Life course mechanisms underlying intergenerational transmission of depressive symptoms

The role of gender, socioeconomic circumstances, and timing of exposure

Janne Mikkonen

University of Helsinki

Faculty of Social Sciences

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HELSINGIN YLIOPISTO
HELSINGFORS UNIVERSITET
UNIVERSITY OF HELSINKI

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Janne Markus Kristian Mikkonen

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Tiivistelmä – Referat – Abstract

Parental depression is one of the most robustly established risk factors of child and adolescent psychopathology. Numerous studies have indicated that offspring of depressed mothers face up to 3-fold risk of exhibiting depressive symptoms compared with offspring whose mother has not had depressive symptoms. Later studies have observed that paternal depressive symptoms pose an almost equal risk to offspring wellbeing. A salient question from a preventive perspective is whether some attributes and environments mitigate or exacerbate the risk of intergenerational transmission, since not all children of depressed parents develop depression themselves.

This study examines the role of parental depression as a risk factor of adolescent depression and analyzes previously hypothesized associations that have thus far remained understudied or have been inconsistent across previous studies. Specifically, the study assesses whether the intergenerational transmission of depression is gender-specific and confounded or modified by socioeconomic status. Moreover, it examines whether the concurrence or recurrence of parental symptoms is particularly harmful and whether the associations vary according to the timing of exposure to parental depression. The interpretation of the results leans on the conceptual framework of life course epidemiology, which understands the development of a disorder as the outcome of biological, psychosocial, and environmental processes that entangle with each other throughout the life course.

The study utilized register-based data containing a 20% random sample of Finnish households with at least one child aged 0-14 at the end of 2000. Purchases of prescription medicines and visits to inpatient and outpatient care were used as proxies for the incidence of depressive symptoms. Cox proportional hazards regression was performed to analyze the incidence of depressive symptoms at ages 15-20 by exposure to maternal and paternal depressive symptoms earlier in life. Exposure to parental depression was measured when children were 9-14 years old, and children's own depressive symptoms were followed-up at ages 15-20. Altogether, the study population included 130,679 children born in 1986-1996.

Based on the results, exposure to maternal depressive symptoms at age 9-14 poses an equally large 2-fold risk for boys and girls. Paternal depressive symptoms put boys at an equal risk as maternal depressive symptoms, but for girls, they pose a slightly smaller 1.5-fold risk. Among adolescents living biological parents, controlling for the effects of socioeconomic factors weakens the association only little and no differences are seen in the risk of intergenerational transmission across the groups of socioeconomic status. Exposure to both maternal depressive symptoms and paternal depressive symptoms poses a larger risk than single exposure for both girls and boys. Exposure at age 9-14 poses a larger risk than exposure at age 0-5. Recurrent maternal depressive symptoms appear to be a particularly severe risk factor.

The results are in line with the life course epidemiological processes of the accumulation and chains of risk: Concurrent exposure to depressive symptoms in both parents and the long-term chaining of parental depressive symptoms put adolescents at highest risk. The results support the idea that maternal depression affects both genders equally, whereas paternal depression affects girls less than boys. Parental depression and low socioeconomic status are mainly independent risk factors of adolescent depressive symptoms and do not cause an interactive effect. Overall, the results advocate a more holistic approach to the prevention of adolescent depressive symptoms, beginning from the identification of familial risk and leading to actions that take into account all members of the family.

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Intergenerational transmission, depressive symptoms, life course approach, adolescents

HELSINGIN YLIOPISTO
HELSINGFORS UNIVERSITET
UNIVERSITY OF HELSINKI

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Tiivistelmä – Referat – Abstract

Vanhempien masennus on yksi lasten ja nuorten mielenterveysongelmien vankimmin vahvistetuista riskitekijöistä. Lukuisat tutkimuksen ovat osoittaneet, että masennuksesta sairastaneiden äitien lapsilla on jopa kolminkertainen kokea masennusoireita verrattuna lapsiin, joiden äidille ei ole ollut masennusta. Uudemmat tutkimukset ovat havainneet, että isän masennus muodostaa lapsen hyvinvoinnille lähes yhtä suuren riskitekijän. Masennuksen ehkäisyn näkökulmasta keskeinen kysymys on, vähentävätkö tai kasvattavatko jotkin ominaisuudet tai ympäristöt masennuksen ylisukupolvisen periytyvyyden riskiä, sillä tiedetään, että kaikki masennuksesta kärsineiden vanhempien lapset eivät itse sairastu masennukseen.

Tämä tutkimus tarkastelee vanhempien masennuksen merkitystä nuorten masennuksen riskitekijänä ja testaa aiemmassa tutkimuskirjallisuudessa esiintyviä hypoteeseja, jotka ovat pysyneet vähän tutkittuina tai joista aiemmat tutkimukset ovat tuottaneet ristiriitaisia tuloksia. Erityisesti tutkimus selvittää, vaihtelevat yhteydet sukupuolen ja sosioekonomisen aseman mukaan sekä heikentääkö sosioekonomisen aseman vakioiminen yhteyksiä. Lisäksi tutkimus selvittää, onko äidin ja isän masennuksen samanaikaisuus ja vanhempien masennuksen toistuvuus erityisen haitallista ja onko ylisukupolvisten yhteyksien voimakkuus riippuvainen vanhempien masennuksen ajoittumisesta. Tulosten tulkinnassa nojaudutaan elämänkaariepidemiologian viitekehykseen, jossa sairauden kehittyminen ymmärretään koko ihmisen elämänkaaren aikana toisiinsa kietoutuvien biologisten, psykososiaalisten ja ympäristöön liittyvien prosessien lopputulokseksi.

Tutkimuksen aineistona käytettiin rekisteriaineistoa, joka sisälsi 20 prosentin satunnaisotoksen kaikista Suomen kotitalouksista, joissa asui vuoden 2000 lopussa 0-14-vuotiaita lapsia. Masennusoireiden tunnistamiseen käytettiin aineistoon kuuluvia Kansaneläkelaitoksen rekisteritietoja reseptilääkeostoista sekä Terveyden ja hyvinvoinnin laitoksen ylläpitämän hoitoilmoitusrekisterin merkintöjä. Masennusoireiden esiintymisen vertailuun ryhmien välillä käytettiin elinaikamallinnuksen menetelmiin kuuluvaa Coxin suhteellisten vaarojen mallia. Altistuminen vanhempien masennukselle mitattiin niiltä vuosilta, jolloin henkilö oli 9-14-vuotias, ja henkilöiden omien masennusoireiden ilmaantumista seurattiin, kun he olivat 15–20-vuotiaita. Pääasialliseen tutkimusjoukkoon kuului yli 130 679 vuosina 1986–1996 syntynyttä henkilöä.

