statistically significant associations than the models including categorical psychopathology scales (Figure 12C and 12D).
6 DISCUSSION

6.1 USE OF PSYCHOTROPIC MEDICATION (AIMS 1 AND 2; STUDIES I AND II)

6.1.1 CUMULATIVE INCIDENCE BY AGE 25 (AIM 1; STUDY I)
The cumulative incidence of psychotropic medication use by age 25 was reported in this thesis, while most previous studies have reported one-year prevalence of psychotropic medication use. Therefore, the comparing of medication use in other studies is difficult. The cumulative incidence of any psychotropic medication use was 15% by age 25 in this study, while the one-year prevalence of any psychotropic medication use in another Finnish register-based study was some 3% in the total age group 0-27 years in 2007 (25). Antidepressants were used by 12% of the sample by age 25 in this study, which corresponds to another recently published Finnish register-based study of the total population (24). The one-year prevalence of antidepressant use in Finland was reported to be 5% among males and 8% among females aged 21-26 years in 2007 (25).

In some previous studies of psychiatric disorders, lifetime prevalence or cumulative incidences have been reported. In a cross-sectional Finnish study from 2003-2005, which used diagnostic interviews and case records of psychiatric treatment, the lifetime prevalence of any axis I psychiatric disorder (i.e. personality disorders not included) was 40% among 19- to 35-year-olds (224). Among those with a lifetime axis I disorder, according to self-reports, 50% had been treated for mental health disorders at some point in the above-mentioned Finnish study (224). Hence, approximately 20% had been treated for mental disorders by age 35 in Finland (224). However, it is of note that in cohort studies which have used diagnostic assessment continuously throughout childhood, adolescence and young adulthood, the lifetime prevalence of disorders is doubled when compared to studies relying on retrospective measures and self-reports (157). For example, the lifetime prevalence of any mental disorder was 83% by age 21 in the Great Smoky Mountain study (61). In sum, there are great variations in design (retrospective/prospective) and in assessment of mental health treatment or psychotropic medication use. Therefore, no conclusions concerning how many with medication use actually had a diagnosable disorder, or how many with a lifetime disorder have used psychotropic medication can be drawn.
6.1.2 POLYPHARMACY USE (AIM 1; STUDY I)
A total of 4% of the cohort had purchased two medications from different medication classes during the same day, which indicates polypharmacy use. Among youths who had psychotropic medication use, the proportion of polypharmacy use was 15% by the age of 20, and increased to 27% by the age of 25.

The most common combination was the antidepressant-benzodiazepine combination, which had been used by 3% of the study population. Every fourth subject who had used antidepressants had used benzodiazepines concomitantly. Vice versa, the majority of the subjects who had used benzodiazepines had used them concomitantly with antidepressants. This common combination may be explained by the fact that mood and anxiety disorders are very often comorbid (128). It is also stated in treatment guidelines that benzodiazepines may be used in the acute phase of depression (19), and as a secondary treatment option after antidepressants in anxiety disorders (103). A preliminary observation from the TORDIA-study (the Treatment of SSRI-resistant Depression in Adolescents study) is that self-harm behavior is more common among adolescents with treatment-resistant depression who are prescribed both antidepressants and benzodiazepines than among corresponding adolescents with antidepressants as monotherapy (39). Therefore, patients with this medication combination should be carefully followed up.

Two out of three subjects, who had used antipsychotics, had used them together with antidepressants at some point. This combination has in previous studies been used in, e.g. psychotic depression, the treatment of comorbid depression and borderline personality disorder (245); fluoxetine-olanzapine has been used in bipolar depression (226), antidepressants to reduce negative symptoms in schizophrenia (246), and to promote sleep in depression (242).

6.1.3 TIMING OF THE FIRST PRESCRIPTION (AIM 1; STUDY I)
Psychotropic medication use remained low before the age of 15, but increased substantially in late adolescence and young adulthood. There are several possible explanations for the increased medication use in late adolescence.

1) Previous studies have shown that help-seeking because of psychiatric disorders is more common in late adolescence than in early adolescence (99, 129). Help-seeking, again, in late adolescence may be common for a variety of reasons. Many life stressors, such as starting to work or study and moving away from home, co-occur with increased help-seeking in late adolescence. Furthermore, some psychiatric disorders, e.g. psychotic and substance-related disorders, typically have their onset in late adolescence (179). However, the increase in depression incidence occurs already in early adolescence (127,
It is also worth noting that only a minority of adolescents with psychiatric problems use mental health services (99, 129, 213, 219).

