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Early-Onset Depressive Disorders,
Related Mental Health Disorders and
Substance Use-A Prospective, Longitudinal

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Tiivistelmä


Tutkimuksessa todettiin, että vakavan masennuksen lisäksi myös nuorten haitallisiksi kokemmat masennusnooreet ovat tärkeä nuoren kehitykseen vaikuttava tekijä. Vakavan masennuksen diagnostiset kriteerit eivät tavoita suurinta osaa masentuneista nuorista. Lievät masennustilat, jotka aiheuttavat toiminnullaista haittaa mm. kouluympäristöstä ja toverisuhteissa, mutta eivät täytä vakavan masennuksen kriteerejä altistavat mm. itsetuhoisuudelle, muille mielenterveyden häiriöille ja päihteidenkäytölle. Tässä tutkimuksessa osoitettiin, että nuoruusikäinen masennus ennustaa merkittävästi päivittäistä tupakointia, usein toistuvaa alkoholinkäyttöä, säännöllistä humalaajuomista sekä nuuskanaan ja huumeiden käyttöä, kun mutta mielenterveydenhäririö, käyttöhäiriö ja jo 14-v alkaneet päihdehäiriöt otetaan huomioon. Masennuksen ja päihteidenkäytön yhteyts on todettavissa myös riippumatta yhteisistä perheitäistä tekijöitä, kuten yhteisestä perimästä ja yhteisestä perheympäristöstä, eli esimerkiksi perheen toimeentulosta. Tutkimustulokset viittaavat siihen, että ei-perheitäiset tekijät, kuten nuoren persoonalisuus, kouluympäristöstä sekä toverisuhteisiin liittyvät tekijät saattavat olla merkityksellisiä masentuneen nuoren päihteidenkäytön kehittymisessä.

Tutkimuksessa todettiin ensikertaa suomalaisessa väestöpohjaisessa pitkittäis-asetelmassa huomattava yhteisarastavuus tyttöjen masennuksen ja tarkkaavaisuushäiriön (ADHD:n) välillä, mikä saattaa olla osasyynä vaikeuteen tunnistaa tyttöjen tarkkaavaisuushäiriön oireita. Vanhempien ja opettajien arvioimina nähä oireet; keskittymisen vaikeudet, yliaktiivisuus ja impulsiivisuus olivat työöllä selvästi poikien oireita harvinaisemmina. Silti ADHD oireet olivat selkeä tyttöjen kehitystä vaarantava tekijä; tässä tutkimuksessa ne ennustivat alkoholin häittillisä käytöitä, alkoholirippuvuutta sekä huumausaineiden tulevaa käyttöä selvästi merkittävämmin kuin poikien ADHD-oireet.

Jatkossa on tärkeää selvittää, voitaisiinko masennusta ja muita varhain alkavia tai kehityksellisiä mielenterveyden häiriöitä paremmin tunnistamalla ja hoitamalla vaikuttaa päihteidenkäytön kehittymiseen. Myös lievemmät masennustilat, jotka aiheuttavat toiminnullaista haittaa mutta eivät täytä vakavan masennuksen oirekriteerejä altistavat mm. päihteidenkäytön merkittävälle lisääntymiselle ja niillä saattaa korkeamman esiintyvyyteen vuoksia olla huomattava kansenanterveydellinen merkitys. Tyttöjen ja poikien alttiudesta päihteidenkäytön kehittymiselle saattaa olla eroja, ja tästä tuleisi päihteidenkäytön ehkäisylä ajatellen tutkia lisää. Psykiatrisen hoidon ja päihdehoidon yhteistyötä nuorilla tulee kehittää.
Abbreviations

ADHD  attention deficit/hyperactivity disorder
APA    American Psychiatric Association
C-SSAGA Semi-Structured Interview for Genetics of Alcoholism
CI     confidence interval
DSM-III-R Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised
DSM-IV  Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DD    depressive disorders
ED    eating disorders
FINHCS Finnish Health Care Survey
FinnTwin12 Finnish Twin Study, suom. Kaksosten Kehitys ja Terveys
GAD    generalized anxiety disorder
MDD    major depressive disorder
ODD   oppositional defiant disorder
OR     odds ratio
SD     standard deviation
UKKI   The Uusikaupunki-Kemijärvi-Study
WHO   World Health Organization
1. Abstract

Aims

Early-onset psychiatric illnesses’ effects scatter to academic achievements as well as functioning in familial and social environments. From a public health point of view, depressive disorders are the most significant mental health disorders that begin in adolescence. Using prospective and longitudinal design, this study aimed to increase the understanding of early-onset depressive disorders, related mental health disorders and developing substance use in a large population-derived sample of adolescent Finnish twins.

Methods

The participants of this study, FinnTwin12, an ongoing longitudinal population-based study, came from Finnish families with twins born in 1983-87 (exhaustive of five birth cohorts, identified from Finland’s Central Population Register). With follow-up ongoing at age 20-24, this thesis assessed adolescent mental health in the first three waves, starting from baseline age 11-12 to follow-ups at age 14 and 17½. Some 5600 twins participated in questionnaire assessments of a wide range of health-related behaviors. Mental health was further assessed among an intensively studied subsample of 1852 adolescents, who completed also professionally administered interviews at age 14, which provided data for full DSM-IV/III-R (Diagnostic and Statistical Manual for Mental Health Disorders, 4th and 3rd editions) diagnoses. The participation rates of the study were 87-92%.

Results

The results of the study suggest, that the diagnostic criteria for major depressive disorder (MDD) may not capture youth with clinically significant early-onset depressive conditions outside clinical settings. Milder cases of depression, namely adolescents fulfilling the diagnostic criteria for minor depressive disorder, a qualitatively similar condition to MDD with fewer symptoms are also associated with marked suicidal thoughts, plans and attempts, recurrences and a high degree of comorbidity. Prospectively and longitudinally, early-onset depressive disorders were of substantial importance in the context of other mental health disorders and substance use behaviors: These data from a large population-derived sample established a substantial overlap between early-onset depressive disorders and attention deficit hyperactivity disorder in adolescent females, both of them significantly predictive for development of substance use among girls. Only in females baseline DSM-IV ADHD symptoms were strong predictors of alcohol abuse and dependence and illicit drug use at age 14 and frequent alcohol use and illicit drug use at age 17½ when conduct disorder and previous substance use were controlled for. Early-onset depressive disorders were also prospectively and longitudinally associated to daily smoking behavior, smokeless tobacco use, frequent alcohol use and illicit drug use and eating disorders. Analysis of discordant twins suggested that these predictive associations were independent of familial confounds, such as family income, structure and parental models.
Conclusions

In sum, early-onset depressive disorders predict subsequent involvement of substance use and psychiatric morbidity. A heightened risk for substance use is substantial also among those depressed below categorical diagnosis of MDD. Whether early recognition and interventions among these young people hold potential for substance use prevention further in their lives has potential public health significance and calls for more research. Data from this population-derived sample with balanced representation of boys and girls, suggested that boys and girls with ADHD behaviors may differ from each other in their vulnerability to substance use and depressive disorders: the data suggest more adverse substance use outcome for girls that was not attenuated by conduct disorder or previous substance use. Further, the prospective associations of early-onset depressive disorders and future elevated levels of addictive substance use is not explained by familial factors supporting future substance use, which could have important implications for substance use prevention.
2. List of original publications

This thesis is based on the following original publications, referred to in the text by Roman numerals (I–IV):


II SIHVOLA E, ROSE RJ, DICK DM, KORHONEN T, LEPPÄMÄKI S, RAEVUORI A, PULKKINEN L, MARTTUNEN M, KAPRIO J. ARE GIRLS WITH SYMPTOMS OF ADHD AT HIGHER RISK FOR SUBSTANCE USE THAN BOYS?-PROSPECTIVE FINDINGS FROM A POPULATION-DERIVED SAMPLE OF GIRLS AND BOYS. SUBMITTED.


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3. Introduction

In Finnish society, psychiatric disorders among children and adolescents are still undetected and therefore undertreated. A substantial public health concern is expressed, since many studies document a possible association between psychiatric morbidity and substance use. Cross-sectional studies provide valid and useful information, but as many psychiatric disorders are lifespan and dynamic by nature, longitudinal studies assessing both space and time are of importance in the research of psychopathology.

It is well documented that depressive disorders are one of the leading causes of disability and ill health in Finnish population. This disease affects to individual’s overall health, academic and working performance, social relationships and may sometimes contribute to one of the highest rates of suicide worldwide (Pelkonen & Marttunen, 2003a), especially when untreated (Birmaher et al., 1996). However, depressive disorders start early in life, and previous literature does not cover sufficiently younger age groups, especially adolescents, who are in a critical developmental period for studying depression (Pelkonen and Marttunen, 2003b). Further understanding of the developmental context of depression during these years; it’s variability of symptoms and comorbidity will be necessary in developing effective interventions to young people thus enabling them to reach their full potential as adults (Rao & Chen 2009).

Recent studies suggest that the incidence of depressive symptoms is rising among 8-9-year-old Finnish girls (Lapset-study, Almqvist et al., 1999). Some but not all large-sample surveys also suggest that the prevalence of depressive symptoms is increasing (Klerman & Weismann 1989, Kovacs et al., 1994, Witchen et al., 1994a, Kessler et al., 1994), the age of onset dropping (Lewinsohn et al., 1993a). This potential cohort effect is consistent with the concomitant rise in the youth suicide rate from 1950’s to 1990s (Costello et al., 2006). Thus, studies using epidemiologic perspective are of vital importance when planning satisfactory health care services for adolescents.

Depression relates to other psychiatric disorders and they have potential effects on worsening treatment response and outcome of depression (Howland, 2009). It seems, that having another distinct disorder along with depressive illness, causes more severe and chronic natural course and associates to increased treatment seeking (Newman et al., 1996, Witchen et al., 1998, Kessler et al., 1998a). Previous research suggests that the most important co-occurring disorders among adolescents and young adults with depression are anxiety disorders, disruptive disorders; such as conduct disorder, and oppositional-defiant disorder and substance use disorders (Biederman et al., 1995, Birmaher et al., 1996, Kessler et al., 2001). Clinical studies are of great importance; however, they might only provide information on those whose seek treatment. Assessing concurrent comorbidity offers limited information, and understanding longitudinal relationships is necessary for preventive actions.
Youth also marks a period crucial for developing substance use habits. Once these deviant behaviors are established, they are likely to continue throughout adulthood. There are studies, which suggest that if substance used is not initiated by age 21, it is unlikely to ever be initiated (Chen and Kandel, 1995). In many countries, smoking and drinking cause a significant public health concern among adolescents. Based on clinical experience, in young psychiatric patients the prevalences of deviant behaviors such as smoking, alcohol and illicit drug use are known to be very high. Even though majority of adolescents do not develop substance use disorders, the use of these addictive substances has been suggested to have similar impact for mental health as substance use reaching the diagnostic threshold. Given the high comorbidity of adolescent depression, it is also of great importance to look for potential mediators, the factors that associate to depression and may promote the substance use itself. Few longitudinal studies have been conducted in adolescence, in a developmental period in which both depressive disorders and substance use emerge. Determining these important pathways may help to identify unique or common risk factors, clarify the etiologic and pathogenic mechanisms and provide information for developing guidelines for preventive actions and treatment programs.

This study is a part of an ongoing longitudinal Finnish Twin Study, launched in 1994 to investigate the developmental genetic epidemiology of health-related behaviors (Rose et al., 2001). From 1994 to 1998, all Finnish families with twins born in 1983-87 were identified from Finland’s Population Register Centre and enrolled into a two-stage sampling design (Kaprio et al., 2002). The first-stage study included questionnaire assessments of all twins and parents at baseline (87% participation rate, 2,724 families) conducted during the late autumn of the year in which consecutive twin cohorts reached 11 years, with follow-up of all twins at ages 14 and 17½ and ages 20-24. The prior investigations of this unique sample have provided genetic epidemiology data on wide range of substance use (e.g., Rose et al., 2001, Rose et al., 2004, Dick et al., 2007, Korhonen et al., 2008) on aggression and hyperactivity impulsivity traits (Vierikko et al., 2004), inattentiveness and smoking (Barman et al., 2004), parental socialization and alcohol use behaviors, pubertal development (Mustanski et al., 2004, Wehkalampi et al., 2008) and leisure activity patterns and overweight (Lajunen et al., 2009), obesity and eating disorders (Keski-Rahkonen et al., 2007, Raevuori et al., 2008). This thesis focused in the first three waves of FinnTwin12, studying prospective longitudinal associations of early-onset depressive disorders with and developing substance use and psychiatric morbidity. Two of the substudies were complimented by twin analysis of discordant twins controlling shared and environmental factors aiming to offer added value to epidemiologic perspective of these diseases.
4. Review of the literature

4.1. Overview of psychiatric epidemiology and longitudinal studies among adolescents

Longitudinal studies are essential of testing causal hypothesis and planning services. Some key studies have established the value of prospective assessments in the field of adolescent psychiatry; beginning with the California longitudinal studies (Elder, 1974, 1998) and the first British Birth Cohort study (Douglas, 1964). More recently, the Dunedin and Christchurch studies, “Children in the Community” (Cohen and Brook, 1987, Cohen and Cohen, 1996) have provided evidence of the links and disruptions between child and adult psychopathology. These studies are characterised by good generalizability due representative sampling, and their capability to study environmental factors and the outcome of behaviours below the diagnostic threshold. The Isle of Wight Studies (Rutter et al., 1970, Rutter 1989b) have been innovative in showing the value of children as informants of their own psychopathology, and in line with other important studies (Richman et al., 1982), in demonstrating the precursorial nature of early psychopathological problems to later psychiatric morbidity. Large scale studies also provide the much needed estimates for service need in populations (Meltzer et al, 2000) and the information on mixed patters of symptoms and how they chance over time. Contemporary psychiatric epidemiology also aims to gather information on risk and protective factors with regard to psychopathology, and the pathways and mechanism through they operate (Laub and Sampson, 2003). Although not focusing on adolescents, two large epidemiological studies, The Epidemiologic Catchment Area Study (ECA) (Robins et al., 1991) and National Comorbidity Survey (NCS) (Kessler et al., 1994) are have been of great importance in established the modern methods, introducing reliable lay-administered structured diagnostic assessments, and the application of sampling strategies.

An advanced scope in psychiatric epidemiology is to study more rare or subtle psychopathology, which can be achieved by psychiatric epidemiology high-risk studies. For example, the study of Owens’ and Johnstone’s (2006) examined the prodromal phase of schizophrenia in a high-risk schizophrenia sample. These designs are obviously limited by the uncertainty of these factors associating to high family loading, and it of importance to combine the high risk data to epidemiological data. Alternatively, designs can be planned that embed the high-risk sample within epidemiological design (Moffit, 2002). Longitudinal studies of adolescents are conducted also in Finland; From a Boy to a Man”; a follow-up study (Sourander et al., 2008) included in the Epidemiologic Multicenter Child Psychiatric Study (Almqvist et al., 1999) and substudies of mental health from Northern Finland Birth Cohorts (NFBC), starting from early development have greatly increased the knowledge on longitudinal aspects of adversities of mental health among Finnish adolescents (Isohanni et al., 2001, 2006, Riala et al., 2007, Hurtig et al., 2007, Jääskeläinen et al., 2008).
4.2 Overview of normative adolescent development

Adolescence can be described as a period of transition from childhood to adulthood. During adolescence, individuals face both important biological and psychological developmental tasks, a sequential process that may be compromised, delayed or even hindered by mental disorders.