Tulosten perusteella äidin masennusoireille altistuminen 9-14-vuotiaana asettaa tytöt ja pojat yhtä suureen kaksinkertaiseen riskiin kokea 15-20 vuotiaana masennusoireita verrattuna niihin, joiden äidillä ei ole ollut masennusoireita. Isän masennusoireet ovat pojille yhtä suuri riskitekijä kuin äidin masennusoireet, mutta tytöille isän masennusoireet ilmenevät pienempänä, puolitoistakertaisena riskinä. Niiden henkilöiden kohdalla, jotka asuivat 9-14-vuotiaina biologisten vanhempiensa luona, sosioekonomisten tekijöiden vakiointi heikentää yhteyksiä vain hieman, eikä sosioekonomisten ryhmien välillä ole havaittavissa eroja masennusoireiden ylisukupolvisen siirtymisessä. Altistuminen sekä äidin että isän masennukselle liittyy sekä tytöillä että pojilla suurempaan omien masennusoireiden riskiin kuin se, että vain toisella vanhemmista on ollut masennusoireita. 9-14-vuotiaana koettu vanhempien masennus on yhteydessä suurempaan riskiin kuin 0-5-vuotiaana koettu vanhempien masennus, jos altistuminen on tapahtunut vain jompanakumpana näistä ajankohdista. Erityisen suuri riskitekijä on altistuminen äidin masennukselle molempina ikäkausina.

Tutkimuksen tuloksissa havaitaan riskien kasautumiseen (accumulation of risk) ja riskien ketjuuntumiseen (chain of risk) liittyviä elämänkaariepidemiologisia prosesseja: molempien vanhempien samanaikainen masennus sekä vanhemman masennusoireiden pitkäkestoinen ketjuuntuminen liittyvät nuoren kohdalla suurimpaan masennusoireiden riskiin. Vanhempien masennusoireet ja sosioekonominen asema havaittiin pääasiassa toisistaan riippumattomiksi, nuorten masennusoireita itsenäisesti ennustaviksi tekijöiksi. Tällöin erityisessä riskissä ovat alemmasta sosioekonomisesta taustasta tulevat lapset, joiden vanhemmilla on ollut masennusoireita. Nuorten masennuksen ennaltaehkäisyssä tutkimuksen tulokset antavat tukea kokonaisvaltaiselle lähestymistavalle, joka ottaa huomioon kaikki perheenjäsenet.

Avainsanat – Nyckelord – Keywords
ylisukupolvisuus, masennusoireet, elämänkaarinäkökulma, nuoret

Contents

1 Introduction

Depressive disorders belong to the most prevalent forms of psychopathology and affect more than 350 million people worldwide (WHO 2012). Estimates of prevalence vary between countries and different studies, but recent surveys have estimated that the lifetime prevalence of depression ranges from 10% to 15% (Lepine & Briley 2011), while the 12-month prevalence of a major depressive episode, the most common form, is on average approximately 6% (Bromet et al. 2011). Despite the commonness of the disorder, globally fewer than half of those affected (and in some parts of the world, less than every tenth) receive proper treatment (WHO 2012).

In 2010, depressive disorders were the second most common cause of years lived with disability and the leading cause of disability-adjusted life years, i.e. the loss of healthy years of life (Ferrari et al. 2013). Depression is associated with mortality and morbidity both in the form of suicides and chronic diseases. Suicide is globally the second leading cause of death in young people aged 15–29 years (WHO 2014), and more than half of the individuals committing suicide suffered from a depressive disorder at the time of death (Hawton & Van Heeringen 2009). Overall, men suffering from unipolar depression have a 20.9-fold likelihood and women 27-fold likelihood to commit suicide compared with the general population (Ösbu et al. 2001). Depression has also been shown to be a significant predictor of the incidence of a wide range of cardiovascular diseases (Van der Kooy et al. 2007). Depression impairs the cognitive and social functioning of an individual at work and home. It is associated with an increased risk of unemployment and lower salary (Whooley et al. 2002) as well as decreased productivity and increased absence from work due to disability days (Broadhead et al. 1990).

What makes depression an especially burdensome disorder is its typical recurring and relapsing nature. More than half of those (50%–60%) who have suffered from an initial major depressive episode will also develop another episode. Of those individuals having a history of two episodes, 70%–80% will experience a third episode, whereas up to 90% of those having experienced three former episodes will have a fourth episode (Monroe & Harkness 2005). Earlier age at first onset is one of the strongest predictors of recurring

depression in adulthood (APA 2013; Blatt & Maroudas 1992), which makes child and adolescent depression an especially important target of preventive actions. Studies have also shown depression in adolescence to be associated with poorer general health, more frequent health care visits, and increased work impairment due to physical health in young adulthood even after controlling for concurrent depression (Keenan-Miller et al. 2007). Among women, adolescent-onset depression is also associated with obesity (Hasler et al. 2005) and lower educational attainment (Fletcher 2010) in adulthood.

One of the most studied and well-established risk factors of depression is having a history of parental depression (Mendes et al. 2012; Keller & Gottlieb 2012), which is also the principal point of interest in the present study. Individuals exposed to parental depressive symptoms during childhood have been observed to face an up to 3-fold risk of developing depressive symptoms during childhood and adolescence compared with individuals whose parents have not suffered from depression (Brennan et al. 2002; Weissman et al. 2006). Such results have been obtained for both maternal and paternal depression (Ramchandani & Psychogiou 2009). The present study aims to elucidate some of the key moderators and mechanisms underlying the intergenerational transmission of depressive symptoms and investigate whether they put adolescents at different risk of exhibiting depressive symptoms. These include the gender of the child, parental socioeconomic status, and the timing, clustering and recurrence of parental depressive symptoms.

The present study belongs to the field of social epidemiology and utilizes the conceptual framework of life course epidemiology to interpret the mechanisms of the intergenerational transmission of depressive symptoms. Life course epidemiology is a multidisciplinary field that examines how biological, social, and environmental characteristics alter the risk of a disease or a disorder throughout different stages of life and how transmission of these attributes shapes the risk throughout generations (Warner & Weissman 2014, 273). It offers a framework that helps to analyze how different determinants of health interact with each other throughout the life span and affect the risk of developing mental disorders (Buka & Lacy 2014). The idea to connect these two points of view was inherited from Rudenstine (2014), who describes the etiology of depression from a life course perspective, and Warner & Weissman (2014), who recognize the common ground between the study of intergenerational transmission and life course epidemiology both trying to understand the

mechanisms behind cross-generational processes (Warner & Weissman 2014, 273). Before these accounts, relatively few authors have approached the intergenerational transmission of depressive symptoms from a life course perspective and recognized the vitality of integrating these two fields of research.