2) The indication of many psychotropic medications is only for the treatment of persons over 18 years of age. Therefore, it is possible that physicians prefer not to prescribe psychotropic medications for adolescents younger than 18 years old.

3) Physicians might consider that the effectiveness of psychotropic medication is not as effective among adolescents as it is among young adults. Therefore, physicians might prescribe psychotropic medications for adolescents more seldom than for young adults.

4) The peak of medication use incidence in late adolescence can possibly be explained by the mental health service system for adolescents versus adults. In another Finnish register-based study, among adolescents younger than 15 years, mainly specialized physicians (e.g. child and adolescent psychiatrists) prescribed antidepressants, while among older adolescents and young adults mainly non-specialized physicians prescribed antidepressants (24). On the basis of this background and the results in this thesis, it can be hypothesized that if a psychotropic medication is prescribed for a child or an adolescent, it is prescribed in some of the relatively few specialized units. On the other hand, if a psychotropic medication is prescribed for a young adult, it is prescribed in practically any service unit, e.g. health centers, occupational health centers, and private clinics. Further studies are needed to obtain more detailed information about pharmacological and non-pharmacological treatment patterns of psychiatric disorders among adolescents versus young adults.

6.1.4 PSYCHIATRIC HOSPITAL TREATMENT AMONG ANTIPSYCHOTIC USERS (AIM 2; STUDY II)

Hospital treatment of psychiatric disorders is mostly used for severe disorders (37). Among antipsychotic users, three out of four had been treated in a hospital for a psychiatric disorder; every third had been treated for a non-affective psychotic disorder. Therefore, the results in this thesis indicate that antipsychotics are mostly prescribed for youth with severe psychiatric disorders in Finland. Similar results are found from a population-based study of 19-35-year-olds in Canada: 42% of antipsychotic users aged 19 to 35 years had a schizophrenia diagnosis in 2006 (4). However, studies from some other countries have shown different patterns. Only one tenth of antipsychotic prescriptions by general practitioners were prescribed for non-affective psychoses in a study of 10-99-year-olds in the UK (121). A study from the USA including all age groups reported that among antipsychotic users, 19% had schizophrenia, 22% had an affective disorder, and 19% had an anxiety disorder according to self-reports in 2004-2005 (77). Studies of children and adolescents in the USA indicate that antipsychotics are mostly
prescribed for behavioral and affective disorders, while approximately every seventh antipsychotic prescription is for psychotic disorders \((59,170)\).

The psychiatric diagnostic groups of hospital treatment differed among males and females with antipsychotic use. Among males with antipsychotic use, almost every second had been treated for a non-affective psychotic disorder, while one out of eight had been treated for an affective disorder. Among females with antipsychotic use, almost every second had been treated for affective disorders, while one out of four had been treated for non-affective psychotic disorders. One explanation for this sex difference is that many non-affective psychoses are more common \((181)\) and start earlier \((240)\) among males, while affective disorders are more common among females \((74)\). That is to say, the distribution of psychiatric disorders among males and females might explain the sex difference.

### 6.2 CHILDHOOD PREDICTORS OF PSYCHIATRIC TREATMENT BY YOUNG ADULTHOOD (AIMS 3-5; STUDIES II-V)

First, the predictors of each outcome are discussed. Second, the outcomes of each predictor are discussed from a broader perspective.

#### 6.2.1 PREDICTORS OF VARIOUS OUTCOMES (AIMS 3-5; STUDIES II-V)

#### 6.2.1.1 Predictors of antipsychotic use (Aims 3 and 5; studies II and V)

Externalizing problems, such as conduct and hyperactivity behaviors, at age eight predicted antipsychotic use among males. Among males who screened positive on the conduct scale at age eight, eight percent had used antipsychotics at follow-up, while only two percent of the screen-negative males had used antipsychotics. This is in line with prior studies that have shown that conduct problems predict psychotic disorders and several other psychiatric disorders \((132)\). Some studies have reported that the association between childhood externalizing behavior and adult psychotic disorder is stronger among males than females \((78,174)\).

Internalizing problems, such as anxiety and depressive symptoms, at age eight predicted later antipsychotic use among females. Females who screened positive on the self-reported depression scale had used antipsychotics three times more often than screen-negative subjects, while males’ reports of depressive symptoms did not predict the outcome. The sex interaction might partly be explained by the fact that antipsychotic medications were often prescribed for affective disorders, which are more common among females.
Furthermore, previous studies have shown that schizophreniform disorders in adulthood are associated with childhood internalizing disorders \(^{132}\). Some studies suggest that childhood internalizing problems especially among females are associated with psychotic disorders in adulthood \(^{78, 174}\). That is to say, different predictors of psychotic disorders among males versus females might also partly explain the sex interaction.