A number of theories of development in adolescence are widely recognized. For example, Blos (Blos 1979) described adolescence as “the second individuation process”, referring to the chance to recap the separation-individuation phase of early childhood. According to Moses Laufer (Laufer 1975), a new perception of self and others develops: this is experienced as part of the pressure to move towards adulthood and as part of giving up safety and dependency of one’s childhood. Perhaps one of the most widely known theories of development is the one created by Erik Erikson in 1968 (Erikson, 1968) who described the formation of identity in adolescence. According to Erikson, during adolescence, the primary developmental task is to find out who one is as an individual, separate from our family. Jean Piaget, a Swiss psychologist described adolescence as the last phase of cognitive development called “the formal operational stage”, which often lasts from age eleven on, a period when adolescents learn how to think more abstractly to solve problems, to think symbolically and develop the ability to use propositional logic, inductive and deductive logic, and combinatorial reasoning.

In adolescence, three phases, early, middle and late adolescence can be distinguished. (Aalberg and Siimes, 1999, Marttunen and Rantanen, 2001). In the beginning of early adolescence around age 12, the physical changes, accelerating growth, puberty and development of female or male secondary sex characteristics emerge. At the same time, adolescent starts the separating process from family and identifies with peers. The middle adolescence, ages 14-17, is characterized by consolidation of self sense while the sense of threat experience from adults is diminished. In mid-adolescence, many adolescents experience the first sexual encounters. The late adolescence, around ages 17-21 is a period when a more adult-like life begins, some adolescents already leave their childhood home, academic and occupation choices are made and adolescents have the ability to commit to romantic relationships. The normal development consist great variability in time frames and between individuals.

4.3 Overview of early-onset depressive disorders

Before the late 1970s, the existence of depressive disorders in children and in adolescents was controversial and depression was viewed as a predominantly adult disorder. After that, a growing body of evidence has established that depressive disorders are experienced by children and adolescents and that the current diagnostic criteria can be applied successfully to them (Birmaher et al., 1996).

There is evidence from different childhood risk factors between juvenile-onset and adult-onset MDD suggest two distinct conditions (Jaffee et al., 2002). Despite similarity of clinical picture, there are differences in neurobiological correlates
and treatment responses between adults and adolescents (Kaufman et al., 2001). Future scientific challenges lie in understanding the etiology of early-onset depressive disorders assessing possible neuropsychological processes and mechanisms behind these illnesses (Goodyer, 2008).

Depressive disorders are rare in childhood, but the rates rise considerably from early teens (Glowinski et al., 2003); possibly due hormonal changes emerging in puberty (Angold et al., 1999b). Social information process, changes in brain physiology (Nelson et al., 2005) and gene-environment correlations may also contribute to substantial increase of depression among teens (Rice et al., 2003). At the onset of puberty, a dramatic female predominance for depressive disorders emerges, for the first time and the earlier onset of the puberty seem to increase the risk for depression and other disorders (Grab et al., 2004). Possible causes for the sex-specific vulnerability have been suggested; higher tendency to ruminate, higher rates of anxiety and increased interpersonal sensitivity in females as well as differences in cortisol metabolism between sexes (Breslau et al., 1995, Nolen–Hoeksma et al., 1999, Stroud et al., 2004). Prepubertal depression is not well studied, a comorbid presentation with conduct disorder has been suggested (Harrington et al., 1997) but there might also be a less common, more severe familial type of depression among those children (Harrington, 2000). Prepubertal depression implies heterogeneity of early-onset depressions: it is associated with lower risk of recurrence, higher risks of suicidal attempts, bipolar disorder and alcohol dependence and lower heritability (Weismann et al., 1999).

Early-onset depressive disorders are associated with significant functional impairment (Puigh–Antigh et al., 1993) and recurrence: 50-70% within 5 years of depressed children and adolescents will develop a recurrence within 5 years. The clinical relevance of early-onset MDD is underscored in previous literature, 5 to 10% of will complete suicide within 15 years of their initial episode of major depression (Rao et al., 1993) and early-onset depressive disorders have been described as potential phenotype for suicidal behaviour (Mann et al., 2009).

4.4. Epidemiology of depressive disorders in adolescence

4.4.1 Prevalence of depressive symptoms and disorders among Finnish adolescents

Many domestic studies with have assessed depressive disorders in older adolescents and adults (The Mini-Finland Health Survey; Lehtinen et al., 1990a, UKKI Study; Lehtinen et al., 1990b, Isometsä et al., 1997, Lindeman et al., 2000, The Health 2000 Study, Aalto-Setälä et al., 2002, Aromaa and Koskinen 2002 and Suvisaari et al., 2009) confirming that depressive disorders are indeed common and disabling diseases. Yet there are very few studies describing epidemiological data for younger adolescents. Starting in 1996, The Finnish Health Care Survey (FHCS96) established a 12-month prevalence of major depressive episodes of 5.3% assessing 509 adolescents aged 15-19 year olds (Haarasila et al., 2001). Based on a handful of studies, that depressive symptoms seem to be common among adoles-
Early-onset depressive disorders, related disorders and substance use

cents, in questionnaire assessments of 600 adolescents the prevalence was 17, 2% (Aalto-Setälä et al., 2002). School-based survey questionnaires have established similar trends for depressive symptoms; prevalences were 18, 4% for girls and 11.1% for boys (Fröjd et al., 2008). In 8-9 year-olds, parents reported the prevalence of 6.2 % for their offspring as being depressed. (Almqvist et al., 1999).

In Finland, these also seem to be changes in epidemiological trends, from 1989 to 2005, self-reported depressive symptoms had increased among girls (Almqvist et al., 1999, Sourander et al., 2008).

4.4.2 Prevalence of depressive symptoms and disorders among adolescents; International studies

In other countries, nationwide surveys have been conducted throughout adolescence. In large-sample studies, the prevalence of major depressive disorder in adolescence has been estimated to range from 0.4% to 8.3% (Lewinsohn et al., 1994, Birmaher et al., 1996). Studies across adolescence show up to 25% lifetime prevalence of major depressive disorder by the end of adolescence (Lewinsohn et al., 1993, Kessler et al., 2001, Costello et al., 2003, Fergusson et al., 2005) and from 1% under age 12 to 17.4% at age 19 and older females (Glowinski et al., 2003). The Dunedin Study reported a one-year prevalence of depression at age 11 was 1.8%, and increased to 4.3 at the age of 15 (Anderson et al., 1987, McGee et al., 1990). Taken into account the heterogeneity of methodologies and instruments used, it seems that in early and middle adolescence the prevalences of unipolar depressive disorders generally vary from 1 to 10%, being lowest in early adolescence.

4.5 Diagnosis of depressive disorders in adolescence

4.5.1 Assessments of adolescent depression

For young people, the term depression is used to describe many different conditions, perhaps of very variable nature. Interpretation of different cut points of symptoms scales, different instruments and scales yields different results. When this is combined with a heterogeneity of depression; its melancholic and atypical features, likely different symptom profiles in boys and girls, high comorbidity typical for adolescents and cultural variation (Weisman et al., 1996) the results may vary widely and be difficult to compare. To overcome this, instead of using self-reports with high sensitivity but low specificity, semi-structured and structured interviews have proven useful. The semi-structured interviews allow additional questions and resemble more clinical assessments compared to structured interviews. However, semi-structured interviews may not be as cost-effective as structured interviews, since they require clinical experience.

There seem to be substantial discrepancy between reports of teachers and parents compared those of adolescents themselves (Roberts et al., 1998, Wu et al., 1999), as symptoms may exist in different environments, e.g. home, school, or may be different by nature in specific environments. The internalizing symp-
toms, such as in depressive disorders may not be noticed by parents or teachers which makes adolescents more reliable informants and supports the use of direct interviews (Fleming and Offord, 1990, Wu et al., 1999). However, adolescents may also exaggerate their substance use level among peers, which needs to studied further since perceptions of peer substance could predict substance use initiation and escalation (D’amico and McCarthy, 2006) A heightened need for peer approval as well as separation from family (Steinberg, 1993) emerges during adolescence, causing, perhaps, an adolescent to be more unwilling to discuss the symptoms with parents. For example, suicidal ideation is rarely endorsed by parents (Rice et al., 2007).

4.5.2 Classification of subthreshold depressions

Previous research states that diagnostic criteria for major depressive disorders can be applied to adolescents (Roberts 1995, Birmaher et al., 1996). However, many depressed adolescents seem to be left below the diagnostic threshold (Kessler et al., 1994, Kessler and Walters 1998, Angold et al., 1999). Concerningly, impairment and outcome of these adolescents may not differ from those with MDD but many of adolescents in need for interventions may not be considered when planning health care services.

The research interest for subthreshold depressive conditions has escalated, at a time when the quality of life and prevention of diseases have come into public health focus. It is well acknowledged that these conditions are a predisposing factor for major depressive disorders, (Georgiades et al., 2006) but the concept of subthreshold depression is too broad (Cujpers and Smith, 2004.)

Minor depression, a depressive condition with impairment and distress caused by depressive symptoms, but with too few symptoms to qualify for a diagnosis of major depressive disorder, is included to one of the residual categories of Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revised (DSM-IV-TR, American Psychiatric Association) Depressive Disorder NOS. This condition is important, because it is significantly related to MDD in adulthood (Kessler et al., 1997). Research from adults suggest, that minor depression may occur either independently of a lifetime history of major depressive disorder or as a stage of illness in the course of recurrent unipolar depressive disorder (Rapaport et al., 2002). In a study of Gonzalez-Tejera et al. (2005), adolescents with minor depression had similar outcomes when compared to those meeting full criteria for MDD in terms of psychosocial correlates and comorbidity. One of the previous studies, National Comorbidity Survey (NCS) reports a lifetime minor depression prevalence of as high as 9.9 % in adolescents and an almost identical course and outcome as MDD (Kessler et al., 1994, 1997). A growing body of evidence supports the importance of this diagnosis included in DSM-V, but more surveys are encouraged to assess the relevance of this condition.
4.5.3 The diagnostic criteria for major and minor depressive disorder in adolescence according to DSM-IV

TABLE 1. DSM-IV CRITERIA FOR MAJOR DEPRESSIVE DISORDER. MINOR DEPRESSIVE DISORDER HAS THE SAME CRITERIA AS MAJOR DEPRESSIVE DISORDER, BUT ONLY 2-4 DEPRESSIVE SYMPTOMS ARE PRESENT, ONE OF THEM BEING DEPRESSED/IRRITABLE MOOD, OR LOST OF PLEASURE (ANHEDONIA) DURING A TWO-WEEK PERIOD.

A. A minimum of five symptoms from the following list have been present during the same 2-week period and represent a change from previous functioning. One of the symptoms must be #1 or #2, as listed below

1) Depressed mood most of the day, nearly every day, as indicated either by subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful)

2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day, as indicated either by subjective account or observation made by others.

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

4) Insomnia or hypersomnia nearly every day

5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness

6) Fatigue or loss of energy nearly every day

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

8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

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

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

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

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism)

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


In adolescents, the criteria according to DSM-IV (APA, 1994) for major depressive disorder (MDD) are similar as in adults, with two exceptions. First, depressed mood as core phenomena may be replaced by irritability. Second, the duration of dysthymia is only 1 year compared to 2 years in adults. Taken that into account; diagnostic requirements are depressed/irritable mood or loss of interest or pleas-
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ure (anhedonia) for at least two weeks plus four additional symptoms, fatigue or loss of energy, feelings of worthlessness, inappropriate guilt, impaired concentration; significant weight loss or gain, increased/decreased appetite, insomnia or hypersomnia, psychomotor agitation or retardation, suicidal ideation or attempts, a significant impairment of functioning and exclusion of bereavement and symptoms attributed to the effects of medication or alcohol use.

The criteria for minor depressive disorders, a residual category of Depressive Disorders NOS in DSM-IV (APA, 1994) are similar than in major depressive disorder except that only two to four symptoms are required. This diagnostic category has not been evaluated among Finnish adolescents before, therefore no comparison data exist.

4.6 Psychiatric disorders related to depressive disorders among adolescents

4.6.1 The concept of comorbidity and its relevance in depressive youth

Three decades ago, a concept of comorbidity was coined by a Yale epidemiologist Alvin Feinstein (Feinstein, 1970). Ever since it has provoked criticism and the use of the term is more or less controversial. Some researchers (Lilienfield et al., 1994) have stated that the term could only be valid in the context of well understood diseases and that the use of this term would not be appropriate unless both conditions are underpinned by a discrete causal agent.

Comorbidity is defined by co-occurrence of two or more distinct disorders in a same individual more often than expected by chance in a period of time (Klerman, 1990, Caron & Rutter 1991, Angold et al., 1999a). However, arbitrary diagnostic cutting points are criticized (Waldman and Lilienfield, 2001). The rates of comorbidity vary extensively depending the study population and diagnostic procedures and whether lifetime or current comorbidity is assessed. Previous research suggest that comorbidity is of special interest among depressed youth because it may associate to psychosocial impairment (Lewinsohn et al., 1995, Newman et al., 1996, Wittchen 1996), suicidality (Marttunen et al., 1991, Lewinsohn et al., 1995) and treatment seeking (Fergusson et al., 1993, Lewinsohn et al., 1995, Aalto-Setälä et al., 2002, Haarasilta et al., 2002). Surprisingly, whether or not comorbidity affects or moderates treatment outcomes has not been addressed in most studies examining comorbidity during childhood and adolescence. (Ollendick, 2008). The earlier the onset, the more frequently comorbidity has been observed (Klein et al., 1999, Alpert et al., 1999). The estimates of prevalences among children and adolescents with depressive disorders are high, from 40 to 90 percent(Angold and Costello, 1993, Rohde et al., 1991, Kovacs, 1996, Biederman et al., 1995) Of adolescents with major depressive disorder, 40-80% have also at least one comorbid disorder, most likely an anxiety disorder (30-80%), a disruptive disorder (30-80)% or a substance use disorder(20-30)% (Anderson and Mc Gee 1994, Birmaher at al., 1996).
Data concerning the longitudinal relationships of early-onset depressive disorders is sparse. Previous research shows that depression in adolescence predicts further episode of major depression and may be converted to bipolar disorder (Kovacs 1996, Birmaher et al., 1998). In addition, an association of major depressive disorders to anxiety disorders and substance use disorders has been described (Rao et al., 1995, Pine et al., 1998, Lewinsohn 2000b) but few solid conclusions can be made on the relationships of early-onset depressive disorders and other mental health disorders. It has been suggested, that anxiety is a precursor for depression, possibly due shared genetic diathesis, while the association of depression and behavioral disorders and substance use could be a result of familial risk factors, such as violence or parental substance use (Fergusson et al., 2002). Interestingly, the most recent report from Great Smoky Mountain Study (Copeland et al., 2009) did not found support for a link between adolescent and young adult depression. In this well known longitudinal population-based study, comorbidity of adolescent depression accounted entirely the predictive associations between adolescent and young adulthood depression, further highlighting the need to understand comorbidity during developmental years.