Before we begin, a few words must be said about the concepts used in the report. The common term "depressive symptoms" is used to refer to the outcome variable and results of the study. This vaguer concept was chosen instead of a more precise alternative, such as "depression" or "major depressive disorder", because the study utilizes administrative treatment data, such as medicine purchases. Although the records include exact ATC-codes for medicines, they do not contain information on the actual underlying disorder, e.g. different forms of depression (discussed in the next chapter). At the same time, the term "depressive symptoms" is used instead of "treatment" because these records are, at any rate, assumed to imply something about the existence of actual symptoms related to depression — at least in most cases. Thus, the present study regards treatment records as *a proxy for the incidence of depressive symptoms*. The implications of these choices are discussed more closely later.

Other difficult concepts are the terms that refer to individuals at different stages of life, such as "child", "adolescent", and "young adult". World Health Organization defines *adolescence* as the period after childhood and before adulthood that covers the ages from 10 to 19 (WHO 2015a). The present study measures exposure to parental depressive symptoms at ages from 9 to 14 and offspring depressive symptoms at ages from 15 to 20, as a result of which the analysis provides mostly information about *exposure in adolescence* and *adolescent depression*. Thus, these concepts are also used to refer to the results of the analysis. When looking at the outcomes of other studies, a slightly wider scope is used: Studies that only examined children or young adults could also be included if they addressed the themes relevant to the present study, as relatively few earlier studies have explored the effects of exposure to parental depressive symptoms in adolescence. What is more, these studies offer a useful baseline with which the results of the current analysis may be compared. Overall, the definitions of developmental stages are relatively inconsistent in scientific literature, and it should be noted that some earlier studies may have used a different age range for adolescence than the one used in this report.

This report divides into seven chapters as follows: Following this introductory chapter, the second chapter *Child and adolescent depression from a life course perspective* describes the symptoms and etiology of depression, takes a look on the recent trends in prevalence and treatment of depression in children and adolescents, and argues why it is vital to investigate depression from a life course epidemiological perspective. The third chapter of the report, *Intergenerational transmission of depressive symptoms*, introduces the main risk factor of depression from the perspective of the present study and reviews the empirical evidence concerning it. The fourth chapter *Aims of the present study* presents the research questions, their hypotheses, and the study design used to answer the questions. The fifth chapter *Data and methods* depicts in detail the selection and definition of the study population, the operationalization of measurements, and the statistical methods utilized in the analysis. The sixth chapter *Results* goes through the analysis systematically. The seventh chapter *Discussion* interprets the results, connects them with earlier research and the life course epidemiological framework, evaluates the methodological choices made in the study, and identifies the need of further research and suggestions for public health policy.

2 Child and adolescent depression from a life course perspective

2.1 Symptoms and etiology

Depression is considered a sub-category of "internalizing problems", which in turn form one dimension of the larger category of "emotional and behavioral disorders". Internalizing problems are inner-directed and refer to such conditions that generate inhibition, withdrawal, suffering, and unease in an individual. Examples of internalizing problems, besides depression, are anxiety, social phobia, substance abuse, panic disorder, and eating disorders. The conceptual counterparts of internalizing problems are "externalizing problems" that are expressed outwardly and typically actualize in the form of hyperactivity, aggressiveness, and violation of social norms and rules. (Forns et al. 2012.)

There are at least three reasons for why the distinction between internalizing and depression might not be that significant in the case of the present examination. First, different forms of internalizing problems have a high comorbidity, and most individuals who have one internalizing disorder have symptoms of additional internalizing problems too (Brown et al. 2001). In adolescence, the highest comorbidity is observed between depression and anxiety (Merikangas et al. 2010), with 25%–75% of adolescents with depressive symptoms expressing also symptoms of anxiety in different studies (Essau & Chang 2009) and anxiety normally preceding depressive symptoms (Kovacs et al. 1989). Second, the same pharmacological treatments have been observed to be effective for both depression and anxiety disorders, implying about a common genetic and etiological framework behind them (Wilkinson 2009) and making studies relying on treatment data unable to distinguish different depression-related or internalizing disorders accurately. Third, in scientific literature, the terms "internalizing" and "depression" are often used incoherently and interchangeably since many studies are not able to separate the whole spectrum of internalizing disorders accurately with the data they are using. Thus, in the present literature review, the decision was made to review studies that dealt with "internalizing", "depression" or "depressive symptoms" but exclude studies that covered exclusively anxiety disorders, substance abuse, panic disorder etc. The results of different studies are referred to using

the same terms as they are using. In addition, as already mentioned in the introductory chapter, the common term "depressive symptoms" is preferred when interpreting the results of the present study.

The clinical and diagnostic features of depression are mainly similar in adolescents and adults, although adolescent depression remains more often undiagnosed, which is possibly explained by the fact that moodiness and irritability are in general more pronounced during adolescence (Thapar et al. 2012). International classification of diseases-10 (ICD-10) lists three core symptoms for a depressive episode of which at least two must be present:

- Depressed mood present for most of the day and almost every day
- Loss of interest or pleasure in activities
- Decreased energy or increased susceptibility to fatigue

In addition, the classification names seven associated symptoms:

- Loss of confidence or self-esteem
- Unreasonable feelings of self-reproach or excessive inappropriate guilt
- Recurrent thoughts of death or suicide, or any suicidal behavior
- Diminished ability to think or concentrate
- Change in psychomotor activity, agitation, or retardation
- Sleep disturbance
- Change in appetite with corresponding change in weight

(WHO 2015b.)

The other major classification system, the American diagnostic and statistical manual of mental disorders (DSM), includes a mainly similar definition in its fourth (at the moment already obsolete) version. ICD-10 specifies certain thresholds for the number of symptoms that must be met for mild, moderate, and severe depressive episodes. In DSM-IV, severity is assessed separately after the criteria for a major depressive episode have been met, based on the number of symptoms present and level of functional impairment. Within both systems, depression may also be classified "psychotic" or "recurrent" (Thapar et al. 2012; Grueberg et al 2005.) The often-used term Major Depressive Disorder (MDD) refers to

the most common form of severe acute depression, but this exact name is only used in DSM-IV. Both classification systems also recognize dysthymic disorder, which is a chronic but less severe form of depressive disorder; bipolar affective disorder, which typically consists of both manic periods of elevated mood and periods of depression; and depressive disorder not otherwise specified (NOS) (Essau & Chang 2009; WHO 2012). Both systems may be considered "non-etiologic" because they are based on perceptible and self-reported symptoms rather than etiological factors (Grueberg et al. 2005).