Frequent bully-victim status predicted antipsychotic use among males, but the association did not remain statistically significant when adjusted with psychopathology scores. This indicates that antipsychotic use among males who are frequent bully-victims at age eight also have other types of externalizing problems, as described above. However, among females, frequent victim status predicted antipsychotic use also when adjusting for psychopathology scores at age eight (findings discussed in more detail in section 6.2.2.5).

Living in a family with other than two biological parents was strongly associated with later antipsychotic use in both sexes (study II). This association may be explained by other risk factors, such as parental history of psychiatric disorder, family discord, child neglect and abuse \(^{244}\), which are associated with living with other than two biological parents.

### 6.2.1.2 Predictors of antidepressant use (Aims 3 and 5; studies III and V)

Externalizing problems at age eight predicted antidepressant use among males, but the association was weak among females. In fact, the interaction between conduct problems and sex was significantly associated with antidepressant use. Previous studies have shown that childhood conduct problems predict adult antisocial personality disorder \(^{167}\), but also adult internalizing problems, such as mood disorders and anxiety \(^{86, 132, 167}\). However, some studies have found an association between childhood externalizing problems and adult internalizing problems only among males \(^{2, 76, 244}\), while other studies have not found any sex differences \(^{55, 86, 132, 194}\). The results in this thesis add to the literature by showing that childhood conduct problems predict later antidepressant use differently among males and females.

Internalizing problems, measured by the self-reported depressive scale and the parent- and teacher-reported emotional scale, predicted antidepressant use in both sexes. This is in line with previous studies, which have reported a strong association between childhood emotional problems and similar adult problems \(^{155, 132}\). A novel finding is that after adjusting for other psychopathology scores and other informant sources, the association between self-reports of depressive symptoms already at age eight and later antidepressant use remained significant. This result emphasizes the use of self-reports of depressive symptoms in middle childhood.
Both frequent bully-only and frequent bully-victim status predicted antidepressant use among males (study V). However, when adjusted with psychopathology scores, the association did not remain statistically significant. Among females, frequent victim status predicted antidepressant use in unadjusted and adjusted analyses of psychopathology scores at age eight (findings discussed in more detail in section 6.2.2.5).

As in the study of predictors of antipsychotic use, living in a family with other than two biological parents at age eight independently predicted later antidepressant use.

6.2.1.3 Predictors of antidepressant costs (Aim 4; study III)

In this thesis, predictors at age eight of any lifetime antidepressant use (yes/no) were first studied. Then, when predictors of any antidepressant use were taken into account, lifetime antidepressant costs were studied. That is, predictors of both any antidepressant use and antidepressant costs were included in the same selection model. The major advantage of the selection model is that it can be tested whether the predictors of antidepressant costs are different than the predictors of any antidepressant use.

Little evidence of predictors of antidepressant costs was found, when predictors of antidepressant use were taken into account. The only statistically significant result in the maximum likelihood (ML) outcome equation of lifetime antidepressant costs was that conduct problems at age eight were inversely associated with higher costs, when antidepressant use was taken into account. As noted above, young males with a history of childhood conduct problems are prescribed an antidepressant by age 25 almost twice as often compared to males without childhood conduct problems. Conversely, once prescribed, the long-term costs might be lower due to early discontinuation of the antidepressant. Possible explanations for why males with a history of childhood conduct problems might discontinue antidepressant medication include, e.g. inappropriately assessed clinical diagnosis, unresponsiveness to the medication, and proneness to impulsivity.

Nonetheless, the result that the conduct scale was inversely associated with antidepressant costs in the ML selection model should be interpreted with caution. First, though the finding was statistically significant, the standard errors in the outcome equation were large, indicating uncertainty. Second, the association was statistically significant in the final ML model, but not in the preliminary two-step model, although the estimates and standard errors were otherwise similar in the two models. Third, the proportion of zero costs was high, i.e. the level of censoring was high. A high level of censoring is common in health economic research (45), and it is one of the caveats of the selection models (44, 189). Despite these analytical challenges, the selection models were chosen as a primary analytic method and the models used in this thesis were well defined. In conclusion, the results
suggest that depressive symptoms at age eight do not predict antidepressant costs differently than antidepressant use. Externalizing symptoms at age eight as predictors of antidepressant use might operate differently as predictors of antidepressant costs. However, for definitive conclusions, the topic should be further studied in other samples.