4.7 Depressive disorders and attention deficit hyperactivity disorder (ADHD)

4.7.1 Definition, etiology and pathology of ADHD

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder which is characterized by different manifestations of inattentiveness and hyperactivity-impulsivity symptoms across childhood, adolescence and adulthood (Barkley et al., 2008). In adolescence, these symptoms may have a pervasive effect on adolescents’ academic achievements and cause adverse effects in family and social environments. The etiology is a complex, poorly understood interplay of early genetic and environmental effects mediated by neurocognitive processes. Secondary and tertiary influences from environment (toxins, harsh parenting) have been identified.

4.7.2 Rates, course and assessments of ADHD in adolescents.

Rates of attention deficit hyperactivity disorder vary from 1% to 8.5% (Barkley, 1998, Froehlich et al., 2007, Smalley et al., 2007), depending on the age, and diagnostic approach. ADHD is a symptom -based diagnosis, requiring the presence of either inattentive or hyperactivity symptoms or both in addition to symptom pervasiveness, impairment and an age of onset prior 7 years. ICD-10 description refers to hyperkinetic disorder, requiring all three symptom types and excluding other disorders such as anxiety. However, DSM-IV excludes ADHD only if it is not better explained by other disorder. In practice, the ICD-category is a subgroup of DSM-IV ADHD. Evidence of scientific validity of subgroups is just starting to accumulate, but the so far is inconclusive. The validity of inattentive type of ADHD is questioned most. However, inattentiveness, such as distractibility,
failure to complete work and disorganization, seems to associate to risks of academic and social underachievement (Solanto et al., 2000). Pure hyperactivity is also troublesome to distinguish from oppositional deficit disorder. Assessments of ADHD in school-age adolescents can be obtained from parent and teachers’ reports showing good sensitivity and specificity (Stein and Perrin 2003, Taylor et al., 2004). However, an interview with parent allowing clinical judgment is the most reliable method.

Solid scientific evidence shows that ADHD continues to adulthood among 50-60% of the cases (Faraone et al., 1996, Hill and Schoener 1996, Spencer et al., 1996, Barkley, 2002). It is of concern, that non-referred adolescents outside clinical settings and with high levels of symptoms without diagnosis, show academic underachievement, continue to be socially impaired, unemployed, without friends, have motor accidents and develop aggressive, antisocial behavior and delinquency (Farrington, 1995). Symptoms of ADHD disappear (or the presentation changes) when individuals age; previous research suggests that 3-5% of individuals in adulthood still have ADHD (National Comorbidity Survey, Kessler et al., 2006). The persistence of ADHD symptoms from childhood to adolescence has been reported also among 457 Finnish adolescents (Hurtig et al., 2007) but little is known about this disease in general population during transition to adulthood.

ADHD is considered to be a phenomenon with male predominance, and only recently, the literature has been extended to females. The female-male ratios range from 10:1 of (clinical samples) to 3:1 (community samples). Clinical experience has demonstrated the importance and burden of ADHD also among females (Quinn et al, 2005). In the large population-based sample of US children, in which 8.7% of the 8-15 year-olds met the diagnostic criteria for ADHD, only 47% of the children had been diagnosed previously. Girls were less likely to have their disorders identified previously and sex ratio was, suggesting referral bias unfavorable to girls, nearly 1:1 (Froehlich et al., 2007). Overall, epidemiological data shows discrepancies among females, since the estimations among women exceed those observed in girls (Arnold, 1996, Barbaresi et al., 2002). Previous research in Finland suggests a male-female ratio of 5.7:1 in general population (Smalley et al., 2007, Hurtig et al., 2007).

4.7.3 The relationships of ADHD, depressive disorders and substance use

Other neurodevelopmental disorders and early-onset as well as late-onset psychiatric problems associate frequently to ADHD in clinical samples. Of these co-existing conditions, substance abuse and substance use disorders underscore the public health importance of understanding ADHD in the context of associated problems (Elkins 2007, Upadhyaya 2008, Bukstein 2008, Wilens, 2008) Comorbid states are also clinically significant and they may require careful monitoring of medication (MTA group, 1999). The importance of substance use related comorbidity with ADHD is one of the most relevant comorbidities in ADHD, since clinical sample assessments suggest that medication of ADHD could have an impact.
for later substance use. However, larger samples without referral bias need to be followed-up to provided additional data to confirm these findings (Volkow and Swanson, 2009).

In clinically ascertained reports, girls with ADHD may be at higher risk than boys for substance use disorders, especially in early adolescence (Biederman et al., 2004). However, girls in clinical settings may be more severely affected and their assessments may not sufficiently characterize attention-hyperactivity/impulsivity spectrum in females (Gaub & Carlson 1997). Only few studies have assessed large-scale population-based samples of boys and girls; Disney et al., 1999 studying 632 girls, found some suggestion that girls with ADHD may be at higher risk for substance use than boys, albeit in this substudy of Minnesota Twin Family Study (Disney et al., 1999), the association of ADHD symptoms and substance use in adolescence was mediated through conduct disorder. A recent study from the same population source suggested that even a single symptom of ADHD independently predicted poor substance use outcome, and concluded that the association of ADHD and substance use may have not been observed consistently in previous literature when studying less-sensitive diagnostic categories (Elkins et al., 2007). In majority of studies, designs are not gender-balanced, and the data of girls is combined with boys for purposes of statistical analysis.

Based on previous scarce research, comorbidity between depressive disorders and ADHD may be clinically significant phenomena (Daviss et al., 2008). However, many studies suffer from small sample sizes, referral biases, differences in diagnostic procedures and possible rater influences (Rucklidge, 2008). Concurrent comorbidity has been stated before, and is especially common in clinical settings; in general population conduct disorders, oppositional defiant disorders (Dick et al., 2005) as well as mild depression (Hurtig et al., 2007) may associate with symptoms of ADHD in adolescents. Just recently, diagnosed and followed up in psychiatric settings, Biederman et al. (2008) state that females with ADHD had a 2.5 times higher risk for major depression at adolescent follow-up compared with control females. However, the research evidence on the association between depressive disorders and attention deficit/hyperactivity disorders is relatively new, and more studies are needed to establish these relationships.

4.8 Depressive disorders and substance use in adolescence

“Smokers may be more prone to depression than nonsmokers,” “Or, people with depression may be self-medicating by smoking, albeit in a deadly way.”
Edward Levin, Ph.D, professor of psychiatry, psychological and brain sciences http://fds.duke.edu/db/aas/pn/faculty/adlevin

“Marijuana is not the answer. Too many young people are making a bad situation worse by using marijuana in a misguided effort to relieve their symptoms of depression,” “Parents must not dismiss teen moodiness as a passing phase. Look closely at your teen’s behavior because it could be a sign of something more serious.” John P. Walters, Director, National Drug Control Policy.
4.8.1 Theoretical frameworks of addiction

Based on cross-sectional settings, it seems justified to assume that there is significant comorbidity between adolescent depression and substance use. However, whether depression causes the use of addictive substances, smoking, smokeless tobacco, alcohol and illicit drugs, is far more controversial. (Armstrong et al., 2002, Niemelä et al., 2006).

The main hypotheses are:

1. Self-medication; a theory according to which addictive substances are used to alleviate psychological symptoms (West et al., 2006). This theory focuses on finding similarities between neurobiology of depression and substance use. For example nicotine, a powerful stimulant, increases dopamine, serotonin, and noradrenalin known from their antidepressant effects and seems to affect the same regions in the brain that appear to be involved in regulating the mood, modifying the chemical imbalances of these neurotransmitters.

2. An alternative hypothesis that baseline substance use is a determinant for later psychiatric symptoms and disorders, such as depressive disorders (Breslau et al., 1998, Whitfield et al., 2000). The extension of this hypothesis is the opponent process theory of nicotine addiction (Solomon and Corbit 1973), according to which negative consequences of smoking could increase over time, as depressive mood (opposing state for initial pleasure state) becomes dominant with regular smoking.

3. The theory on common vulnerability, according to which common factors, for example genetic factors could predispose to both depression and substance use. These two may be correlated, or joined together by genetic factors involved in dopamine transmission.

Further, the pathways between mental disorders and substance use may be influenced also by confounding factors. Given the high comorbidity of adolescent depression, it is also of great importance to look for potential mediators in these associations. For example, depression could lead to alcohol use, but not without the presence of conduct disorder in individuals.

4.8.2 Diagnostic criteria for adolescent substance abuse and dependence according to DSM-IV

The current diagnostic criteria according to DSM-IV for substance abuse derived from adults include a maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by recurrent substance use a) resulting in failure to fulfill major obligations at work, school or home, b) in situations in which it is physically hazardous (driving), c) relates to legal problems .d) or continues despite having persistent or recurrent social or interpersonal problems caused by the effects of substance.

Substance dependence is a maladaptive pattern leading to clinically significant impairment and distress, requiring also three of the following in the same 12-month
period: 1) tolerance, 2) withdrawal; both tolerance & withdrawal representing physiological dependence if present, 3) a behaviour in which the substance is often taken in larger amounts or over a longer period than was intended, 4) a persistent desire or unsuccessful efforts to cut down or control substance use, 5) a great deal of time is spent in activities necessary to obtain the substance, 6) important social, occupational or recreational activities are given up or reduced because of substance use, 7) continuation of substance use despite the knowledge of having persistent or recurrent physical or psychological problem that is likely to be caused or exacerbated by the substance (APA, 1994).

The research has considered reconceptualization of substance use disorders in adolescents focusing on tolerance, withdrawal and negative consequences of substance use (Martin et. al, 2006, Crowley, 2006.) However, the empirical studies to change and develop the current diagnostic criteria are lacking.

4.8.3 Implications for assessments of adolescent substance use behaviors

Alcohol and use of other psychoactive potentially active substances is a significant public health problem. However, the criteria for substance abuse and dependence are not generally met and the adolescents are not usually appreciative for assessments or treatment. Not all symptoms are a prodrome for dependence (Practice guidelines for the treatment of substance use disorders in DSM-IV-TR, APA, 2006), but initial use of substances, often on a trial basis, may escalate as a graduate process to a full level of dependence (Orleans and Slade 1993). Thus, the assessments of frequency, quantity and duration of substance use may have importance in a developmental period of adolescence when substance use habits are established although uniform criteria for substance use is lacking. In adolescence, transition from use to abuse and sometimes even dependence occurs even in shorter time periods. Previous research demonstrates that substance misuse below the diagnostic requirements needs to be considered as risk behavior in adolescents (Rohde et al., 1996, Harrison et al., 1998). Adolescents may have a developing problem with substance dependence but not meet criteria for either substance abuse or dependence (Deas, 2006). Thus, If looking at diagnostic categories for substance use disorders, youth at risk for substance use disorders as well as those with already harmful substance use won’t be identified nor receiving much needed interventions.

Assessment of adolescent substance use is not straightforward. Face-to-face interviews may lead to underreporting of substance use by adolescents while self-report data obtained by questionnaire yields more accurate information (Gforoer et. al., 2006) In the USA, the discrepancy between self-report to other informants has guided different research strategies to assess adolescent substance use. For example, during an interview, a self-reported questionnaire on drug abuse history can be administered, then a computer self-administered interview, ideally supplemented by toxicology laboratory screens (Turner et al., 1998).
4.8.4 The relationship of depression and smoking behavior in adolescence

Smoking is to be seen as a major public health concern due to its several adversities. In terms of psychological correlates, co-occurrence with depressive disorders, as well as other psychiatric morbidity, is well documented (Brown et al., 1996, Fergusson et al., 1998, Breslau et al., 1998). Previous studies among Finnish adolescents emphasize the role of smoking as a robust marker for subsequent psychopathology, such as suicidal acts, and severe substance-use-related problems (Riala et al., 2004, 2007). Previously, an increase in smoking among Finnish girls was reported (Rimpelä et al., 2002), but the current data suggests that the trend is declining (Adolescent Health Habit and Life Style Survey, Rimpelä et al., 2007). Smoking frequency among Finnish adolescents may be lower than in the past, but still almost 25% of 16-18-year-olds smoke (Rimpelä et al., 2007).

Prospective studies during adolescence, in a developmental window for both depressive disorders and smoking behavior, have yielded inconclusive results regarding this important relationship. Previous research on relationships between depression and smoking in adolescence has suggested bi-directional causation, such that depression increases the risk for smoking, while regular smoking also can lead to depressive episodes (Patton et al., 1998, Wang at al., 1999, Wu & Anthony 1999, Goodman & Capitman 2000, King et al., 2004, Rice et al., 2007) and reciprocal relationships (Windle & Windle 2001). Depression may also increase the risk for smoking initiation (Brown et al., 1996, Kandel & Davies 1986). Common vulnerability for depression and smoking has been documented in adult females (Kendler et al., 1993), although not all findings support this hypothesis (Dierker et al., 2002). Other hypotheses, e.g., depression enhances genetic predispositions for smoking, emphasize the importance of early-onset depression in developmental trajectories of substance use (Audrain Mc Govern et al., 2004). Recently, it has also been suggested that the association of depression and smoking could be stronger among females than males (Duncan & Rees 2005, Steuber & Danner 2006).

4.8.5 The relationship of depression and alcohol use in adolescence

According to last survey of Adolescent Health and Life Style Survey, 60% of 14-year-old Finish adolescents abstain from alcohol, but only 40% of the 16-year-olds. However, the drunkenness-oriented drinking may be increasing, especially in 18-year-old boys.

International studies document the undeniable association of alcohol use and depression (Lewinsohn et al., 1993a, Feehan et al., 1994, Newman et al., 1996, Rohde et al., 1996, Costello et al., 1999, Kandel et al., 1997). The trajectories for drinking in adolescence are poorly understood. One possibility from an etiological perspective is that alcohol may be consumed because of expectations that it relieves depressive mood, a hypothesis described as a negative affect regulation model or self-medication (Sher et al., 2004). Previous studies suggest that early
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symptoms of depression may associate also with later alcohol use in children and adolescents (Wu et al., 1999, Kumpulainen et al., 2002, Aalto-Setälä et al., 2002), but perhaps, only when associated with high levels of conduct disorder symptoms (Pardini et al., 2007). While alcohol appears to be a consequence of depression, it can also lead to negative life events that precipitate depression (Libby et al., 2005, Kuo et al., 2006). It is also possible, that life events associating to later problematic alcohol use, such as a loss or a separation from a biological parent (Isokanni et al., 1994, Seljamo et al., 2006) may be linked to adolescent depression.