Major depression is a multifactorial disease with several etiological background factors that are entangled with each other (Kendler et al. 2002). First of all, there is no doubt that the inheritance of depression is to some extent genetic. Flint and Kendler (2014) state that no high-quality adoption study of major depression has been performed, so the evidence on the role of genetic factors in its etiology comes solely from twin studies. A meta-analysis of six studies, the broadest so far, estimated heritability (the proportion of phenotypic variation in a population that is due to genetic variation) for major depression to be 37% (95% confidence intervals 31–42) (Sullivan et al. 2000). In the largest sample to date, the heritability of liability to major depression was found to be significantly higher in women (42%) than in men (29%) (Kendler et al. 2006). What is more, family studies have also revealed that major depression is overrepresented among individuals with first-degree relatives with a history of depression (Sullivan et al. 2000). This subject will be discussed in more detail in the next main chapter. Since findings on heritability of depression have generally been restricted to major depression and not to subclinical depressive symptoms, heritability of depression in childhood and adolescence is less clear (Goodman & Gotlib 1999).

Lately, there has also been a growing attempt to spot significant genetic markers for major depression via Genome-Wide Association Studies (GWAS), but so far, the results have been meager (Dunn et al. 2015; Flint & Kendler 2014). A typical GWAS contains one million or more single nucleotide polymorphisms (SNPs) — DNA sequence variations that occur at least in 5% of the population — and examines their relation to disease. Although former so-called candidate gene studies found evidence for as much as six genes with significant associations to depressive symptoms, none of these nor any of the most commonly studied candidate genes have been managed to verify in Genome-Wide

Association Studies that may be considered more reliable. (Dunn et al. 2015.) Now, it seems apparent that there does not exist a single "depression gene"; instead, there are several genes with weak effects, each of them forming a small portion of the total genetic risk for depression (Rudenstine 2014, 91). In addition, the role of genes in the etiology of mental disorders may not be considered deterministic or independent; rather, genes interact with the environment, and certain combinations of genetic and environmental vulnerabilities finally shape the risk for disorder. One of the most influential findings was made by Caspi et al. (2003) whose study suggested that a functional polymorphism in the promoter region (5-HTTLPR) of the serotonin transporter gene (SLC6A4) moderates the association between stressful life events and depression so that those carrying the risk allele exhibited more depressive symptoms after stressful events. Several studies have tried to replicate this interaction with both positive and negative results, and the debate is still ongoing about whether it really exists (Dunn et al. 2015).

Episodes of depression are usually preceded by an exposure to stressful life events, even though stress does not in most cases lead to depression. However, some people seem to be more vulnerable to stress than others are and some people also experience more stressful events in general. (Hammen 2005; Keers & Uher 2012.) According to the stress generation model, individuals with a high risk for depression tend to create such negative events in their lives that are dependent of their own actions (Hammen 1991). The "kindling hypothesis", formed by Post (1992), instead, suggests that stressful life events are more predictive of the initial onset than later episodes of depression. This theory is supported, for instance, by the study of Lewinsohn et al (1999). In addition, some studies indicate that more severe stressors are typically needed to trigger the first episode than further episodes (You & Conner 2009), which may be interpreted as a manifestation of sensitization, i.e. the gradual loss of resilience to stress, after the "sensitization hypothesis" (Rudenstine 2014, 91). Moreover, in parallel with the accumulation of risk model, those exposed to several stressors have a considerably higher risk of depression compared to those who were exposed to only one adversity (Lewinsohn et al. 1999). Stressful events that occur early in life have particularly severe and long-term impacts. Several studies have indicated that early life traumas and adversities, such as physical, sexual, and emotional abuse, are associated with a heightened risk of later-life depression (Mullen et al. 1998). Chronic stressors that

affect relationships, such as peer victimization (Young et al. 1997) and negative relationships with parents (Rueter et al. 1999), seem to be especially harmful (Thapar et al. 2012).

Depression in adolescence is also linked to the pubertal hormonal changes, although they may not be considered the direct cause of the onset of depression (Thapar et al. 2012). Instead, they more likely operate by sensitizing the brain to the harmful effects of stress (Hyde et al. 2008). Hormonal increased sensitivity to stress has also been suggested as an explanation to the gender difference in the prevalence of adolescent depression (discussed below) because hormonal changes in adolescent girls have been found to be more strongly associated with increased rates of depressive symptoms than physical development and chronological age (Angold et al. 1999). Also temperament and personality have been suggested to mediate the relationship between adverse life events and depression by influencing how an individual processes his or her experiences and makes sense of them (Rudenstine 2014, 92; Thapar et al. 2012). This, in turn, affects the individual's self-perception and may affirm either a positive or negative self-image, the latter linking the adversity more likely to depressive symptoms (Rosenbaum et al. 1991; Rudenstine 2014, 92).

2.2 Recent trends in prevalence and treatment of depressive symptoms

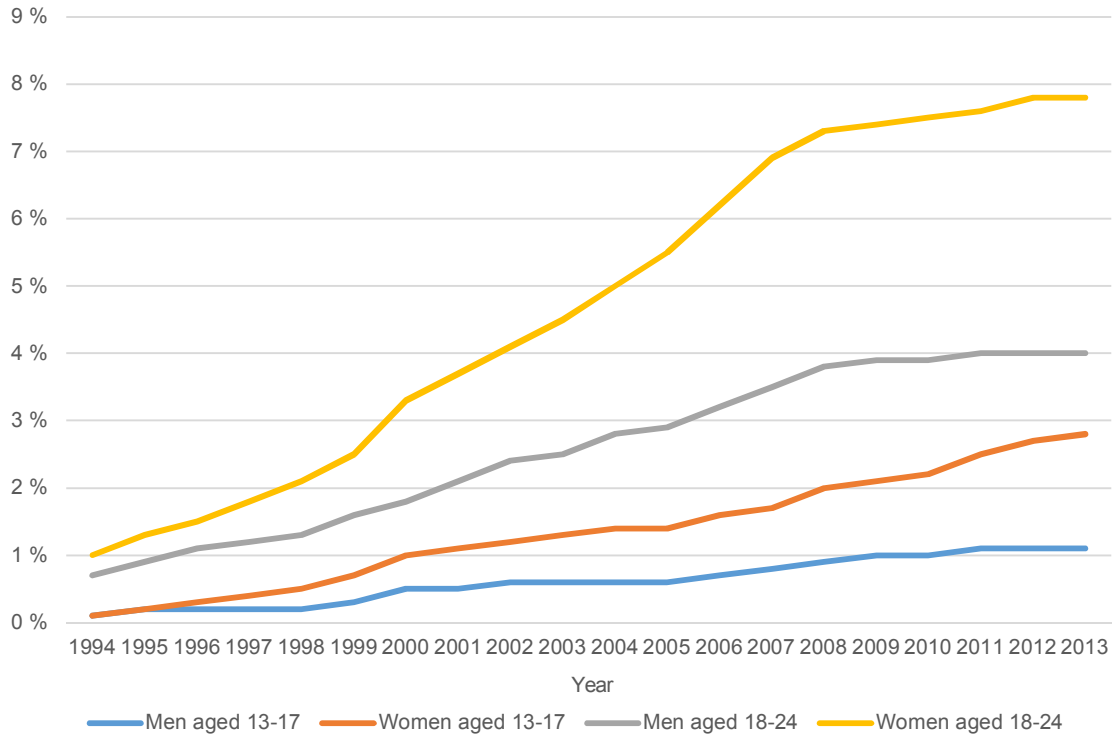
According to research based on diagnostic interviews, the prevalence of depression is fairly low among preadolescent school-aged children (<3%) (Cohen et al. 1993), but increases rapidly thereafter up to 12.6% lifetime prevalence by age 16 years and 15.4% by age 18 years (Merikangas et al. 2010). Based on prospective studies, most people seem to have their first incidence of depression by the age of 18 years (Kim-Cohen et al. 2003), and the largest increase in depression rates occurs already between ages 15 and 18 (Hankin et al. 1998; Birmaher et al. 1996; Hankin et al. 1998). In a meta-analysis of Costello and colleagues (2006), the prevalence of major depressive disorder and dysthymia was 5.9% among 13-18-year-old girls and 4.6% among boys of the same age. Although most of the studies in the analysis were from the United States, it also included some studies conducted in Europe. However, different measures, time frames and methods used make it complicated to judge whether there exists true differences between the continents.