### 6.2.1.4 Predictors of psychiatric hospital treatment (Aims 3 and 5; studies IV and V)

A wide range of predictors at age eight were associated with psychiatric hospital treatment (PHT). Among males, externalizing problems most strongly predicted hospital treatment for any psychiatric diagnosis. Among females, self-reported depressive symptoms at age eight had the strongest independent predictive association with PHT. These results are in line with previous studies showing that childhood psychopathology predicts intensive psychiatric treatment (78, 132, 238).

The combination of conduct and emotional problems increased the risk of later PHT among both males and females more than the other studied psychopathology combinations at age eight. This group of children was small and consisted of approximately 4% of the total sample. Nonetheless, every fifth male and every eighth female, who had concurrent conduct and emotional problems at age eight, had been treated for a psychiatric disorder in a hospital by age 25. Previous population-based longitudinal studies have shown that childhood comorbid internalizing and externalizing problems among males are associated with substance use (82) and suicidality (82) in adulthood. In addition, it was shown in a previous report based on the military call-up data of the males in the current cohort, that comorbid conduct-emotional problems predict several psychiatric disorders in early adulthood (214). A new finding in this thesis is that comorbid externalizing and internalizing problems predict treatment for psychiatric disorders in both sexes, not only in males.

Both frequent victim and frequent bully-victim status predicted PHT in both sexes. In addition, frequent bully-only status predicted PHT among males. However, when adjusting with psychopathology scores at age eight, only frequent victim status among females predicted PHT (findings discussed in more detail in section 6.2.2.5).

### 6.2.1.5 Predictors of hospital treatment of psychosis and other diagnostic classes (Aim 3; study IV)

Both externalizing and internalizing problems at age eight among males predicted hospital treatment of psychotic disorders. However, only conduct problems predicted treatment of psychotic disorder independently among males. Among females, parent- and teacher-reported emotional problems
predicted treatment of psychotic disorder in the univariate model. The term equifinality is often used to refer to the fact that a variety of problems in childhood can predict a specific disorder in adulthood (52). The results in this thesis are in line with the few studies which have reported sex-specific information on childhood psychopathology and later psychotic disorders (78, 174). Most longitudinal population-based studies about childhood psychopathology and later psychotic disorders have not reported separate estimates for males and females (46, 116, 132, 214). However, other developmental sex differences than childhood psychopathology have also been found. For example, neurodevelopmental deficits are more severe among preschizophrenic males than females, and females have a later onset of schizophrenia symptoms than males (240).

Hospital treatment of mood and anxiety disorders was predicted by similar problems in childhood in both sexes, which is in line with previous studies (132, 214). Conduct problems and non-intact family structure predicted treatment of substance-related disorders, in line with earlier studies (81, 214, 239).

6.2.2 OUTCOMES OF VARIOUS CHILDHOOD PREDICTORS (AIMS 3 AND 5; STUDIES II-V)

6.2.2.1 Externalizing problems (Aim 3: studies II-IV)

Conduct problems at age eight independently predicted hospital treatment of substance-related disorders in both sexes, when other psychopathology variables were taken into account. Among males, conduct problems also independently predicted antipsychotic use, antidepressant use and hospital treatment for any psychiatric diagnosis and of psychotic disorders. The term multifinality has been used to describe how one characteristic predicts several different outcomes (52). The results in this thesis are in line with previous studies showing that conduct problems in childhood predict several different adverse outcomes in adulthood (132, 167, 205). Therefore, the results strengthen the view that early identification of children with conduct problems might provide an opportunity to prevent several adverse outcomes by offering these children targeted interventions (100). Novel findings in this thesis were that the predictive impact of childhood conduct problems on many outcomes in adulthood shows differences among males and females. Future studies are needed to replicate, e.g. why conduct problems predict antidepressant use strongly among males and weakly among females (54).

Hyperactivity problems predicted several outcomes among males, when the hyperactivity scale was analyzed as a single predictor. However, when other psychopathology scales were included in the same models, the hyperactivity scale did not predict any of the studied outcomes.
independently. This indicates that co-occurrence of hyperactivity problems and other psychopathological problems account for the majority of predictive associations described above. Some prior clinical (35) and population-based (194) studies have also shown that pure hyperactivity problems without any other types of comorbid psychiatric problems do not have a strong impact on adult adverse outcomes.