4.8.6 The relationship of depression and smokeless tobacco use in adolescence

Despite efforts to ban its use, smokeless tobacco is used in Finland in early adolescence, especially among boys and athletes (Haukkala et al., 2006). Smoke-free laws make it impossible to smoke and the price of cigarettes has increased leaving smokeless tobacco as an alternative to smoking. Among 18-year-old Finnish boys, 42% of the boys had experimented smokeless tobacco (Rimpelä et al., 2005). The Adolescent Health and Lifetime Survey 2007 suggested that the use of smokeless tobacco may be increasing among Finnish girls (Rimpelä et al., 2007). The physical consequences are well known, increased heart rate, receding gums and oral cancer being then most commonly known to associate to smokeless tobacco use. However, smokeless tobacco may have effects other than direct adverse physical health-related consequences similar to smoking cigarettes, cross-sectional designs suggest that smokeless tobacco may also associate with mood-related symptoms (Coogan et al., 2000, Tercyak et al., 2002). Whether it potentially contributes to nicotine dependence is, unclear (Haukkala et al., 2006) and more studies are warranted.

4.8.7 The relationship of depression and illicit drug use in adolescence

Among US adolescents, at least some lifetime use of illicit drugs was found among over 20% of the 8th grade students (age 13-14) Johnston et al., 2006). The results of the same study also suggested that most adolescents that have used illicit drugs have used it rarely, while there was a smaller minority who reported relatively frequent use. In the European School Survey Project on Alcohol and Drugs (ESPAD), 11% of Finnish adolescents, mostly age 15-16 had used cannabis and 3% reported the use of other type of illicit drug (Metso et al., 2009).

Depressive disorders and illicit drug use covary in epidemiological studies conducted in adults, but links between them in adolescence are less clear. Previous studies have reported on early drug use as a predictor of depression (Brook et al., 1998, Lynskey et al., 2004, Hayatbakhsh et al., 2007) but the role of adolescent depression as a risk factor for later drug use has received less attention. However, a preliminary finding among adolescents in residential treatment showed that baseline depressive symptoms predicted poor substance use treatment outcome (Subramaniam et al., 2007). Further, childhood symptoms of depression and anx-
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4.9 Depressive disorders and eating disorders in adolescence

4.9.1. The prevalence and incidence of eating disorders

Eating disorders (ED) are debilitating illnesses that generally develop in adolescence. Strikingly, there are few studies assessing adolescents, and virtually no reliable estimates of prevalence or incidence of these disorders during adolescence. Finnish longitudinal twin studies form older age cohorts (FinnTwin16, Keski-Rahkonen et al., 2007) have established the lifetime prevalence of 2.2% for anorexia nervosa and 2.3% for bulimia nervosa in Finnish females. In Finnish males, EDs are rare, at least in the context of symptom presentation of current diagnostic requirements (Raevuori et al., 2009). Bulimia and bulimic symptoms may be more common than previously thought in adolescence; prevalence rates of 1.8% for females and 0.3% for males have been reported (Kaltiala-Heino et al., 1999). International comparisons suggest that in a high-risk group of adolescent and young adult females the prevalence of anorexia nervosa is 0.0-0.9% (Hoek, 2006). A large longitudinal study of the Dunedin cohort (Silva and Stanton, 1997, Arsenault et al., 2000) showed that by the age of 21, 1.4% of the females have developed an eating disorder.

The true incidences are still unknown and depend much of the sampling and assessments (Treatment guidelines for DSM-IV-TR disorders, Compendium APA, 2006). In Finland, incidence for anorexia nervosa was 490/100 000 person years (Keski-Rahkonen et al, 2007) and 300 /100 000 person years for BN (Keski-Rahkonen et al., 2008). A recent study among Finnish adolescents (Isomaa et al., 2009) suggested substantially higher incidences compared to previous international (Hoek and van Hoeken, 2006) and Finnish studies (Keski-Rahkonen et al., 2007). More studies are warranted to confirm whether rates of these disorders are underestimated in adolescence.

4.9.2 The developmental and clinical features eating disorders during adolescence

Eating disorders during adolescence have particular developmental features. First, partial syndromes are of importance as they may represent the same impairment levels as stringent diagnostic categories (Patton et al., 2008). Most adolescents fail to fulfill stringent criteria for anorexia or bulimia nervosa: instead, they receive the diagnosis “eating disorders not otherwise specified, (EDNOS)”. This heterogeneous category includes a wide range of eating pathology. Binge eating disorder may also occur in adolescence (Fairburn, 2000), but it thought to be relatively rare. An unpublished population finding among under 30-year-olds suggest that prevalence of BED is 0.3% in Finnish population. (Keski-Rahkonen et
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al., unpublished observation). In adults, EDNOS is the most commonly encountered type of eating disorders in clinical practice (Fairburn et al., 2007, Machado, 2007, Eddy, 2008), possibly because it captures individuals with unremitting symptoms and individual migrated between the diagnostic categories (Hoek, 2006). In adolescents, roughly 50-60% of cases may belong to this category (Nicholls et al., 2000, Fairburn et al., 2005). Previous literature suggests that subthreshold cases, for example cases that fail to meet the frequency for binges or weight criteria for anorexia, warrant the same clinical attention than diagnostic cases (Crow et al., 2002, Fairburn et al., 2007, Stice et al., 2009). On the other hand, those with less severe, possibly self-limitating illness should be distinguished from more severe cases. A challenge presented by adolescence is presence of normative concerns about their changing body weight and shape, which need to be distinguished from extreme and rigid attitudes in eating disorder sufferers. Further, the developmental stage, which often means pursuing independence from parents, needs to be taken into account in assessment and management of adolescent-onset eating disorders.

The clinical presentation of eating disorders in adolescence includes typical core eating disorder pathology, binge-eating, vomiting, laxative use, extreme exercise, self-judgment and evaluation by weight or shape (Fairburn, 2005). The male-female ratio in adolescence may be lower than 10:1, established in adult literature (Doyle and Bryant-Waugh, 2000). There also seems to be a subgroup of eating disorder patients among whom impulsive behaviors; such as self-mutilation and substance use are frequent (Boisseau, 2009). Personality styles similar to adults have been described (Thompson-Brenner et al., 2008). Some cases are self-limiting while others, especially prepubertal cases may be life threatening (Strober, 1997, Råstam, 2003). Those cases that do continue to adulthood are usually self-perpetuating and respond poorly to treatment.

4.9.3 The relationship of eating disorders, depressive disorders and associated disorders

Eating disorders associate with mood disorders, especially depression and anxiety. Other axis I disorders, such as anxiety disorders, especially social phobia as well as personality disorders and traits (Johnson et al., 2002, Salbach –Andrae, 2008,) relate to adolescent eating disorders. In clinical practice, symptoms of anxiety and depression are common in patients, especially in patients with bulimia nervosa. Psychiatric comorbidity among eating disorders patients indicates a treatment contact (Fairburn et al., 1996). In practice, comorbidity often associated to more severe illness and may complicate treatment of eating disorders. The causes for this are not well understood. Biological and psychological factors combine mood and eating behavior. The common neurotransmitters regulating both mood and eating have facilitated the understanding of these phenomena but the deeper nature of the covariation between depressive disorders and eating disorders is unknown. It is possible that depressive disorders predispose vulnerable individuals to eating disorders. Reverse causation is also possible: persistent eating disorders can lead to depressive disorders. The comorbid pattern may also
derive from shared vulnerability of the disorders, in which case the same under-
lying factors would regulate both conditions (Keel et al., 2005, Wade et al., 2000,
Lilenfield et al., 1998).

Adult studies suggest significant comorbidity between eating disorders and de-
pression, possibly due shared genetic factors (Braun et al., 1994, Walters & Kend-

In juvenile girls, clinical and epidemiological studies suggest associations be-
tween symptoms of eating disorders and depression in adolescents (Rowe et al.,
2002, Silberg et al., 2005, Marmorstein et al., 2008). Despite substantial documen-
tation of the association between depressive disorders and eating disorders the
developmental relationships of juvenile eating disorders and other mental disor-
ders are poorly understood. Eating disorders and depressive disorders are un-
likely to have simultaneous onset, but the sequence in the development of these
disorders remains unknown because of inconclusive and mixed results. In some
studies, eating disorders have preceded other forms of psychopathology (Ivars-
son et al., 2000, Stice et al., 2001, Marmorstein et al., 2008), while in others, eating
disorders have followed the same disorders (Johnson et al., 2002, Measelle et al.,
2006, Silberg et al., 2005, Biederman et al., 2007). Only one study has explored the
possible causes behind the associations of depressive disorders and eating disor-
ders in juvenile girls, suggesting a distinct genetic effect in early adolescence and
shared environmental effects in later adolescence (Silberg et al., 2005).

4.10 Genetic epidemiology studies in the covariation of
depression, related disorders and substance use

4.10.1 Defining genetic epidemiology

Genetic epidemiology aims to differentiate the effects of genes and environment,
in order to primarily estimate the amount of genetic factors (Morton, 1982). Re-
cently, it has become easier to examine individual gene variants to in relation to
disease outcome and to investigate the causal role of environmental factors. Fur-
ther, genetic approaches can be used to map out the role of environmental factors
in the etiology of mental illness in people with different genetic profiles. It seems
that the advances in genome revelation have added value of longitudinal genetic
epidemiology research providing links for clinical psychiatry.

4.10.2 Genetic epidemiology studies of depressive disorders in
adolescence

Depressive disorders in adolescence show high heritability indicating high ge-
netic loading, number of studies reporting heritability in range of 60–80% (Thapar
and McGuffin 1994, Eaves et al., 1997, Hudziak et al., 2000, Happonen et al., 2002,
Scourfield et al., 2003). Differences in these estimates exist due different measure-
ments, age groups, instruments and informants (Thapar and McGuffin 1994,
Todd and Botteron 2001, Rice et al., 2002, Thapar and Rice, 2006). Changes in the
Early-onset depressive disorders, related disorders and substance use

importance of genetic and environmental influences across development have been documented; the adolescent onset depressive symptomatology has a higher heritability than child-onset symptoms (Scourfield et al., 2003). At ages 8-11, environmental factors may contribute to depression substantially more than genetic effects (Eley et al., 1998, Thapar and McGuffin, 1994). The study of Scourfield et al. (2003) suggested that the influence of shared environment is more important in prepupal children compared to adolescents, for whom the non-shared environmental factors are more important. Among subject of current thesis, Minna Happonen found that estimates of additive genetic effects were significant for depressive symptoms for both boys and girls at the age of 11-12, ranging from 28% to 71%. Significant common environmental effects were found only in MNPI ratings of teachers and parents. (Happonen et al., 2002) Due to these past efforts of genetic epidemiology studies trying to understand the nature of early-onset depressive disorder, they have become a focus for genetic linkage and association studies (Wigg et al., 2009).

4.10.3 Genetic epidemiology studies on substance use in adolescence

Adolescent initiation of substance use, a powerful predictor of adult substance use diagnosis, is influenced primarily by environmental rather than genetic factors (Mc Gue et al., 2000, Han et al., 2002). However, in adolescence influences change through development; familial environmental factors are critical in influencing use in early adolescence and gradually decline in importance through young adulthood. Genetic factors, by contrast, have little or no influence on substance use (tobacco, alcohol and cannabis) in early adolescence but it seems that they gradually increase in their effect with increasing age (Kendler et al., 2008). The substantial correlations seen in levels of substance use in across substances are largely the result of social environmental factors in adolescence, with genetic factors becoming progressively more important through early and middle adulthood (Mc Gue et al., 2000, Han et al., 2002, Kendler et al., 2008, Hopfer et al., 2008). The high correlation of genetic factors across ages suggests that early use may sometimes signal an early expression of a developmentally stable genetic predisposition (Derringer et al., 2008). Data from longitudinal Finnish Twin Studies suggests the importance of genetic effects on drinking patterns increasing dramatically from adolescence to young adulthood (Rose et al., 2001). At age 14, genetic influences accounted for only 18% of the variance in drinking initiation in girls, by age 18 genetic factors accounted for half of the variation. Conversely, the importance of common environmental effects decreased significantly from adolescence into adulthood, accounting for>70% of the variance at age 14, but only ~15% of the variance by age 18. Along with traditional twin modeling of the estimates, there has been increasing interest in identifying the specific environments that influence substance behavior, and how these environments interact with genetic predispositions (Dick et al., 2007).
4.10.4 Genetic and environmental effects in the covariation of depression and substance use

Once comorbidity is established, several etiologic mechanisms are possible; in addition to bidirectional causal pathways, the co-occurrence of two distinct disorders may be caused by third underlying factor, such as common genes which may increase the risk for both these disorders. Former twin studies in the field of depression and substance use aim to evaluate the genetic and environmental effects on the covariation of two diseases (Han et al., 1999, Kaprio et al., 1995, McGue et al., 2000, Kendler et al., 2003, Kuo et al 2006, McCaffery et al., 2008). Unfortunately, most genetic epidemiology studies studying depression, related disorders and substance use have focused on adults. An exception is Virginia Twin Study of Adolescent Behavioral Development (VTSABD). The investigators of the study, Silberg et al., (2004) have evaluated causes of association between substance use and both conduct disturbance (CD) and depression in adolescent boys and girls. The patterns of correlations across the two waves of this study were consistent with conduct disturbance leading to substance use in both males and females, but depression leading to smoking, drug use and, to a lesser extent, alcohol use in girls. In this study, the co-occurrence in both disorders partially reflected a shared liability but, in girls, genetic influences played an important role in the comorbidity involving depression, whereas in both sexes (but especially in boys) environmental factors played a substantial role. The National Longitudinal Study of Adolescent Health (Add Health, Harris et al., 2003), has evaluated relationship of depression and smoking in adolescence suggesting significant non-shared environmental correlations and, only in females the existence of common genetic vulnerability (Mc Caffery et al., 2008).

4.10.5 Discordant twin methods

Besides causal models, it is of importance to enhance understanding of the role of familial factors, such as childhood environment or dispositional genetic factors. Twins represent a pair of individuals naturally matched on both their genetic background and their shared environment. The method is based on identifying discordance; namely the pairs, in which the other twin is diagnosed with the illness while the co-twin is not. Thus, studying twins discordant for particular disorders offers an elegant way to control familial background, e.g., family structure, status, and parental history (Dick et al., 2005, Eriksson et al., 2005). In brief, if the within-twin-pair analyses replicate the association found among twins as individuals, it rules out the confounding effects associated with shared family background, i.e. family structure or family history of disorder. The importance of these tests is highlighted, since most of the prospective associations in clinical patients and population rests in individuals. This method has been used in Finnish Twin Cohorts previously, adjusting for family-within confounds, Korhonen et al., (2007) found that in twins discordant for illicit drug use, early smoking was a significant predictor.
4.10.6 Gene and environmental interactions

Teasing apart genetic and environmental factors on behavior is not straightforward because of the likelihood that genes correlate with environment. Genes may influence sensitivity to the environment (Eaves et al., 2003) and heritability may vary according to environmental circumstances. Further, genetic risks for an outcome may also be expressed through greater exposure towards environmental stressors (gene-environment correlation, rGE) (Rutter et al., 2006). Adolescents at genetic risk for depressive phenotypes may be exposed to increased social adversity (rGE) and more susceptible to developing symptoms in response to these risks (G x E) (Caspi et al., 2003, Lay and Eley 2008).