The prevalence estimates from Finland are relatively well in line with the ones from the United States. In a Finnish study based on self-reports, 4.7% of Finnish 14–16 year old girls and 2.2% of boys reported symptoms of severe depression, while 13.4% of girls and 6.3% boys reported symptoms of moderate depression (Torikka et al. 2014). Another Finnish study using semi-structured interviews evaluated the lifetime prevalence of minor depression in 14-year-old Finnish adolescents to be 15.8% for girls and 8.3% for boys, but for major depression merely 3.9% and 0.9%, respectively (Sihvola et al. 2007).

These figures hint that the proportion of individuals having symptoms is somewhat larger than the proportion of individuals receiving treatment. In a register-based study, following all Finnish children born in 1996, 1.2% of boys and 1.7% of girls had received either inpatient or outpatient care for depression and mood disorders (ICD-10: F32-F39) by age 14 years. Depression had a high comorbidity with both anxiety disorders (30.7%), and stress and adjustment disorders (22.5%) which are usually diagnosed at an earlier age than depression. Based on these observations, the authors reckoned that some children receiving a diagnosis of depression were at an earlier age diagnosed with stress and adjustment symptoms or anxiety disorders. (Gyllenberg et al. 2013.) The differences observed between diagnostic interviews and treatment registers could in part be due to the underdetection of depressive symptoms in adolescents (Leaf et al. 1996).

The use of antidepressant medication among adolescents and young adults has increased rapidly during the last two decades. In Finland, 5.4 per 1000 under 27-year-olds used antidepressant medication at least once in 1997, whereas in 2007 the proportion had risen up to 18.8 per 1000. The incidence of antidepressant medication increased at a parallel pace among 16–20-year-olds and 21–26-year-olds throughout the whole period from 1997 to 2007. A smaller increase was also seen among individuals aged 11–15 years. (Autti-Rämö et al. 2009.) Figure 1 demonstrates the rate of change in one-year prevalence of antidepressant medication between 1994 and 2013. The increase has been particularly rapid among 18–24-year-old women, for one-year prevalence was almost 8% in this group in 2013, while it was roughly 3.5% in the beginning of millennium. The gap between men and women in prevalence has also widened during the same period.

Figure 1 One-year prevalence (%) of antidepressant medication use among population aged 13–17 and 18–24 by sex in Finland, 1994–2013



Source: National Institute for Health and Welfare 2015.

Other countries have experienced similar trends in the use of antidepressants. In the United Kingdom, prevalence of antidepressant medication amongst adolescents aged 16 to 18 years rose from 8.52% to 23.9% between January 1992 and December 2001, while the general prevalence among 0–18-year-olds increased 1.6-fold (Hsia & McIennan 2009). Similar observations were made in Saskatchewan, Canada where there was a 1.61-fold increase between 1983 and 2007, the increasing trend being the most pronounced among adolescents aged 15 to 19 (Meng et al. 2014). These patterns are consistent with findings in the United States (Vitiello et al. 2006), Taiwan (Chien et al. 2013), and Germany (Hoffman et al. 2014). Meanwhile, there has been a parallel, although distinctly slower, increase in the prescription of antipsychotics in Europe and North America (Verdoux et al. 2010), which applies to Finland, as well (Autti-Rämö et al. 2009). Comparing the trends in different countries is not straightforward because the age groups and measurement periods used in studies vary and national practices of drug reimbursement differ. Even so, the general

worldwide trend of increasing prescription of antidepressants and other psychiatric medication for children and adolescents seems evident.

Gyllenberg et al. (2011) list several plausible explanations for the increase: major depression may have become more common and the threshold for seeking help thereby lower; new antidepressant medications with fewer side effects, (especially selective serotonin reuptake inhibitors, SSRIs) have been introduced since the late 1980s; and the use of antidepressants for a range of conditions, such as panic disorder, social phobia, and posttraumatic stress disorder, has been supported in new clinical guidelines (Gyllenberg et al. 2011). The most important message here is that the increase in the use of antidepressants might be caused by other factors than an increase in the true prevalence of depression.

According to a review of 18 population-based studies by Keyes & Liu (2014, 48), most of the evidence indicating an increase in the prevalence of major depression among younger birth cohorts was based on cross-sectional study designs relying on retrospective recall of lifetime depressive episodes. Such findings were especially made in the 1980s and the 1990s, for instance by Klerman & Weismann (1989), Burke et al. (1991), and Lewinsohn et al. (1993). Studies conducted in the 2000s using more reliable designs have, instead, produced more inconsistent results: A meta-analysis of data from more than 60,000 children and adolescents by Costello et al. (2006), thus far the most rigorous according to Keyes & Liu (2014), and a systematic review by Richter et al. (2008) found no evidence to claims that adolescent depression would have become more common during the past 30 years. Keyes & Liu (2014, 48) conclude in their review that the former studies may have been subject to recall bias and the observed increases in prevalence might more likely be explained by increased awareness and attention. On the other hand, Thapar et al. (2012) remark justifiably that changes in classification and assessment methods of depression make it difficult to draw direct conclusions about whether the prevalence of depression in adolescents has truly increased over time.