6.2.2.2 Internalizing problems (Aim 3; studies II-IV)
The emotional scale and/or the self-reported depressive scale independently predicted antidepressant use and hospital treatment of any psychiatric diagnosis and mood disorders in both sexes. In addition, the scales independently predicted treatment of anxiety disorders among males and antipsychotic use among females. In sum, internalizing problems at age eight predicted outcomes that are mainly related to internalizing problems. The term homotypic continuity has been used to describe the finding that certain problems in childhood predict similar problems in adulthood (67). The results in this thesis are in line with previous studies, which have reported a strong association between childhood emotional problems and similar adult problems (55, 132).

6.2.2.3 Comorbid externalizing and internalizing problems (Aim 3; study IV)
The combination of externalizing and internalizing problems at age eight was studied with regard to one outcome, namely, hospital treatment of any psychiatric disorder. The combination of both externalizing and internalizing problems increased the risk of PHT six-fold among males and four-fold among females, while the “pure” externalizing and internalizing classes increased the risk three-fold among males and two-fold among females. The context of the findings has been discussed in more detail in section 6.2.1.4.

6.2.2.4 Self- versus parent- and teacher-reported problems (Aim 3; studies II-IV)
In studies II-IV, self-reported problems and parent- and teacher-reported problems were studied in parallel. Both reports by the children themselves and by the adults predicted several outcomes. Though agreement between informants is usually low, it is justified to use several informants, because different informants perceive different aspects of a child’s situation. However, little is known about the predictive value of self-reports in early school years, because other population-based cohorts with outcomes in adulthood have not included self-reports as early as age eight (214).
Novel findings in this thesis were that the self-reported depressive symptoms at age eight independently predict antidepressant use and hospital treatment of mood disorders in both sexes. The results indicate that adults do not necessarily notice depressive symptoms among eight-year-old boys and girls, although the children’s own report of depressive symptoms may be a marker for possible later internalizing disorders requiring hospital treatment or antidepressant medication. These findings have implications for early detection of children at risk.

6.2.2.5 Bullying and victimization (Aim 5; study V)

Bullying behavior, victimization of bullying behavior, and being both bullied and victimized predicted several outcomes. Males who were both bullied and victimized at age eight had the highest risk of several psychiatric outcomes. Females who were frequently victimized at age eight were at risk of a wide range of outcomes regardless of their psychiatric symptoms at age eight.

There were two groups that included bullying behavior, namely, the frequent bully group and the frequent bully-victim group. The prevalence of frequent bully and of frequent bully-victim status at age eight was 6% and 3%, respectively, among males, while it was only 0.6% and 0.2%, respectively, among females. That is, the overall rate of bullying was rather low, and bullying behavior was more common among males. In a study with data from 25 different countries, the prevalence of bullying varied between 9% and 54% (163). An explanation for the lower prevalence rates in this thesis, is that study V included only frequent bullying and the children were eight years old at assessment, while the country comparison study included both occasional and frequent bullying and the samples consisted of students at average ages of 11.5, 13.5 and 15.5 years (163). The more strict definition of bullying in study V was justified by previous findings that frequent bullying substantially increases the risk of later psychiatric disorders among males, while occasional bullying increases the risk at most moderately (197). The finding that bullying was more common among males is in line with previous findings showing that males have higher levels of aggression and impulsivity (22, 50, 68).

Every second male who was a frequent bully-victim at age eight had undergone either psychotropic medication treatment or hospital treatment of a psychiatric disorder by age 25. This is in line with previous findings indicating that males who are both bullies and victims have the poorest long-term prognosis (118, 216). Being a frequent bully, but not a victim, also increased the risk of psychiatric treatment in adulthood, but to a smaller extent than being both a bully and a victim. However, psychiatric symptoms among frequent bully-victims and frequent bullies explained the association with later psychiatric outcomes. Among the few females who were frequent bullies at age eight, the risk of psychiatric treatment by age 25 was also
increased. The small number of subjects in this group warrants caution in interpreting this result. Previous studies have used the term “gender-paradox” to describe the fact that antisocial or bullying behavior is uncommon among females, but when such behavior is present among females, the impairment is worse than among corresponding males (43, 147). The implication of these findings is that both males and females who present bullying behavior should be evaluated for psychiatric symptoms, because the combination of bullying behavior and psychiatric symptoms can be a marker of psychiatric long-term outcomes.