The genotype x environment interaction (G x E), can also be used when trying to resolve pathways affecting to the development of a specific outcome. To site an example, how genes and environment affect complex behavior; genetic differences in anxiety create later genetic differences in depression, genes that affect early anxiety increase sensitivity (G × E) to adverse life events; and genes that increase risk to early anxiety increase exposure to depressogenic environmental influences (rGE). Thus, additional genetic effects, specific to depression, further increase sensitivity to adversity. Most studies are only ongoing in this field, but the importance of gene x environment interaction is highlighted in modern genetic epidemiology.

4.11 Motivation for the study

Previous prospective longitudinal studies have not yet given conclusive results regarding the role of early-onset depressive disorders in adolescence which is a period of rapid growth and maturation. Few studies have taken into consideration the changes across development, as different influences specific to a certain age may exist. Age- standardized samples minimize the variation due age differences, but are rarely used. Besides the conclusion that depressed do not seem to outgrow their symptoms and are at risk for major depression in adulthood (Fogel, 2006), many of the maladjustment and adversities related to early depressions are not sufficiently documented. Clinical samples that deepen the understanding of depressive disorders and their clinical correlates among those who seek treatment may be vulnerable to referral bias. A large number of adolescents have depression never assessed and their implications to mental health and financial cost are poorly understood. Some studies provide only a retrospective view for younger age groups, which further affect reliability of reports. Solid descriptive statistics of older age groups in Finland have been described (Aalto-Setälä et al 2002, Haarasilta et al., 2001) but a limited number of comparable longitudinal assessments studying outcomes of early onset depressive disorders in adolescence have been documented. Although a growing body of evidence supports the importance of clinically relevant stress associated with minor depression among adolescents (Gonzalez-Tejera et al., 2005), only cross-sectional and short-term results are currently available.
The substance use prevention programs are not as successful in girls as they are in boys (Kumpfer et al., 2008). Previous literature may have failed to take into account the role of depression, body image, social assertiveness and gender-based differences in developing substance use. In many clinical but also community-based samples, examining disorders with male predominance, the amount of girls is insufficient or they are omitted. Further, the girls referred to assessments, for example depression and conduct disorders may already be severely affected and do not represent the disease in population level. However, even if the depressive disorders do not lead to treatment, the depression itself, and the behavioral combinations with other psychiatric disorders may have far-reaching, understudied consequences later on. Attention- deficits are poorly understood among girls and treatment is usually delayed (Quinn, 2005). Gender differences are suspected among subjects with ADHD regarding substance use (Disney, 1999) however, the small number of categorical diagnoses in young girls prohibits comparisons to boys in most samples.

Overall, most previous works conducted in genetically informative samples are adult samples. It is not likely, that the results would be applicable to adolescents since key risk exposures interplay with genes and are likely to vary across development (Vineis and Kriebel, 2006, Dick et al. 2007). Controlling the shared familial factors has not been extended to adolescents, and their role in genetically informative samples, such as adolescent twin samples is virtually unknown. Yet it clearly is of great importance to assess the role shared familial factors among young people.
5. Aims of the study

The study aimed to investigate early-onset depressive disorders, their relationship to other mental health disorders and developing substance use in a prospective, longitudinal setting in a population derived sample.

The study consisted of four substudies, which addressed the following:

1. Is minor depressive disorder clinically significant in adolescents and what is its relationship to major depressive disorder (MDD)? (I)

2. Do early-onset depressive disorders relate to ADHD and substance use? Are there gender differences in these potential associations and does CD modify this comorbidity? (II)

3. Are early-onset depressive disorders of importance in developmental trajectories of smoking behavior, illicit drug use, smokeless tobacco use, alcohol use and intoxication and eating disorders? Are these prospective associations explained by differences in the familial factors: genes, family structure or family income supporting future adverse behaviors? (III)

4. Do early-onset disorders associate prospectively and longitudinally to developing eating disorders? (IV)
6. Methods

6.1 FinnTwin 12 study - A longitudinal Twin Family Design

Figure 1. Flow Chart. Overview of data collection for all twin families in FinnTwin 12

6.2 Sample and procedure

From 1994 to 1998, all Finnish families with twins born in 1983-87 were identified from Finland’s Central Population Registry and enrolled into a two-stage sampling design (Kaprio et al, 2002). The first-stage study included extensive questionnaire assessments of some 5600 twins and their biological parents at baseline (87% participation rate, 2724 families) conducted during the late autumn of the year in which consecutive twin cohorts reached 11 years, with follow-up of all twins at ages 14 and 17½.

Nested within this population representative study was an intensive assessment of a sub-sample of 1035 families, comprising about 40% of all twins, most (72.3%);
748 families) selected at random. About one-quarter of the sub-sample (27.7%; 287 families) was enriched with twins assumed to be at elevated familial risk for alcoholism, based on one or both parents’ elevated scores on an 11-item lifetime version of the Malmö-modified Michigan Alcoholism Screening Test (Seppä et al., 1990). The study has carefully assessed the differences between the total random sub-set and enriched sample and no statistical differences has been found between any of the variables assessed in these substudies. The reviewers of each sub-study have had access of total comparison data of the total sample and the enriched sample. Thus, all the sub-studies present analysis of the full sample in order to retain maximum statistical power.

Both co-twins and their parents from this sub-sample were interviewed using the SSAGA (Semi-Structured Assessment for the Genetics of Alcoholism, Buzholz et al. 1994), a widely-used, reliable instrument providing lifetime diagnoses for alcohol abuse and dependence, major depressive disorder, anxiety disorders, conduct disorder, oppositional defiant disorder (ODD), attention-deficit-hyperactivity disorder (ADHD) and eating disorders. The interview pays special attention to the interrelationship of substance use and psychiatric diagnoses but because SSAGA is a comprehensive interview, it can be used in other types of studies where substance abuse but is not necessarily the main focus of the study (Schuckit, 1995, Hesselbrock et al. 1999). Assessments of non-responders at each stage revealed no evidence of selection associated with family structure, parental age, residential area, type or sex of the twins, or other systematic bias. All interviewers had previous interview experience and were Masters of Psychology, Health Care, or registered nurses; they were trained at Indiana University’s Institute of Psychiatric Research at Indiana University’s Institute of Psychiatric Research using standard COGA-interview training procedures and were supervised by an experienced psychiatrist, Dr. John Nurnberger, Jr. (Edenberg, 2002). The mean age at interview was 14.19 years, with 75% of interviews completed between 14.0 and 14.3 months of age, and all interviews completed before age 15. The final interview sample (1852) consisted of 945 boys (51%) and 907 girls (49%), a participation rate of 90%.

Subsequently, during 2000 - 2005 at the average age of 17½, twin participants from all five birth cohorts were approached again with a mailed follow-up questionnaire including substance use assessments. A total of 1545 interviewed adolescents (83% participation rate) born 1983-87 replied at age 17 (754 females, 49% and 791 males, 51%). Non-respondents did not significantly differ from respondents in baseline depression status, sex, or age.

Zygosity of twins was determined from well-validated questionnaire method supplemented by information from parents, photographs and genotyping (Goldsmith, 1990, Kaprio et al., 1995). Data collection procedures were approved by the Ethics Committee of the University of Helsinki and by the Institutional Review Board of Indiana University, Bloomington.
6.3 Relevant data collection procedures for current study

This study collected data from multiple informants. Figure 2 presents an overview of the data collection. From here on, only relevant parts of measures utilized in current thesis are described in detail.

6.4 Assessments of adolescent mental health in FinnTwin12

Several measures of adolescent mental health were available. From baseline assessments at ages 11-12 (Figure 1) the Teacher Rating forms of MNPI were used and are henceforth described in more detail. At age 14, a polydiagnostic interview (SSAGA), highly standardized for adolescents’ age, using DSM-classification was conducted. The diagnostic system at the intake was DSM-III-R; however, many disorders could be scored for DSM-IV diagnosis as well. The SSAGA provided diagnoses and symptom counts for psychiatric disorders including alcohol abuse and dependence and general information of adolescent’s mental health such as, medical history information, and suicide attempts. This study also utilized information from questionnaire assessments from first three waves (ages 11, 14, 17½) including wide range of questions related to mental health and substance use.
6.4.1 Depressive disorders, suicidality, treatment seeking and medication

At age 14, both co-twins and their parents from this sub-sample were interviewed using the Finnish translation of the adolescent SSAGA (C-SSAGA-A, Semi-Structured Assessment for the Genetics of Alcoholism) providing diagnostic information on all criteria of DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edn) major depressive disorder (MDD). Because of the low prevalence of DSM-IV MDD, (2.32%) and the clinical significance of minor depressive disorder in adolescents (Kessler at al., Gonzalez-Tejera et al 2005), we chose to include minor depressive disorder cases along with major depressive disorder cases in our analyses under the heading Depressive Disorder (DD). Minor depressive disorder (MD) was defined as meeting all criteria for MDD, except for the number of symptoms required. MD required the presence of at least two symptoms of MDD, one of them being depressed/irritable mood or anhedonia nearly every day for at least two weeks, and excluding adolescents with a previous history of DSM-IV MDD or dysthymia (presence of depressed/irritable mood nearly every day over a year and a report of at least two additional symptoms). All cases of depressive disorders were classified as early-onset depressive disorder cases.

6.4.2. Suicidality, treatment seeking and medication

In addition to diagnostic information of depressive disorders The SSAGA interview includes questions on service use, medication and suicide plans, suicide attempts and the severity of attempt from scale 0 to 4. All positive responses were asked to be explained in detail (Kuperman et al., 2001).

Appendix 1. Suicidality, treatment seeking and medication assessments in SSAGA.

When you were depressed (thinking of those at least two weeks when things were really tough on you at age x.)
Were there times when you wished you were dead?
Did you think a lot about death or dying?
Did you think about a way to kill yourself?
Did you try to kill yourself?

Suicidal attempts:
Have you ever tried to kill yourself?
How many times?
How old were you? Could you tell me what happened?
Life danger during attempt
No Danger........................................................................................................1
Went to a doctor .............................................................................................2
Was admitted to a hospital ............................................................................3
Was treated at intensive care unit ...............................................................4
Early-onset depressive disorders, related disorders and substance use

Unknown...................................................................................................9

Severity of attempt
Denies being serious ..............................................................................1
Says that was serious only at some level, but not really .......................2
Says it was for real, but is ambivalent ..................................................3
Says it was serious attempt to take one’s life......................................4

Treatment seeking & Medication
Talking about those at least two weeks you were depressed and things were really hard on you.
Did you have a doctor’s appointment or appointment with some other professionals?
Were you given medication for your symptoms?
How many times did you see a doctor on this?
Were you admitted to a hospital?
How long did you stay at the hospital?
Did they give you any medication at the hospital?

6.4.3 Related mental health disorders and symptoms

6.4.3.1 ADHD and ADHD symptoms

At age 11-12, A multinomial peer nomination inventory (MNPI) and its parallel versions-MNPI Teacher and MNPI parental Rating Forms were administered to twins. MNPI was developed for Finnish Twin cohorts by professor Lea Pulkkinen (Pulkkinen, 1987) and has high reliability, internal consistency and discriminative validity (Pulkkinen et al., 1999). It includes three dimensions; 1) behavioural problems; inattention, hyperactivity, impulsivity and aggression and adjustment; 2) constructiveness, compliance and social activity and 3) emotional problems; depression and anxiety. The original MNPI included 30 items, in developing this instrument for Finnish Twin sample, additional items were added to Teacher Rating Forms and Parental Forms to enrich the coverage of ADHD, depression and anxiety, tested and refined in pilot studies to be appropriate for age , following closely the DSM-IV descriptions. Further analysis has demonstrated its ability to differentiate behavioural problems, e.g. aggression from hyperactivity (Pulkkinen et al., 1999). In MNPI, teachers rating items are presented in the form of statements (e.g., is hyperactive, does not wait for his turn). The teachers were asked to rate each twin on every item on a four point scale where 0=does not apply, 1=applies sometimes, 2=certainly applies, 3=applies in a pronounced way.

At age 14, the diagnosis of ADHD was made according to DSM-III-R, the diagnostic system in use, when planning the design of the current study and when the intake began. DSM-III-R does not take into account subtypes of ADHD, and lacks symptoms of current classification, thus diagnosis of ADHD was not made for DSM-IV. However, studying symptoms was prompted by the suggestions of previous research (Elkins et al., 2007) confirming that symptoms of ADHD by diag-
nostic interview have proven useful, and the dimensional variables of inattentiveness and hyperactivity may be more informative in ADHD than less sensitive diagnostic category.

6.4.3.2 Oppositional defiant disorder, generalized anxiety disorders and conduct disorders

At age 14, based in semi-structured interview, the other major types of disorders; generalized anxiety disorder (GAD), ODD and conduct disorder, as were analyzed according to DSM-IIIR/ DSM-IV criteria.

6.4.3.3 Eating disorders

At age 14, eating disorders were analyzed in the same interview (SSAGA) using both full DSM-IV criteria and broader ad-hoc definition (meeting at least 2/4 of current diagnostic criteria). At age 17½ the adolescents were asked: Do you have or do you think that you have ever had an eating disorder? 6 alternatives were given: 1) yes, anorexia nervosa, 2) yes, bulimia nervosa, 3) yes, both anorexia and bulimia nervosa, 4) yes, an other type of an eating disorder, 5) I have not had an eating disorder and 6) I don’t know. The reliability of questionnaire assessments have been studied by authors in Finnish population previously and despite their simplicity, they showed satisfactory and more specific and sensitive detection of lifetime eating disorders compared to the longer and more elaborate EDI subscales (Keski-Rahkonen and Sihvola, 2006).

6.4.4 The assessments of substance use in FinnTwin12

6.4.4.1 Smoking behavior, smokeless tobacco, alcohol use disorders and illicit drug use at baseline

At age 14, adolescent tobacco use was measured by semi-structured interview at age 14., by multi-item non-diagnostic section of C-SSAGA-A, comprising of 23 items assessing any use and regular use of tobacco products (cigarettes, smokeless tobacco, cigars, pipe), age of first and regular use, time since last use and amount, frequency and duration of regular use of each tobacco product. Based on those items, groups of experimenters, occasional and daily users were formed as well as users of smokeless tobacco. Illicit drug use was analyzed from its individual section of semi-structured interview, and was defined as a report of use of any illicit drugs, such as marijuana, amphetamine, ecstasy, LSD, codeine or methadone. The never-smokers, never smokeless-tobacco users and those who had never used illicit drugs were used as reference group. Alcohol abuse and alcohol dependence were diagnosed according to DSM-III-R, based on diagnostic sections.