Regardless of measurements used, depressive symptoms in adolescence, after puberty, seem to be more common in girls than in boys. Both genders experience an increase in depression after puberty, but during mid-adolescence females begin to exhibit depressive symptoms almost twice as likely as males (Angold et al. 1998, McGuinness et al. 2012;

Nolen-Hoeksema & Girgus 1994; Piccinelli & Wilkinson 2000; Ge et al. 2001); accordingly, the lifetime prevalence of major depression is also 2-fold among females compared with males (Lewinsohn et al. 1993). Also Kessler et al. (1994) observed that 20%–25% of women and 10%–17% of men suffer from depression during their lifetime. According to Thapar et al. (2012), this 2:1 ratio may be considered one of the most robust findings in the epidemiology of depression. As was noticed from Figure 1, there is also a distinct gap between men and women in the use of antidepressant medication which has nothing but widened during the last two decades: In 2013, Finnish women aged 18–24 years were almost twice as likely to use antidepressants than men of the same age. Although the general prevalence of antidepressant medication is seemingly lower at age 13–17, the gender gap was even more pronounced in this age group in 2013.

In their critical review, Piccinelli & Wilkinson (2000) discuss several often-suggested explanations for the predominance of females in depression. They conclude: "Clinically important risk factors for predominance of females in depression are: sexual abuse and adverse childhood experiences; role limitation with associated lack of choice, role overload and competing social roles; psychological attributes related to vulnerability to life events and coping skills." In addition, the authors highlight that "gender differences in depression are genuine" even though they might partially reflect artifactual determinants, such as measurement procedures and differences in reporting of symptoms (Piccinelli & Wilkinson 2000.) In the same vein, Hyde et al. (2008) posit that girls face substantially more stressors in adolescence than boys do. Alongside social and environmental explanations, some studies have found potential genetic explanations for the overrepresentation of women in those suffering from depression (Abkevich 2003; Holmans et al. 2004).

2.3 Life course approach to depressive symptoms

Life course epidemiology focused originally on the long term biological, behavioral, and psychosocial processes that associate early life conditions and exposures with development of chronic diseases in adulthood (Kuh & Ben-Shlomo 2004, 3). The field of study has its roots in the works of professor David Barker and his team who famously posited that old-age chronic diseases are "programmed" during embryological development, for instance as a result of undernourishment during pregnancy — a claim later well-known as the "Barker

hypothesis" (Barker 1998). The term "life course epidemiology" was coined in the 1990s by Diana Kuh and Yoav Ben-Shlomo in order to bring the three different epidemiological approaches dealing with similar questions and aims closer to each other: adult lifestyle risk factors, fetal origins of adult disease, and social determinants of health (Kuh & Ben-Shlomo 2004, 3). Nowadays, life course approach may be considered one of the mainstream paradigms in social epidemiology, although its concepts have also become an essential part of general chronic disease epidemiology. Life course epidemiological approach is inherently interdiciplinary, accepting perspectives, concepts, and methods from different fields of study ranging from sociology to neuroscience (Koenen et. al 2014, 14).

Subsequently, life course perspective has also been applied to other kinds of questions than merely chronic disease epidemiology, such as the study of mental illness. In the past two decades, there has been an intense increase in research on the life course epidemiology of mental disorders, which has been catalyzed by the aging into adulthood of several birth cohorts (a prerequisite for life course studies), the integration of biological measures and genetic information in existing cohorts, and the revolution in our understanding how exposure to environmental adversities may affect neurological development and thereby the emergence of mental disorders (Koenen et al. 2014, 13-14). A life course approach to mental disorders offers a framework that helps to analyze how different determinants of health interact with each other throughout the life span and affect the risk of developing mental disorders (Buka & Lacy 2014).

As Sasha Rudenstine (2014, 88) puts it, "There is abundant rationale for considering depression from a life course perspective." Although depression is usually divided in subclasses based on symptom expression, these symptoms tend to overlap and do not strictly confine different subtypes of depression (Blatt & Maroudas 1992). On the contrary, as Blatt & Maroudas (1992) have suggested, depression is not merely a "clinical disorder", but "an affect state that ranges from a mild and appropriate transient reaction to difficult life events, to a profound and sustained disabling clinical disorder involving dysphoria, distorted cognition, and neurovegetative disturbances." Therefore, focus should be held in the life experiences that cause the onset and manifestation of depression and fundamentally shape the differences in clinical picture (Blatt & Maroudas 1992). In addition, as was discussed above, depression is at present typically understood as a disorder associated with

both biological and environmental mechanisms that intertwine in a complex manner over time (Rudenstine 2014, 88), which is a standpoint that life course epidemiology is particularly familiar with.

Life course epidemiological framework typically separates three different conceptual life course models: critical and sensitive periods, cumulative influences, and pathway influences. Suffice it to say such distinctions are, of course, above all conceptual and do not imply that different mechanisms are fundamentally unattached in reality (Pillas et al. 2014, 305). Next, these three conceptual models are briefly introduced before taking a deeper look on the principal life course mechanism of depression from the viewpoint of the present study, i.e. intergenerational transmission.

2.3.1 Critical and sensitive periods

Life course influences arising from critical and sensitive periods emphasize the significance of certain age periods in human development during which specific key competencies should be achieved because it may be difficult or even impossible to achieve them at a later age (Pillas et. al. 2014, 305). Ultimately, these mechanisms are linked to the increased plasticity of the brain during certain developmental periods. The difference between *sensitive* and *critical* periods lies basically in the strength of their long-term effect, the latter referring to practically irreversible processes. Sensitive periods represent those periods in an individual's early-life development during which the brain is particularly vulnerable to environmental disruptions and exposures have particularly strong and sustained effects on mental health. (Heim & Binder 2012.) On the other hand, also positive interventions that have taken place during these time frames have the most significant long-term impact. Critical periods, instead, refer to such specific time frames when certain experiences are vital for the normal development of mental health later in life. Disruption of development during these periods may not be fully compensated with subsequent positive exposures. (Pillas et. al. 2014, 305.) Theories on critical and sensitive periods are probably the most difficult ones to prove because both precise measures of certain early-life age periods and a long follow-up are essential.

2.3.2 Cumulative influences

Models of cumulative influences refer to the notion that several negative exposures are typically worse than just one and that the effect of multiple exposures may turn out to be even stronger than the sum of its parts. Two distinctions can be made: First, accumulation may occur either due to multiple exposures to the same risk factor (e.g. former episodes of depression increase the risk of a new episode) or because of exposures to several different risk factors (parental depression and low socioeconomic status). Second, the impact of several negative exposures can be either additive or multiplicative so that the risk of mental disorder either increases gradually with the number of adversities experienced or becomes markedly pronounced due to a certain combination of adversities. Although research has more often focused on the accumulation of negative exposures, also protective factors tend to accumulate. Underscoring the accumulation of harmful and protective factors leads to a more holistic approach to the prevention and treatment of mental disorders. (Pillas et al. 2014, 306–308.)