The prevalence of being a frequent victim of bullying behavior at age eight was 6% among males, and 4% among females. Females who were victims of bullying behavior at age eight were at risk of several psychiatric outcomes by age 25, regardless of the level of psychiatric symptoms at age eight. Males who were victims at age eight were at modest risk of some psychiatric outcomes, but the predictive association was explained by the psychiatric symptoms at age eight. These results are in line with previous cross-sectional and short-term follow-up studies showing that victimization is associated with psychiatric outcomes especially among females (23, 38, 130, 134).

One explanation for why victimization is associated with later psychiatric treatment more strongly among females than among males is that the type of bullying and victimization among females is different from that among males. Relational forms of victimization, such as being a victim of social exclusion and gossip, are more common among females than males (70-72, 176). Among males again, physical victimization is more common (70, 72). A previous cross-sectional study showed that indirect forms of victimization, such as being excluded and ignored, were more strongly associated with depressive symptoms than direct forms of victimization, such as being hit and kicked (233). Therefore, it is possible that females have experienced psychologically more traumatic forms of victimization than males. A further possible explanation is that adults might more easily notice physical victimization among boys than relational forms of victimization among girls. If adults notice victimization and interfere at an early point, it is possible that the victimization does not continue for a long time and the long-term prognosis is better.

6.2.2.6 Family characteristics (Aim 3; studies II-IV)

In line with several other studies, living with other than two biological parents predicted a wide range of outcomes (85, 239). However, a non-intact family should not be seen as a risk per se. There are several problems associated with both intact family structure and psychiatric outcomes among offspring, such as psychiatric problems among parents, disadvantageous child-rearing practices, financial problems, family violence, and weak parental support (85, 244). Lower parental education level than completed
upper-secondary school showed very few associations with the studied outcomes. It is possible that more specific measures of the parents’ education, cognitive abilities, work, or salary would have shown associations with the studied outcomes. Unfortunately, more specific family characteristics were not assessed in this cohort.

6.3 METHODODOLOGICAL CONSIDERATIONS

The strengths and limitations of the thesis are summarized in Table 9. First, the general design issues of the cohort are listed, such as the nationwide design. Second, the baseline methodological issues are inspected. Third, the methods at follow-up are shown, that is, the methodological issues related to register-based research.

In summary, the major strengths of the cohort used in this thesis include the representativeness of the source population, the nationwide design, the large sample size, the use of several informants at age eight, and the use of reliable nationwide registers at follow-up to assess psychotropic medication use and hospital treatment. The use of registers made it possible to track all the subjects with a correctly documented personal identification code. Therefore, the attrition was small and due to random error. Furthermore, the registers used in the thesis are very reliable with regard to the timing of the hospital treatment and the purchase date of the medications. The major limitations of the thesis are the use of only one baseline assessment, the lack of information about childhood psychiatric diagnoses, the lack of more specific information about the family, and limitations related to register-based research. The registers are developed and maintained for administrative purposes and not primarily for research purposes. Therefore, information that could be of interest from a research point of view, such as indications of medications, is not necessarily recorded in the registers. Furthermore, register-based research cannot assess certain outcomes, which can only be studied if the study subjects are contacted. Such outcomes include, e.g. psychiatric symptoms in the population and whether the subjects actually continue to use the medication after the purchase. However, based on the finding that the majority of psychotropic medication users and 80% of antidepressant users purchase the medication twice or more often, it is indicated that the medication is actually used.

In comparison with other population-based cohorts from childhood to adulthood (reviewed in section 2.2.2), the cohort used in this thesis has general strengths to study predictors of certain service use patterns. These strengths are mainly related to the large, nationwide, representative sample, the use of nationwide registers, and the linkage procedure with unique personal identification codes. For example, the purchase date of the first antidepressant and the subsequent cumulative costs of antidepressants cannot be reliably assessed using questionnaires or interviews. In other
studies where service use is assessed with questionnaires or interviews, the
timing and cumulative costs of specific forms of service use are hard to assess
reliably. However, such studies have the strength to assess a wide range of
service use forms, e.g. primary care, private physicians, and social services
(64).

Table 9  Summary of strengths and limitations by methodological issues.