6.4.4.2 Smoking behavior, smokeless tobacco, alcohol use and illicit drug use at follow-up

Outcome variables at age 17½ were based on self-report questionnaire including detailed questions about substance use:
Smoking behavior. “Have you ever tried smoking” and a multi-categorical follow-up: “Which of the following best describes your current smoking”. The response alternatives were: 1) I smoke 20 cigarettes or more/day; 2) 10-19 cigarettes/day; 3) 1-9 cigarettes/day; 4) I smoke once a week or more often, not daily; 5) I smoke less than once a week; 6) I’m no longer smoking; and 7) I have experimented with smoking, but I don’t smoke. Alternatives 1, 2 and 3 were defined as daily smokers, 4 and 5 as occasional smokers; and 7 as experimenters. In multinomial regressions, the never smokers formed the reference group. In final models, when excluding previous users, the adolescents who were not currently smoking (6) were also excluded to avoid the inclusion of potential former heavy smokers.

Smokeless tobacco use. “Have you ever tried smokeless tobacco? How many times so far?” The alternatives were 1) No, I haven’t (defined as abstainers); 2) once (defined as experimenters); 3) 2-50 times; 4) more than 50 times; and 5) I use smokeless tobacco regularly. Alternatives 3), 4) and 5) were considered users. Those who had never used smokeless tobacco were defined as abstainers and formed the reference group.

Illicit drug use. “Have you ever tried illicit drugs (marijuana, hash or similar drugs). Response options were: 1) never (abstainers); 2) 1-3 times (experimenters); 3) 4-9 times or 10-19 times (moderate use); and 4) more than 20 times (frequent use). In multinomial regressions, the abstainers formed the reference group.

Alcohol use frequency and intoxication. “How often do you use alcohol, even in small amounts, like half a bottle of beer or a sip of wine?” and “How often do you use so much alcohol that you become intoxicated?” Nine response options were given: 1) daily; 2) a couple times a week; 3) once a week; 4) a couple times in a month; 5) once a month; 6) once in a couple months; 7) 2-4 times a year; 8) once a year or more rarely; and 9) I don’t use alcohol. In multinomial analyses, since only one person reported daily alcohol use, categories 1) and 2) were collapsed as frequent users; 3), 4) and 5) as moderate users; 6), 7) and 8) as occasional users; and 9) as abstainers. To assess intoxication, alternatives 1), 2), and 3) were considered frequent intoxication, 4), 5) and 6) were considered recurrent and 7), 8) as occasional intoxication. In both drinking frequency and frequency of intoxication, alternative 9) was considered as abstaining and non-intoxicating, respectively, and used as reference category.

6.5 Statistical methods
6.5.1. General biostatistics

Descriptive statistics in substudies I-IV were generated with Stata Software (Versions 8.2, and 9.2, Stata Corporation, College Station, TX, USA). For lifetime prevalences of minor and major depressive disorders and other psychiatric disorders, confidence intervals were calculated. Significant differences in means and distributions between genders were tested with design-based F-tests and standard procedures for survey data (svy options is STATA). When appropriate, comparisons in subgroups, significant differences in means and distributions between
diagnostic groups were tested with two-sample Wilcoxon rank-sum (Mann-Whitney) and Fisher’s exact tests. A probability level of $p<0.05$ (two-tailed) was considered statistically significant.

In all analysis considering individuals, the effect of twin study design on standard errors was taken into account by studying twin pairs as sample clusters (Williams, 2000, Woolridge, 2002) to adjust $p$-values and confidence intervals to correct for the non-independence of observations within twin pairs. The option cluster in Stata (Stata, Stata Corp) takes into account the correlated nature of twin data, based on generalized estimation equations (Pickles, 1998).

6.5.2 Logistic Regression Models

The univariate and multivariate associations between baseline and follow-up variables were investigated using logistic regression models. Substance use outcome measures at age 17.5 were multi-level and multinomial logistic regression models were applied to the data (substudies II, IV). Models were built sequentially and odds ratios and 95% confidence intervals were calculated:

In substudy II, significant differences in means and distributions between genders were tested with design-based F-tests and standard procedures for survey data (svy options is STATA). To study the relationships of DSM-IV based ADHD symptoms and substance use multinomial logistic regression was applied to data. First, a multinomial logistic regression model to study the association with the outcomes was examined. Second, potential confounding covariates of daily smoking behavior, illicit drug use, and comorbid psychiatric disorders were added to the model. To determine whether sex differences were present in the associations, sex by diagnosis or sex by symptoms interaction terms were added to the logistic models. Given the rarity of reports describing female participants with externalizing symptoms and substance use outcomes, models were fit separately for boys and girls. Gender differences were further tested with likelihood-ratio tests to confirm significant differences between coefficients in models separately fit to data from boys and girls.

In substudy III, univariate and multivariate associations of baseline early depressive disorders with follow-up substance use were examined with multinomial logistic regression using never-users as the reference group. First, a multinomial logistic regression model to study the association of early-onset depressive disorder with the particular substance use outcome was examined. Second, potential confounding covariates (baseline alcohol use disorders, smoking, smokeless tobacco use, and illicit drug use) and comorbid psychiatric disorders were added to the model. Finally, to investigate whether early-onset depressive disorders also predicted substance use in those who were not users at baseline, users of each outcome variable in question, (for example, smokers at baseline when predicting future smoking) were excluded from the analysis.

In substudy IV, logistic regression analyses were conducted to test the predictive value of Axis-I disorders for the development of eating disorders. First, a uni-
variates logistic regression model to study the association with eating disorder and another Axis I disorder was examined. Second, other Axis I mental disorders were added to the model. Finally, to investigate whether Axis I disorders also predicted eating disorders among those without eating disorders at baseline, the adolescents with baseline eating disorders were excluded from the analysis.

6.5.3. Conditional logistic regression models (substudies III, IV)

In substudies III and IV, the investigation of whether the associations of independent and dependent variables replicate after controlling for shared genes and shared family environments, including differences in family structure, status, parenting styles, parental models and family history, conditional logistic regression analyses were conducted among all informative twin pairs discordant for both predictor (early-onset depressive disorders at 14) and follow-up outcome (substance use or eating disorders at 17½). All within pair -models were built and tested similar to multivariate logistic regression models between pairs, with conditioning on the twin pair. Odds ratios and 95% confidence intervals were calculated.
7. Results

7.1 Lifetime prevalences of minor depression and major depressive disorder by gender (I)

A large proportion of depressed adolescents fulfilled the criteria for potential valid subtype of depression for adolescents, minor depression. Exclusive to each other, the DSM-IV diagnosis of minor depression was substantially more common than major depressive disorder (12.0% vs. 2.3%). Lifetime prevalences of minor depression and major depressive disorder exhibit statistically significant gender difference (P<.001) with female having a twofold difference for minor depression and fourfold for MDD (Table 1).

Table 1. Lifetime prevalences of minor depression (MD) and major depressive disorder (MDD) in 1852 14-year-old Finnish adolescents (mean 14.14) according to a semi-structured interview

<table>
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<tr>
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<th>MD</th>
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<tr>
<td></td>
<td>N</td>
<td>Prevalence (%)</td>
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<tr>
<td>TOTAL SAMPLE, N=1852</td>
<td>222</td>
<td>12.0 (10.5-13.5)</td>
</tr>
<tr>
<td>GIRLS, N=907</td>
<td>144</td>
<td>15.8 (13.5-18.2)</td>
</tr>
<tr>
<td>BOYS, N=945</td>
<td>78</td>
<td>8.3 (6.5-10.0)</td>
</tr>
<tr>
<td>F:M ratio</td>
<td>2.1</td>
<td>(1.5-2.8)</td>
</tr>
</tbody>
</table>

MD=minor depression, MDD=major depressive disorder, F: M ratio=female: male ratio, OR=odds ratio

7.2 Suicidality, treatment seeking and comorbidity among depressed youth

Subject with both diagnoses (MD and MDD) were considerably impaired and qualitatively similar. Suicidal ideation, suicide plans and suicide attempts were significantly associated to both minor depression and major depressive disorder. Most attempts were serious attempts of taking one’s life and 60% of them led to a contact with medical professional. Only a third of adolescents with major depressive disorder had sought or been referred to a physician, due to their depressive condition. Suicidal ideation in the total interview sample of 1852 adolescents was 6%, compared to 32% among adolescents with MD and 54% among those with MDD.

As expected, comorbidity was high, 30.6 % (68) with minor depression and 53.5% (23) of adolescents with DSM-IV MDD had at least one comorbid diagnosis. 21.7% (48) of minor depression and 30% (13) of MDD cases had one, 5.9% (13) and 14.0%
Early-onset depressive disorders, related disorders and substance use

(6) had two, 2.3% (5) and 2.3% (1) had three, 0.9% (2) and 4.7% (2) had four lifetime comorbid diagnoses plus depressive disorder. Recurrence and low treatment seeking were associated with early-onset depressive disorders at the age of 14.

Table 2. Multivariate logistic regression for suicidality, service use among adolescents with minor depression (MD) and major depressive disorder (MDD).

<table>
<thead>
<tr>
<th></th>
<th>MD</th>
<th></th>
<th></th>
<th>MDD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% OR 95%CI</td>
<td></td>
<td>% OR 95%CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Suicidality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ideation</td>
<td>31.8 27.5</td>
<td>(15.8-48.0)***</td>
<td>53.5 14.3</td>
<td>(6.3-32.1)***</td>
<td></td>
</tr>
<tr>
<td>suicide plan</td>
<td>8.6 7.6</td>
<td>(3.6-16.3)***</td>
<td>27.9 18.0</td>
<td>(5.9-54.3)***</td>
<td></td>
</tr>
<tr>
<td>suicide attempt</td>
<td>2.3 3.8</td>
<td>(1.0-14.4)*</td>
<td>11.6 12.3</td>
<td>(1.8-81.2)**</td>
<td></td>
</tr>
<tr>
<td><strong>Service use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>doctor’s appointment</td>
<td>6.8 4.9</td>
<td>(2.1-11.4)***</td>
<td>32.6 26.8</td>
<td>(10.1-71.3)***</td>
<td></td>
</tr>
<tr>
<td>antidepressant</td>
<td>1.4 8.0</td>
<td>(0.8-77.5)</td>
<td>4.7 22.0</td>
<td>(2.9-166.4)***</td>
<td></td>
</tr>
</tbody>
</table>

(All models were adjusted for sex and clustered sampling) MD=minor depression, MDD= major depressive disorder, OR=odds ratio

7.3 The concurrent and prospective relationships of early-onset depressive disorders, ADHD and substance use (II)

In multinomial logistic regression models adjusting for other psychiatric disorders, the association of attention deficit/hyperactivity disorder and depressive disorders was significant only in girls (OR 2.06, 95%CI 1.38-3.07). When depression was present with ADHD, more than half (54%) of the girls, against 38% of the boys, smoked daily. In multinomial regression models, when comorbidity was taken into account, the combination of depressive disorders and ADHD increased concurrent risk for daily smoking nearly six-fold (OR 5.78, 95%CI 1.28-26.0) among girls compared to girls with neither disorder.

At baseline age 11-12, parent and ratings of DSM-IV inattentiveness, hyperactivity and impulsiveness for boys were significantly higher (Design-based F-tests, all p<.001) compared to girls (table 1, substudy II). Substance use outcome of DSM-IV based ADHD symptoms was assessed at age 14 and 17.5.

Significant interactions with sex (p-level <.01) were present in multinomial logistic regressions with baseline DSM-IV ADHD symptoms and follow-up interview assessments of illicit drug use and alcohol use disorders as well as illicit drug use and at age 17.5. Controlling for conduct disorder (CD), both teacher’s and parent’s report consistently predicted daily smoking behavior at age 14 among both boys and girls. Only among females were baseline DSM-IV ADHD-symptoms also prospectively associated with alcohol abuse and alcohol dependence diagnoses, and illicit drug use (table 2, substudy II). Gender differences were further tested.
Early-onset depressive disorders, related disorders and substance use

with likelihood-ratio tests to confirm significant differences between coefficients in models separately fit to data from boys and girls. At follow-up age 17.5, controlling for CD and previous substance use, baseline symptoms were significant predictors of frequent alcohol use (participants who reported alcohol use at several at least couple times a week) and illicit drug use (participants who reported illicit drug use more than 20 times) only in girls. Parents’ and teachers’ reports did not always mark a consistent pattern of substance use outcome, even though in many categories substance use outcome was unfavorable to girls compared to boys. Inattentiveness reported by both informants was a strong predictor of illicit drug use in young females across adolescence (table 2, substudy II).

7.4 Early-onset depressive disorders and substance use (III)

Early onset depressive disorder predicted elevated levels of use for measured outcomes of substance use/abuse at age 17½. Table 3 presents the distribution of the five outcomes; smoking behavior, smokeless tobacco use, illicit drug use, alcohol use and intoxication frequency by depressive disorder status at baseline age 14. To cite an example, 39 % of adolescent twins with depressive disorders at age 14 reported daily smoking at age 17½, compared to 26 % of adolescents without baseline depressive disorders, a 1.5 elevation in risk; 30.5 % of those without DD at baseline reported they were never smokers at follow-up, compared to less than 20 % of those with baseline DD. Similarly, frequent use of illicit drugs at age 17 was elevated 3.6 times among those with DD at age 14. Overall, early-onset depressive disorders were robustly associated with elevated levels of addictive substance use, and, with but one exception, DD elevated prevalence of substance use/abuse consistently among both girls and boys.
Early-onset depressive disorders, related disorders and substance use

Table 3. Distribution of all measured of levels smoking behavior, smokeless tobacco use, illicit drug use and alcohol use at three-year-follow-up (mean age 17.5) among adolescents with and without depressive disorders (DD, DSM-IV major or minor depressive disorder) at age 14.

<table>
<thead>
<tr>
<th>DD at Baseline</th>
<th>No baseline DD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>females</td>
</tr>
<tr>
<td>Smoking behavior</td>
<td></td>
</tr>
<tr>
<td>Never-smokers</td>
<td>18.8%</td>
</tr>
<tr>
<td>Experimentation</td>
<td>32.9%</td>
</tr>
<tr>
<td>Occasional</td>
<td>9.4%</td>
</tr>
<tr>
<td>Daily(^1)</td>
<td>38.9%</td>
</tr>
<tr>
<td>Smokeless tobacco</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>76.0%</td>
</tr>
<tr>
<td>Experimentation</td>
<td>15.3%</td>
</tr>
<tr>
<td>Use</td>
<td>8.7%</td>
</tr>
<tr>
<td>Illicit drug use</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>74.7%</td>
</tr>
<tr>
<td>Experimentation</td>
<td>17.3%</td>
</tr>
<tr>
<td>Moderate (4-19 times)</td>
<td>4.7%</td>
</tr>
<tr>
<td>Frequent (&gt;20 times)</td>
<td>3.3%</td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
</tr>
<tr>
<td>Abstainers</td>
<td>10.7%</td>
</tr>
<tr>
<td>Occasional</td>
<td>21.3%</td>
</tr>
<tr>
<td>Moderate</td>
<td>60.0%</td>
</tr>
<tr>
<td>Frequent(^2)</td>
<td>8.0%</td>
</tr>
<tr>
<td>Intoxication</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>16.7%</td>
</tr>
<tr>
<td>Occasional</td>
<td>26.7%</td>
</tr>
<tr>
<td>Recurrent(^3)</td>
<td>50.0%</td>
</tr>
<tr>
<td>Frequent</td>
<td>6.6%</td>
</tr>
</tbody>
</table>

In most cases, early onset depressive disorders associated longitudinally and prospectively to the most elevated levels of measures substance use outcome at age 17½ (Figure 3).
Early-onset depressive disorders, related disorders and substance use

Figure 3. The distribution of the significant outcomes at age 17½ by depressive disorder status at baseline age 14.