2.3.3 Pathway influences

Models of pathway influences highlight the impacts of path dependency. Broadly, pathways refer to a process where an exposure at one stage of life heightens the risk of an exposure at a later stage et cetera. However, a few distinctions can also be made here since pathways manifest themselves via trajectories, transitions, and chains of risk. Where trajectories refer to different longitudinal sequences of risk and protective factors leading to different mental health outcomes, transitions are single events that occur within such trajectories and are often tied to certain stages of life (such as moving away from parents). The temporal linkage of several negative exposures leading to one another may form a "chain of risk" that raises the probability of a mental disorder throughout the life course. The links that form a chain can be biological, social, or psychological in nature, and typically, all of these entangled. Moreover, two different forms of chains of risk have been identified. In the first form, all links of the chain have their own direct influence alongside the fact that they temporally increase the probability of one another (e.g. financial strain mediates the association between job loss and depressive symptoms). In the other type, a final "trigger exposure" is required for the disease risk to actualize, and without this trigger, the prior harmful

exposures may have only minor significance (e.g. exposure to several negative life events lowers the resilience towards stress until one major adversity such as parental loss triggers depressive symptoms). Emphasizing the role of pathway influences raises awareness about the common trajectories that often lead to mental disorders, but also pays attention to the plurality of individual pathways. In addition, it helps to recognize the several opportunities to break the chain of risk throughout the life course. (Pillas et al. 2014, 306-310.) Trajectory models are especially well suited to the study of major depression because of the disorder's relapsing and recurring nature, and early average age at first onset (Rudenstine 2014, 89).

3 Intergenerational transmission of depressive symptoms

3.1 Evidence on the intergenerational transmission of depressive symptoms

Parental depression is one of the most studied and well-established risk factors of child and adolescent psychopathology (Weissman 2006; Wickramaratne & Weissman 1998; Goodman & Gotlib 1999; Brennan et al. 2002; Goodman et al. 2011; Mendes et al. 2012; Keller & Gottlieb 2012). In a 20-year longitudinal study, an offspring with at least one depressed parent faced a 3-fold risk of depressive symptoms compared to an offspring of non-depressed parents (Weissman 1997; Weissman et al. 2006). In general, observed intergenerational effects are stable, but fairly weak: A meta-analysis, pooling together 121 studies, produced a correlation of 0.23 (95% confidence interval .22/.24) for maternal depression and offspring internalizing problems (Goodman et al. 2011). Most studies exploring the topic have found an association and tend to show that children of depressed mothers face a 2- to 3-fold risk of exhibiting depressive symptoms compared with children unexposed to maternal depression, but the effects vary to some extent according to the timing of exposure, the significance of which will be discussed later on.

Although most studies have focused strictly on mothers, the familial origins of depression have been examined from other angles too. A meta-analysis of five family studies found an odds ratio of 2.84 for increased risk for depression in first-degree relatives of depression probands (Sullivan et al. 2000). On top of that, also paternal depression has been perceived to pose a risk to the wellbeing of offspring. A recent study by Reeb et al. (2014) found that exposure to paternal depressive symptoms when in early adolescence (at age 13) predicted offspring depressive and anxiety symptoms at age 21, controlling for baseline youth symptoms, maternal depressive symptoms, and other known correlates of internalizing problems in early adulthood. In addition, contrary to the authors' expectations, the effect of paternal depressive symptoms was not moderated by maternal depressive symptoms. (Reeb et al. 2014.) These results are in line with a review article on paternal psychiatric and children's psychosocial development (Ramchandani & Psychogiou 2009), and several other

studies on paternal depression as a risk factor for offspring depression and internalizing problems (e.g. Bögels & Phares 2008; Kane & Garber 2009; Spector 2006), although maternal depression has sometimes been found to moderate the relationship so that the effect of paternal depression is lower or even non-existent without the presence of maternal depressive symptoms (Brennan et al. 2002; Kahn et al. 2004). A study by Klein and colleagues (2005) suggested that paternal depression is only associated with adolescent and young adult depression that is at least moderate in severity, possibly implying a stronger genetic component.

It seems plausible that intergenerational transmission of depressive symptoms might also be a two-way relationship where the effect of parental depression on offspring depression is partially a result of reverse causation. In addition to parent-to-child effects, there might exist child-to-parent effects whereby child characteristics, such as a difficult temperament or behavioral problems, exacerbate or even contribute to the causes of parents' depression (Goodman et al. 2011; Ramchandani & Psychogiou 2009). A study by Gross et al. (2008) found reciprocal associations between boys' externalizing problems and mothers' depressive symptoms in which disruptive behavior of children at age 5 to 10 years first increased depressive symptoms in mothers which further predicted youth antisocial behaviors at age 10 to 15 years. No research has yet studied reverse causation for paternal disorders (Ramchandani & Psychogiou 2009). In most study designs, it is presumably difficult to separate child and parental effects; therefore, causation and direction of the association are not established by correlational studies (Kramer et al. 2003). However, a growing evidence also suggests that improvements in maternal depression are followed by improvements in child mental health (Pilowsky et al. 2008).

Although nearly all studies have observed an association of some extent between parental and offspring depressive symptoms, the exact effect sizes have varied considerably between them. In fact, the effect sizes of different studies vary to such a degree that it is questionable whether they should be compared at all without paying precise attention to the study designs used. Divergent sampling techniques, demographically non-representative target populations, and alternative measurements of mental health outcomes account for some of the differences in the observed effect sizes. Studies on intergenerational effects are often based on clinical samples where study participants (i.e. mothers and fathers) have already

sought services for themselves, which leaves people with subclinical and non-treated depression out of reach. These so-called "high-risk samples" are especially useful when studying the mechanisms of transmission — both harmful and protective factors — because not all children of depressed parents develop depressive symptoms themselves (Warner & Weissman 2014, 273). Moreover, some mental disorders are relatively rare; thus, if initially healthy persons are examined, huge study samples need to be drawn to ensure statistical power. On the other hand, there is always the question whether the results obtained from high-risk studies represent the entire population. (Buka & Lacy 2014, 17.) As one may guess, Goodman et al. (2011) found the effect sizes between maternal depression and offspring internalizing symptoms to be significantly larger for clinical samples than nationally or regionally representative community samples. The authors add, however, that it is still left to be examined what in particular separates women who seek treatment and women who do not among mothers suffering from depression (Goodman et al. 2011). According to works of Kessler et al. (1999) and Kendler (1995), treatment seeking in depressed women is related to higher education, older age, impairment, a comorbid anxiety disorder, and more symptoms of depression.