<table>
<thead>
<tr>
<th>Methodological issue</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
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<tbody>
<tr>
<td>Nationwide cohort</td>
<td>Few child psychiatric population-based cohorts are nationwide. Such nationwide studies have not previously been linked to nationwide registers, making high follow-up rates possible. It was possible to calculate the incidence of medication use with the cohort design (study I; most other studies have reported 1-year prevalence).</td>
<td>Some personal identification numbers were lost or incorrectly documented.</td>
</tr>
<tr>
<td>Sample size</td>
<td>A unique sample size making it possible to, e.g., study males and females separately, study interactions, and study rare events, such as psychotic disorders.</td>
<td>The sample size was relatively small for some rare outcomes.</td>
</tr>
<tr>
<td>Age-homogenous cohort</td>
<td>A cohort of children born in the same year was chosen, so the whole spectrum of disorders could be addressed; also the disorders occurring more seldom.</td>
<td>The age effect of increased psychotropic medication use in late adolescence could not be ruled out by the period effect, i.e. that the increase was due to an increase in psychotropic medication use during those years. However, no sudden increases of psychotropic medication use among young people can be found between 1997 and 2005, according to another Finnish study (ref. 25).</td>
</tr>
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Methods at baseline
Questionnaires  
The standardized brief questionnaires could be administered in a classroom setting and by sending the questionnaires to the parents: three different informants obtain a large sample size at relatively low cost  
Lack of more specific information such as psychiatric diagnoses.
**Discussion**

**Table 9 continued (methods at baseline and follow-up)**

<table>
<thead>
<tr>
<th>Methodological issue</th>
<th>Strengths</th>
<th>Limitations</th>
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<tr>
<td><strong>Methods at baseline</strong></td>
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<tr>
<td>Bullying/victimization questions</td>
<td>The same questions to all three informants. Possible to combine information about a strict definition of bullying/victimization (bullies/is bullied frequently according to at least one informant versus never or sometime bullies/is bullied).</td>
<td>Lack of more specific information about bullying/victimization: - bullying/victimization: - bullying executed by males or females - physical aggression, verbal aggression or social exclusion</td>
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<tr>
<td>Family variables</td>
<td>The study includes information about family structure.</td>
<td>Lack of information about more specific family characteristics and events in the family environment, such as rearing practices, weakened parent support, parent-child discord, maltreatment, family violence, financial problems and psychiatric problems among parents.</td>
</tr>
<tr>
<td>Assessment once at age 8</td>
<td>Includes self-reports already at age 8, which is earlier than in prior population-based studies from childhood to adulthood.</td>
<td>With one “snap-shot” of childhood problems, the study lacks information to specify whether the problems were present once or if the problems continued for a longer time.</td>
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<tr>
<td><strong>Methods at follow-up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The use of nationwide registers</td>
<td>Possible to link the nationwide sample and to obtain a low attrition rate. The attrition was due to random error, such as incorrectly recorded identification numbers.</td>
<td>Not possible for the researcher to affect what kind of information is gathered in the registers.</td>
</tr>
</tbody>
</table>
Table 9 continued  *(methods at follow-up)*

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<tr>
<th>Methodological issue</th>
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<td>Methods at follow-up</td>
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| Nationwide prescription register         | - Nationwide reliable information about the used medication, the date of the purchase and the cost of the medication.                                                                                      | - At the time of the study, the register lacked information e.g. about the indication of the medication or the prescriber  
- The register was established in 1994, when the subjects were 12-13 years old. However, the use of psychotropic medication under that age has been very low and it is thus unlikely that the lifetime prevalence estimates are affected.  
- Lack of information on whether the subjects actually used the medication. However, the clear majority of users made at least two purchases, which indicates actual use. |
| Finnish hospital discharge register      | - Nationwide reliable information about the diagnosis that was set during the inpatient treatment, and about the date of the admission.  
- According to previous studies, the diagnostic validity of psychotic disorders in Finnish inpatient treatment is good among adults.                      | - Lack of information about the diagnostic validity of e.g. anxiety disorders.  
- Only minority of subjects with psychiatric disorders end up in hospital treatment, except subjects with schizophrenia and other psychotic disorders. |


7 CONCLUSIONS

7.1 MAIN FINDINGS

The finding that 15% of the study population had used any psychotropic medication and 12% had used antidepressants by age 25 extends previous findings indicating that psychotropic medication use is common among young adults. However, previous studies have mainly reported psychotropic medication use during one year. Therefore, this thesis extends previous findings of one-year prevalence by assessing psychotropic medication use prospectively from early adolescence to young adulthood.