DD=depressive disorders. Daily smoking = from 1 cigarette to over 20 cigarettes/day. Smokeless tobacco use 2-50 times or more, Frequent alcohol use= recurrent intoxication= couple times in a month to daily intoxication, Illicit drug use= used more than 20 times

7.4.1 The prospective associations of early-onset depressive disorders and substance use

In multinomial logistic regression models early-onset depressive disorders predicted daily smoking (odds ratio 2.29, 95%CI 1.49-3.50, p<.001), smokeless tobacco use (OR = 2.00, 95%CI 1.32-3.04, p=.001), frequent illicit drug use (OR = 4.71, 95%CI 1.95-11.37, p=.001), frequent alcohol use (OR = 2.02, 95%CI 1.04-3.92, p=.037) and recurrent intoxication (OR = 1.83, 95%CI 1.18-2.85, p=.007) three years later.

The results remained significant after adjusting other psychiatric disorders and substance use disorders and more importantly, were replicated also among those without previous substance use.

In Table 4, model 1, which adjusted for sex differences and clustered sampling of twins, shows that at three-year follow-up, early-onset depressive disorders
Early-onset depressive disorders, related disorders and substance use

strongly predicted all later substance use. Model 2 reports results of a model that adjusted for other early-onset psychiatric disorders, as well as all other types of previous substance use, and excluded all participants with previous use of a particular substance, for example previous smokers. Results from Model 2 suggest that depression predicted future daily smoking even among those who were not daily smokers at baseline. Similar patterns of significant associations after excluding baseline users were observed for smokeless tobacco use, frequent illicit drug use, frequent alcohol use and recurrent intoxication among adolescents.

Table 4. The Odds Ratios of multi-level smoking status, illicit drug use, smokeless tobacco use, alcohol frequency and intoxication at follow-up (age 17.5) according to early-onset depressive disorders at baseline (age 14) among Finnish twins born 1983-87 (N=1545).

<table>
<thead>
<tr>
<th></th>
<th>Model 1 (Bivariate OR, 95%CI)</th>
<th>Model 2 (Multivariate OR, 95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95%CI</td>
</tr>
<tr>
<td><strong>Smoking behavior</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-smokers</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Experimentation</td>
<td>1.40</td>
<td>.91-2.16</td>
</tr>
<tr>
<td>Occasional</td>
<td>1.37</td>
<td>.77-2.44</td>
</tr>
<tr>
<td><strong>Daily</strong></td>
<td>2.29</td>
<td>1.49-3.50</td>
</tr>
<tr>
<td><strong>Smokeless tobacco use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-users</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Experimentation</td>
<td>1.88</td>
<td>1.20-2.96</td>
</tr>
<tr>
<td><strong>Use</strong></td>
<td>2.00</td>
<td>1.32-3.04</td>
</tr>
<tr>
<td><strong>Illicit drug use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-users</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Experimentation</td>
<td>1.66</td>
<td>1.05-2.64</td>
</tr>
<tr>
<td>Moderate (4-19 times)</td>
<td>1.67</td>
<td>.80-3.45</td>
</tr>
<tr>
<td>Frequent (&gt;20 times)</td>
<td>4.71</td>
<td>1.95-11.37</td>
</tr>
<tr>
<td><strong>Alcohol use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstainers</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Occasional</td>
<td>1.31</td>
<td>.75-2.31</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.32</td>
<td>.80-2.20</td>
</tr>
<tr>
<td>Frequent</td>
<td>2.02</td>
<td>1.05-3.91</td>
</tr>
<tr>
<td><strong>Intoxication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Occasional</td>
<td>1.19</td>
<td>.73-1.95</td>
</tr>
<tr>
<td><strong>Recurrent</strong></td>
<td>1.83</td>
<td>1.18-2.85</td>
</tr>
<tr>
<td>Frequent</td>
<td>1.26</td>
<td>.62-2.58</td>
</tr>
</tbody>
</table>
7.4.2 Discordant twin analysis of early-onset depressive disorders and substance use

Analysis of twins discordant for early-onset depressive disorders confirm predictive associations of early-onset depressive disorders with smokeless tobacco use and frequent drinking at age 17½, in within-family replications with co-twins matched on half or all their segregating genes, and on their family structure, socio-economic status, and household environment.

The longitudinal association of depressive disorders and substance use was run in the same setting. In the total sample, 150 twin pairs were discordant for baseline early-onset depressive disorders (i.e., one twin in each pair met criteria for DD while the co-twin did not); these 150 pairs formed the target study group for our within pair-analysis. Among these 150 pairs, we then identified the subset of pairs discordant as well for each substance use outcome at follow-up, asking of these informative pairs, whether it was the depressed co-twin that exhibited substance use/abuse at follow-up.

For example, 46 of the 150 twin pairs discordant for depressive disorder at age 14 were discordant as well for daily smoking at age 17½. And in 30 of these 46 doubly discordant twin pairs, the co-twin depressed at baseline was the daily smoking twin at follow-up (30/16 = unadjusted odds ratio = 1.875). Conditional logistic regression models were employed to adjust these odds ratios for sex differences and observed (Table 5) significant sex-adjusted associations for smokeless tobacco and frequent alcohol use. Additional conditional logistic regression analyses demonstrated that the relationships with smokeless tobacco and frequent alcohol use remained significant after excluding the opposite-sex twin pairs.

Table 5. Substance use outcomes at age 17½ in twin pairs (N=150 pairs) discordant for Early-Onset Depressive Disorders and substance use at follow-up.

<table>
<thead>
<tr>
<th>Substance Use Outcome</th>
<th>No. of pairs</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Smoking</td>
<td>32/46</td>
<td>1.83</td>
<td>.98-3.42</td>
</tr>
<tr>
<td>Smokeless Tobacco</td>
<td>19/32</td>
<td>5.63</td>
<td>1.27-24.8</td>
</tr>
<tr>
<td>Drug Use</td>
<td>11/16</td>
<td>1.67</td>
<td>.40-6.97</td>
</tr>
<tr>
<td>Frequent Alcohol Use</td>
<td>14/22</td>
<td>3.75</td>
<td>1.07-13.20</td>
</tr>
<tr>
<td>Regular Drunkenness</td>
<td>31/56</td>
<td>1.43</td>
<td>.82-2.53</td>
</tr>
</tbody>
</table>

Abbreviations: CI=Confidence Intervals; OR=Odds Ratios.

*Fraction of pairs discordant both for depressive disorder at baseline and substance use at follow-up in which the co-twin depressed at baseline was the twin who met the substance use outcome. The odds ratios were calculated using conditional logistic regression. The odds ratios were adjusted for sex, other covariates examined were conduct disorder, attention-deficit (ADHD), oppositional-deficit (ODD), substance use and generalized anxiety disorders, but none were significant predictors. All models excluded baseline users.
7.5 The prospective associations of early-onset depressive disorders, generalized anxiety disorders and eating disorders (IV)

7.5.1 Lifetime prevalences of DSM-IV anorexia nervosa and bulimia nervosa

Lifetime prevalences for DSM-IV anorexia and bulimia nervosa were 0.32% (95%CI 0.06-0.58) and 0.05% (95%CI 0-0.10), respectively. Broad syndromes, defined ad-hoc as the presence of at least 2/4 current DSM-IV diagnostic criteria, were considerably more common (N=73, 3.9%). The most frequent eating disorder symptoms at the age of 14 were binge-eating, body image concerns and fear of gaining weight while being underweight.

Among 1545 adolescents at follow-up, the prevalences for self-reported anorexia and bulimia nervosa were 1.4% (95%CI 0.74-1.99) and 0.7% (95%CI 0.23-1.13), respectively.

7.5.2 Early-onset depressive and generalized anxiety disorders as predictors of eating disorders in late adolescence

In longitudinal analysis, major depressive disorders and generalized anxiety disorders at age 14 were strongly associated with eating disorders at follow-up at age 17 ½. These relationships between generalized anxiety and EDs and depressive disorders and EDs were statistically significant also among those without baseline eating disorders and eating disorder symptomatology. Because of high comorbidity of these two disorders, the sample was stratified based on lifetime diagnoses of major depressive disorders and generalized anxiety into four groups; those with neither baseline diagnosis, those with both, those with major depressive disorders alone and those with generalized anxiety alone. The presence of major depressive disorder in combination with generalized anxiety disorder increased the likelihood of future disorders compared to mood or anxiety disorders alone (adjusted odds ratio, 11.3). The results remained significant after adjustment of other mental disorders at baseline and excluding baseline eating disorders (Table 3, substudy 4).

7.5.3 Early-onset depressive disorders as predictors of eating disorders in adolescence-discordant twin analysis

The prospective analysis of depressive disorders and eating disorders was then complimented by examining these associations within discordant twin pairs. 42 pairs were identified to be discordant for eating disorders at follow-up, among them 10 sister-sister pairs were also discordant for baseline early-onset depressive disorders and generalized anxiety disorders and were analyzed further. In 8/10 pairs it was the depressed one who went on developing an eating disorder while the co-twin, without any symptoms of ED of DD or GAD at baseline, stayed healthy.
The main finding of discordant twin analysis was that within a twin pair with shared family background, the twin affected with depressive or generalized anxiety disorder was 4 times more likely to develop an eating disorder. In conditional logistic regression models adjusted for sex and all other Axis-I disorders this translated to increased risks of co-twin with MDD (OR 1.29, 95%CI 1.02-1.64) and similar, but statistically nonsignificant trend of co-twin with GAD (OR 1.60, 95%CI .75-3.43) for later eating disorders. Given the rarity of these traits in population, the power of discordant analysis to exclude familial factors or established causality was limited.
8. Discussion

8.1 Summary of main findings

8.1.1 Minor depressive disorder during adolescence- clinical correlates and adverse outcomes (I)

Although providing descriptive statistics was not a primary aim of the study, depressive conditions with impairment but below the diagnostic threshold of MDD, were relatively common among Finnish participants, similar to international studies. (National Comorbidity Survey (Kessler et al., 1998, Lewinsohn et al., 2004). The results of the first substudy suggested that a categorical diagnosis of major depressive disorder reflects severe cases, but depressive conditions defined according to diagnostic criteria for minor depression, with similar case definition of disability and distress, but with less number of symptoms, was also associated with important clinical correlates such as suicidality, comorbidity and recurrence resembling those meeting full diagnostic requirements for MDD. The findings are in line of minor depressive disorders in adulthood (Rapaport et al., 2002) extending these findings to adolescents.

Overall, the findings of the substudies of this thesis support the role of minor depression causing clinically relevant stress and psychiatric morbidity, in line with previous evidence from cross-sectional and short-term reports (Lewinsohn, 2000, Cuijpers, 2004, Gonzalez-Tejera et al., 2005).

The results do not imply that minor depression necessarily is a distinct condition. However, they established that this category represents clinically significant depressive symptoms rather than evanescence in adolescence and further relates to hypothesis that psychiatric disorders manifest as a phenotypic continuum (Leigh, 2009). Further, the results also support a more dimensional approach to depression, as a spectrum of overlapping disorders, potentially ranging from bipolar I depression to major depressive disorder (Benazzi, 2006). Thus, developing better-fitting diagnostic models is essential for adolescents to provide accurate estimates for service planning.

8.1.2 The prospective relationships of depressive disorders, ADHD, symptoms of ADHD and substance misuse among adolescents (II)

While externalizing disorders, conduct disorders, and oppositional defiant disorders were associated with ADHD in both boys and girls, the strong predictive and concurrent associations of ADHD with depressive disorders was found only in girls. That finding suggests that the awareness of this behavioral combination among girls may be important in the early identification of adolescent girls with ADHD in the community. The prospective analyses of substance use outcome of ADHD behaviors are limited to a 7 year time span; clearly, these results do not permit confident conclusions of causality. However, the short-term outcome of substance use of girls with ADHD symptoms was unfavorable: results from this
gender-balanced sample support prospective associations of symptoms of ADHD with alcohol abuse and alcohol dependence and frequent illicit drug use only among girls. The population-based findings from other cultures (Disney et al., 1999, Elkins et al., 2007) are few, but suggestive that even symptoms of ADHD might predict substance abuse problems. This data adds substantial evidence in that girls may be at higher risk compared to boys, and that the girls’ risk may are not attenuated by conduct disorder, a strong predictor for substance abuse. The current analysis also suggest that dimensional predictors may be informative, perhaps more so than categorical diagnosis of ADHD. Further, restricting analyses to diagnostic categories only may be misleading, since risk factors may operate across a range of these symptoms.

This finding, even reported before in clinical sample (Biederman et al., 2008) has great provas. The potential unfavorable substance use outcome among girls warrants more studies in relations of externalizing conditions and substance use by gender. Medicalization of all ADHD symptoms is not advisable, but for the very least, whether early recognition and interventions among girls with behavioral symptoms of ADHD hold potential for substance use prevention further in their lives calls for more research.

8.1.3 Dual diagnosis - a self-medicating strategy or something else?

The results of third substudy suggested that early onset depressive disorders signal the subsequent substance use; interestingly, most recent studies also confirm increasing involvement of substance use among youth with early-onset depressive disorders (Wu et al., 2008). In this study, many of the findings highlighted the importance of early-onset depressive disorders in non-referred adolescents as well as early symptoms since many were antecedents of future adverse outcomes. This seems to be a trend also in other recent epidemiological studies in Finnish adolescent samples. (Niemelä et al 2009, from boy to a man study, Huurre et al., 2009, in press).

In principal this speaks for theoretical background of self-medicating hypothesis; are young people making their situation worse as a misguided effort to relieve the symptoms of depression? The results are age-dependent, but it seems that depressed adolescents are in particular vulnerable. Interestingly, the results of this study have been recently confirmed in young males (Niemelä et al., 2009). However, none of the studies have been able to formally establish causality.

Analysis of twins discordant for early-onset depressive disorders confirm predictive associations of early-onset depressive disorders with smokeless tobacco use and frequent drinking at age 17½, in within-family replications with co-twins matched on half or all their segregating genes, and on their family structure, socio-economic status, and household environment. Interestingly, the novel findings within the twin pair parallel the findings of individuals, allowing us to rule out the third confounding factor common to siblings. In this field, no comparable previous results were available for familial aspects of disorders and health-related behaviors associated with early-onset depression.
Although exploratory, these findings do suggest that the association of depression and substance use is not explained by familial factors, such as family income, instead the influence of peers or dispositional personality traits may be of importance. In the context of developmental theories, this could relate to increased family conflicts and critical thinking which emerges in adolescence creating a heightened need for peer approval in adolescence. Severing family ties can further lead to over identification with the peer group, identity confusion and excessive rebellion. (Steinberg 1993). Thus, at least from a theoretical point of view, the importance of peers in developing substance use would be meaningful. Could a depressed individual be more vulnerable to those influences, perhaps due lower self-esteem?