The other main finding is that childhood mental health problems predict certain types of psychiatric treatment in adulthood differently among males and females. For example, conduct problems predict antidepressant use more strongly among males than among females; self-reported depressive symptoms predict antipsychotic use among females, but not among males; and being a victim of bullying predict psychotropic medication use and PHT among females, regardless of other childhood psychiatric problems, while among males, victimization shows only modest associations with the same outcome.

7.2 IMPLICATIONS FOR PUBLIC HEALTH AND CLINICAL PRACTICE

The results in this thesis and in several other studies show that a diversity of mental health problems in middle childhood is associated with psychiatric treatment in adulthood. Short-term treatment trials have shown that many of these childhood mental health problems can be treated effectively (195). This suggests that intervening in children at risk can reduce psychiatric problems during a short follow-up. Whether these effects can be extended into adult life is not certain, because there are no long-term follow-up studies of preventive interventions of childhood mental health problems (165). However, other types of childhood intervention studies have shown promising long-term results (101, 102). For example, in a study of 3-4-year-old African-American disadvantaged children, the intervention consisted of morning programs at schools and home visits by a teacher (102). At follow-up at age 40, the intervention group had higher rates of school graduation, higher salaries, less welfare assistance, and fewer arrests than the control group (102). Therefore, it is likely that prevention of mental health problems in childhood also has long-term effects.

If the screening for prevention is systematic, it is important to remember that there are a number of screening criteria to be fulfilled (165). Some of these
criteria are fulfilled in accordance with current knowledge; for example, the preventable conditions are important health problems \( \text{(65, 162, 205)} \). However, the possible stigmatization, the potential of labeling, and the extra workload \( \text{(165)} \) in schools, primary care, and specialized care remain important questions if universal screening for prevention is applied.

In Finland, school health care includes health check-ups throughout primary school (age 7-15) \( \text{(210)} \). These routine check-ups are performed by public health nurses and physicians and focus on physical health, mental health, and the well-being of the family \( \text{(210)} \). However, these check-ups, which sometime include questionnaires concerning psychiatric symptoms, are not named under the national screening programs (screening for breast cancer, cervix cancer and fetal chromosome and growth defects during pregnancy) \( \text{(154)} \). Thereby, the assessment of mental health problems among school-aged children is not completely systematic, but should be performed routinely according to the government decree from 2009 \( \text{(210)} \). The findings in this thesis have implications for these health care check-ups in schools, but also in primary care, and specialized care. Several psychiatric treatment forms in adulthood were predicted differently among males and females. These findings highlight the need to consider mental health problems sex-specifically when evaluating the prognosis of mental health problems in early school years.

7.3 IMPLICATIONS FOR FUTURE RESEARCH

The lifetime use of psychotropic medication and the age of onset of psychotropic medication treatment should be further studied in other countries, because currently most studies have reported one-year prevalence of medication use. One important tool that could be used to study these pharmacoepidemiological issues are the Nordic prescription registers \( \text{(5, 93)} \).

The general problem with observational longitudinal studies is that it is difficult to draw certain conclusions of causality. Researchers aim to minimize the problem by checking for potential confounders, which could explain the association. A limitation of this thesis is that it includes childhood characteristics from only one time-point, and it might have missed important confounders. The sex-specific findings in this thesis should be further analyzed in other population-based studies. For example, are the predictive associations among males and females explained by variations in genetic background, prenatal factors, or coping strategies of problems in the family? The study of sex-related issues is important, because they can contribute to the understanding of causal mechanisms involved in the development of psychopathology \( \text{(201)} \). Furthermore, would the positive predictive value of the studied outcomes be higher if information on predictors from other age periods were combined with the currently used information? For example, would it be more achievable to include information on early childhood
Conclusions

development and mental health problems in both childhood and adolescence when studying adverse outcomes in adulthood? These issues would be of importance when studying at what age or at what combinations of age periods possible screening should be performed.

The outcome in this study was related to treatment of mental health problems in adolescence and young adulthood. It is possible that the positive predictive value would have been higher if the outcome had also included untreated cases of mental health problems. Therefore, the sex-specific findings need replication using other outcomes, such as questionnaire or interview-based information on mental health problems. From a more general point of view when considering screening, other outcomes are also of interest, such as unemployment, social exclusion, and criminal offences.

Finally, as noted above, there are mainly short-term follow-up studies of preventive interventions. Therefore, there is an urgent need for long-term follow-up studies on how much screening and prevention of childhood mental health problems can reduce similar problems in adulthood. When conducting these studies, the cost-effectiveness of the interventions should also be taken into consideration.
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David Gyllenberg
Helsinki, March 2012
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