8.1.4 The prospective analysis of affective disorders and eating disorders

Partial eating disorder syndromes were of importance representing the same impairment levels as strict diagnostic categories. Although limited number of cases fulfilling diagnostic criteria for DSM-IV anorexia nervosa and bulimia nervosa prohibited formal comparisons, it was evident that broad syndromes were qualitatively similar to full disorders. Few comparable studies conducted in adolescence strongly support these findings (Patton et al., 2008). However, it is likely, that broad categories also include individuals with less severe symptoms and both clinically significant and non-significant groups exist among adolescents not fulfilling the diagnostic criteria. Recent evaluations suggest, however, that the adolescent cases remaining in subthreshold categories have same features (Sancho et al., 2008, Schmidt et al., 2008) undergo the same developmental course, and thus may differ only in pathological severity from full syndromes.

The results showed that depressive disorders and generalized anxiety disorders were strongly associated to eating disorders in adolescence. The possible role of negative affect trait in causal processes and maintaining eating disorders (Stice et al., 2002) have been suggested and may associate to these findings. Even though eating disorders are not as common as mood disorders in adolescence in Finland, they are of great importance also because of these associations to concurrent and prospective psychopathology. The analyses also partially control for shared genetic effects (the discordant twins included DZ twins, who share 50% of their genetic variation). Together with observed temporal precedence of generalized anxiety and eating disorders, these analyses suggest that early depression and generalized anxiety may be important factors in a causal pathway in developing eating disorders in adolescence.
8.2 Methodological considerations

8.2.1 Strengths and limitations

The purpose of the study was to explore relationships of early-onset depressive disorders, other psychopathology and substance use in a gender-balanced sample of adolescents. The FinnTwin 12, a population based twin study served this purpose well, since it offers a rich design of professionally administered age-standardized interview, as well a multiple source of other informants, such as parents and teachers. Thus, the study had good means of overcoming the bias cause by large age differences and under-balanced sex ratios. The high participation rates were also an advantage. Further, comorbidity was controlled for, which is of importance because evidence suggests linkage of substance use to several psychiatric disorders, especially externalizing disorders. Any relations observed between other psychiatric disorders and substance abuse in studies that fail to take into account the overlap with conduct disorder, a strong, well documented predictor for substance use, may be spurious (Flory & Lynam, 2003). Finally, the within-family analysis of depression-discordant twin pairs offered an incisive control of the role of familial factors in these developmental relationships.

The twin studies have been criticized because of their alleged non-generalizability due to differences in intrauterine and familial environments of twins compared with singletons. However, research beginning early in life, demonstrates that the twins have similar emotional and behavioural problems, psychiatric symptoms (Kendler et al., 1995), and even similar brain volume measures (Hulshoff et al., 2002) compared to singletons. While the twinship must be considered as a limitation when interpreting the results of individual analyses, the previous literature as well as analysis from FT12 support the generalizability of the findings to adolescent population. The FinnTwin 12 study has a rich design multiple informants: the twins of the study had 23200 classmates (11903 boys and 11297 girls) who participated in classroom evaluations which provided an opportunity to compare the behavioral differences between twins and singletons. These comparisons suggest that the differences between twins and singletons are small and they are highly similar in their behavior. The small differences suggested that twinship may be an advantage, as twins were more social compared to their classmates (http://wiki.helsinki.fi/display/twinstudy/Kaksosten+kehitys+ja+terveys+ja+tutkimus). Regarding adolescent depression, clear evidence for differences in rates of depression between twins and singletons has not been documented. A previous study of longitudinal samples of twins and singletons aged 8-17 found no differences between twins and singletons in their depression scale scores (Angold et al., 2002). In an earlier report of these same twins participating to FinnTwin12 at the age of 12, depressive symptoms did not differ in prevalence between them and 25 000 classmates (Pulkkinen et al., 2003). The results regarding the prevalence rates and clinical characteristics from this study of twins are consistent with those of other epidemiological studies (Lewinsohn et al., 1994, 2004, Ford et al., 2003) and depressive disorders among the twins are likely to be similar to those found in the nontwin population.
Both using symptom rating scales and interviews as methods have their advantages. The symptoms scales are sensitive and usually work well for screening and following up the changes in symptom profiles during interventions. Semi-structured interview, used in the current study, however, provides diagnosis, with higher threshold and, higher specificity, probably resulting lower prevalences compared with self-reports of structured interviews. When compared with studies using similar methodology, the results are alike (Ford et al., 2003, Canino et al 2004). The disadvantage of semi-structured interviews is non-cost-effectiveness and the demand of solid clinical expertise. In this study, the interviewers were highly skilled and well trained.

Using self reports as follow-up assessments is an obvious limitation. However, evidence from Finnish population suggests that self-reports of smoking behaviour is correlates well to levels of cotinine in blood, and thus may a reliable method to address smoking behavior (Vartiainen et al., 2002).

Although the primary aim of the study was not to provide estimates of prevalences of early-onset depressive disorders in Finnish population, specific considerations for generalizability of the results are made. Most of the intensively studied subsample (72, 3%) was selected at random from population-based ascertainment, but a part was enriched with a potential familial risk for alcoholism based of mMAST-screen of the parents. A series of model-fitting analyses to diverse phenotypes nave been performed to test for potential bias introduced by the sample enrichment, and no evidence that model-fitting results were systematically affected have been found(Rose et al., 2004). No significant differences between the mental health assessments, e.g. early-onset depressive disorders were found in direct comparisons of the subsample of enriched adolescents and the randomly selected subsample (Sihvola et al., 2008, complementary analyses). However, it is possible that the effects, perhaps in terms of increased liability for depression, will emerge later in life.

The analyses of depression-discordant co-twins represents a new, and perhaps important effort in understanding the association of early-onset depressive disorders and substance use in the context of familial confounds, but because of limited sample of doubly discordant pairs, the results should be viewed more suggestive than definitive. The findings confirmed significant associations of early-onset depressive disorders and use of smokeless tobacco and alcohol, but given the small number of informative twin pairs, the lack of association for other outcomes should not be interpreted as evidence that familial confounds underlie those associations. The power of further statistical analyses among MZ and DZ twins was inadequate and prohibited further conclusions about genetic factors.
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8.3 Clinical implications

The importance of early onset depressive disorders in the trajectories of wide range of substance use has obvious important clinical implications for the prevention of substance abuse among adolescents. Along with externalizing behavior problems, including conduct, attention deficit hyperactivity, and oppositional defiant disorder, which all have been identified as strong predisposing risk factors for later substance use, adolescents with early-onset depressive disorders should be identified as at-risk group for developing substance use. However, the majority of the depressed youth reported impairment in several environments, but had too few depressive symptoms to fulfill the diagnostic criteria for major depressive disorder. Thus, reliance on less-sensitive categories among adolescents is may cause failure to observe these important pathways, despite of obvious clinical utility of strict categories. The possible connection of common symptoms among adolescents, (such as representation of minor depression and ADHD behaviors) to substance use and substance use disorders in adolescence, in period for the foundation to substance use habits raises a substantial public health and clinical concern. Prevention, screening, identification and considering intervention options should perhaps be extended beyond categorical diagnosis among youth.

The potential unfavorable substance use outcome among girls with ADHD behaviors warrants more studies in joint relations of externalizing conditions and substance use by gender. Substance use prevention does not seem to be as effective in girls as it is in boys (Kumpfer et al., 2008), and there may be underlying factors why substance use prevention programs are not equally successful among genders. Early identification and treatment of ADHD in girls may be of great importance for substance use prevention. For both boys and girls, screening of substance use along when attention-deficit hyperactivity disorder seems likely, would be worthwhile.

Suggested by these results, developing elevated levels of addictive substance use, such as tobacco use, alcohol use, intoxication and illicit drug use among adolescents with early-onset depressive disorders is not explained by familial factors supporting future substance use may also have important implications for substance use prevention programs in individuals during early adolescence. Treatment programs among depressed or substance misusers could have a more synergistic point of view and co-operation between them should be emphasized, rather than separating treatment units for psychiatric care and substance use.

Diagnostic criteria for eating disorders should be carefully reassessed and, perhaps, relaxed towards better understanding the nature of these diseases in adolescence. The most severe cases are referred to specialized assessment and treatment, but many remain unidentified and do not receive adequate interventions. Undiagnosed and undertreated comorbid psychiatric illnesses may also affect the outcome of treating eating disorders (Keski-Rahkonen et al., submitted). Therefore adolescents who exhibit depressive and/or anxiety disorders could also be screened for eating disorders. Clinical experience shows that the treat-
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ment and pharmacological and psychotherapeutic interventions of patients with comorbid eating disorder may differ from others and benefit from special expertise. Valid preventive programs for eating disorders would require surveys on excessive scale, because eating disorders are relatively low prevalence illnesses. However, more careful screening is warranted in high-risk groups, for example young girls with depression.

8.4 Implications for future research

Epidemiological studies: The long term mental health outcome of early-onset depressive disorders and the role of familial factors

The prospective analyses in this study are limited to a 7 year time span; clearly, these results do not permit confident conclusions of causality. However, the follow-up of these individuals will hopefully address the substance use outcomes in adulthood. Studies with long-term follow-up should reveal the potential importance of early-onset disorders and whether or not they have an effect on participant’s lives in terms of substance use disorders as well as psychiatric disorders in adulthood.

One of the important finding of this study the was the significant longitudinal relationship of early-onset depressive disorders and substance use and other psychiatric morbidity regardless of familial factors needs to be confirmed in future twin studies. The finding perse warrants further studies exploring factors such as dispositional personality traits, perhaps antisocial traits, and influence of peers on in the context of developing substance use. This study used novel methods aiming to test that outcome factors were not explained by 3rd confounding factors, however, more studies using new methods to test causal effects of environmental factors on children and adolescents’ developmental outcomes are warranted.

From a more general point of view, further studies, examining etiology and developmental course of these diseases, beginning with at-risk children and adolescents, earlier in development than current studies are of importance to deepen the life-span developmental conceptualizations of these diseases. An interesting question is, whether these early-onset illnesses at all represent the same illnesses as in adults, or whether they are in fact distinct disorders with different developmental pathway and causalities compared to adult disorders.

Clinical studies; effectiveness of interventions of early-onset depressive disorders

This study offer an epidemiologic perspective to depressive disorders in adolescent population, but it has implications for future studies with clinical approach. Many adolescent of the study had never been referred nor even told about the symptoms, however, they had relevant clinical distress and were showed to suffer from adverse outcomes at follow-up. Thus, it would be important yet challenging, to study the potential interventions among them. Subclinical depressions even with impairment in adolescence are rarely treated with medication in clinical settings, but whether or not they could benefit from a motivational inter-
view, assessments of comorbid disorders, or psychotherapeutic interventions could be studied further.

Substance use and gender issues
At present time, the participants of this study are in the process of follow-up at ages 20-24, in a known risk period for substance abuse (Hawkins et al., 1992, Biederman et al., 1997). This study as well as other prospective longitudinal ongoing studies need to address the relationships of early-onset psychopathology to later-onset substance use disorders. Evaluation, whether treatment of prior predictive psychopathology, for example depression, conduct problems or attention deficits has an effect on later risks on substance use seems crucial.

A research area that needs attention is gender differences in the relations among early-onset depressive disorders, attention deficit hyperactivity/impulsivity disorders, eating disorders and substance use. It is plausible, that given the clear sex differences in prevalences of e.g. eating disorders and in adulthood substance abuse and dependence diagnoses (DSM-IV) there may be differential relations among them for males versus females. Categorical diagnoses of externalizing disorders are rare among females in the community, therefore large-scale studies are encouraged, since substance use is substantial public health concern, and in females it might also have particular significance to their offspring’s lives. It is unclear, whether young females would benefit from substance use preventive programs that are different from boys. Prospective research should extend through developmental years and include a sufficient number of both genders using multiple reporters to investigate these important relationships. Protective factors for substance use outcomes should also be studied, as they are an important but neglected topic of research.

8.5 Conclusion
This study sought to address the important issue in the fields of early-onset depressive disorders, related mental health disorders and developing substance use among adolescents. The relationships between the predictors and substance use, abuse and dependence outcome were studied over 1,500 individual twins followed-up from 11 years of age through age 17½. This study provided novel findings in concurrent and longitudinal relationships of early-onset depressive disorders, ADHD, eating disorders and substance use, which may have important implications for future research, clinicians, mental health professionals and public health. In conclusion, early-onset depressive disorders should be considered to be significantly related to future substance use behaviors among both boys and girls, similar to the better established relationships of externalizing disorders and substance use in adolescence.

Minor depression has recently received international attention, (Johnson et al., 2009) and it seems that this common condition may also have financial significance related to severe cases of mental disorders. When data from a community-based prospective longitudinal study from another culture were used to investigate the association of minor depressive disorder during adolescence with ad-
verse mental health outcomes during adulthood, the results indicated that minor depressive disorder during adolescence was associated with elevated risk for subsequent psychiatric disorders during adulthood, and clinically relevant impairment after corresponding and co-occurring disorders were controlled statistically (Johnson et al., 2009). Should an effort made to support these young people, rather than only offer interventions to those with ‘serious’ depressive illness, severe problems with conduct and attention, and substance use disorders?

The prospective associations of early-onset depressive disorders to other mental health disorders received a special attention in substudies of this thesis. Interestingly, many of these other, often co-morbid disorders among depressed signaled unfavorable outcome for substance use, although this data, in line with previous research (Hawkins 1992, Mc Gue 1997), clearly noted the powerfulness of conduct problems to substance use outcomes. This study had a comparable proportion of boys and girls, which helped to understand the potential gender differences in these relationships. Results from this sample, derived from a large nationwide population-based study support prospective associations of early-onset depressive disorders and symptoms of ADHD, both associated with alcohol abuse and alcohol dependence and frequent illicit drug use among girls. This data adds substantial evidence in that girls with ADHD behaviors may be at higher risk compared to boys, and that the girls’ risk may are not attenuated by conduct disorder, a strong predictor for substance abuse. Inattentiveness especially may play more of a role in developing substance use than previously thought. Whether early recognition and interventions among girls with behavioral symptoms of ADHD hold potential for substance use prevention further in their lives calls for more research.

The study also took advantage of the genetically informative sample of twins, and explored these relationships among twin pairs discordant for diverse phenotypes, using novel methodology to examine the outcomes of these illnesses while taking into account the shared familial factors. It is necessary to consider the independence of familial factors as an exploratory finding, which needs to be replicated in future studies. However, the influence of peers as well as other environmental factors, society in individuals, seems to be worth examining further, as well as exploring the effect of environmental influences to genetic background. Although these relatively short-term results (prospective analyses limited to 3-7 year time span) warrant new studies and even larger samples with larger numbers of affected males and females are needed to truly determine the effect of sex on severe psychopathology, they represent important steps to deepen the understanding of longitudinal relationships of early-onset psychopathology, developing substance use and substance use disorders in the community.
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