Different definitions, operationalizations, informants, and measurement instruments of depressive symptoms may also contribute to the variation in effect sizes. In general, either clinical diagnostic tools or self-report symptom rating scales are used, the latter being a more common practice in community studies (Goodman et al. 2011). Burt et al. (2005) explored the implications of using single informant and time point data (quite a common practice in the field) versus multiple informant and time point data in their study on the mediating role of parenting. When measures of depression, parenting, and offspring outcome were all based on maternal report, the authors were able to replicate the positive result about the mediating effects of parenting from previous literature. When they instead used multiple measurement tools and informants, and data gathered in several time points, the finding replicated no longer. By this, the authors wanted to emphasize "the importance of independent data" to avoid overestimates caused by retrospective reports and use of single informants. (Burt et al. 2005.) Similarly, a meta-analysis showed that the association between maternal depression and child outcomes is the strongest when depressed mothers provided the information on child mental health outcomes compared to, for instance,

teacher's and clinicians' reports as well as children's self-reports. On the other hand, using clinical diagnosis instead of self-report of maternal depressive symptoms had only a minor influence on the effects of maternal depression on children's internalizing problems and general psychopathology. (Goodman et al. 2011.) In the same vein, Lyons-Ruth et al. (2008) remark, "The child correlates of maternal depression have been similar whether depression has been defined by psychiatric diagnostic criteria or by depressive symptom scales, and both sets of findings have been well replicated." Cross-sectional studies relying on retrospective self-recall of depressive symptoms are typically not considered a robust design option for life course studies as the temporal sequence between exposure and disease is commonly cloudy (Buka & Lacy 2014, 19-20). Especially the earliest studies of intergenerational transmission conducted in the 1980s have been criticized for their small sample sizes, lack of control groups and reliance on self-report methods (Beardslee et al. 1983).

In addition to delicate remarks on diverse sampling strategies and measures, some authors have underscored the need of genetically informed study designs when studying intergenerational mechanisms of mental health (Goodman et al. 2011; Sellers 2012). As we discussed in the previous chapter, clinical depression has a moderate genetic component that apparently in part underlies the association between parental and offspring depression. According to Ramchandani & Psychogiou (2009) children whose fathers have mental illness seem to be at increased risk of psychopathology, via both an increased probability of carrying risk genes for depression, and the influence of paternal psychopathological illnesses on the environment, for example, via an increased risk of exposure to adverse life events. At least as for antisocial behavior of fathers, children seem to face such a combination of risk factors (Jaffee et al. 2003).

The first study to directly test the extent to which the association between parental depressive symptoms and offspring psychopathology is caused by environmental (instead of genetic) influences was done by Tully and colleagues (2008), comparing the effects of maternal and paternal depression in biological and non-biological children. The study used structured interviews to measure the lifetime prevalence of depressive symptoms in parents and general psychopathology in adolescents at age 16. For maternal depression, the analysis produced an odds ratio of 3.61 in non-adopted adolescents and 1.97 in adopted

adolescents. Both effects were statistically significant but the difference between them was not. For paternal depression, the investigation found an odds ratio of 0.95 in non-adopted adolescents and 1.78 in adopted adolescents, but neither one was statistically significant. The authors reckoned this to imply a stronger genetic component in transmission of risk from depressed fathers than from mothers. (Tully et al. 2008.) Unfortunately, the analysis was not conducted separately for boys and girls, although some earlier examinations have shown boys to be at greater risk when exposed to paternal depression (Ramchandani et al. 2005, Ramchandani & Psychogiou 2009).

One example of genetically informed designs are the so-called gene–environment interaction studies mentioned in the previous chapter. In a candidate gene study, youth possessing at least one A allele of the oxytocin receptor gene (OXTR), shown to be relevant to social functioning, and who also had a history of maternal depression exhibited the highest levels of depressive symptoms at age 15 (Thompson et al. 2014). What is more, another study of gene-environment interaction revealed that youth with the SS genotype of the 5-HTTLPR gene experienced greatest increases in depressive symptoms when exposed to elevations in maternal symptoms three months earlier (Oppenheimer et al. 2013). Nevertheless, these findings should be interpreted with care, since they have not been replicated in other studies; hence, there is a high likelihood of them being false positives (Flint & Kendler 2014). Genes and environment may also interplay with each other so that, for instance, in some circumstances or at some stages of life, genetic heritability of a trait may be higher than in some other circumstances (Rutter et al. 2006). Overall, few studies have explored gene–environment interactions or gene–environment interplay of intergenerational psychopathology.

Since the link between parental and offspring depression has already been well-established, further research has focused more and more on elucidating the biological, environmental and social mechanisms underlying the association (Burt et al. 2005). An influential model developed by Goodman and Gotlib (1999) recognizes four different mechanisms of intergenerational transmission of maternal depression: genetic heritability of depression, innate dysfunctional neuroregulatory mechanisms (for instance affected by exposure to maternal depression during fetal development), exposure to mother's maladaptive cognitions, behaviors and affect; and exposure to stressful environment. In addition, the

model lists several possible moderators that put different groups at a different risk of intergenerational transmission: mental health and availability of father, timing and course of maternal depression, and characteristics of the child (temperament, gender, intellectual and social-cognitive skills). (Goodman & Gotlib 1999.) Next, we will discuss in more detail three potential moderators and mechanisms of intergenerational transmission that are particularly interesting from a life-course perspective.

3.2 Gender of the child

Gender of the child may modify the relation between parental and offspring depression, although there are separating views whether girls or boys face a greater risk and whether the direction and size of the effect is different for maternal and paternal depression. To begin with, it should be stressed that women experiencing more depression in general does not necessarily imply that they would suffer more severely from depression in parents too. In other words, the intergenerational transmission might — but does not necessarily — explain the gender difference in the life course risk of depressive symptoms, discussed earlier.

Again, the majority of past studies covered exclusively maternal depression: Some of them argued that girls are more vulnerable to maternal depression than are boys (Burt et al. 2005), others concluded just the other way around — especially if the exposure occurred at a young age (Essex 2003, Carter et al. 2001) — and some found no significant moderating effect at all (Bureau et al. 2009). As far as paternal depression is considered, the meager evidence suggest that boys might be more vulnerable to its effects, especially during early development, which could be partly due to the fact that fathers often spend more time with their sons than with their daughters (Ramchandani et al. 2005, Ramchandani & Psychogiou 2009). Overall, the moderating effect of gender has been suggested to differ according to the developmental phase of the child, as it is not clear whether these gender differences persist during adolescence (Bureau et al. 2009; Ramchandani & Psychogiou 2009). Since the dispute remains unresolved, Goodman et al. (2011) strongly encourage researchers to "report findings separately by gender, to develop and test genderspecific models of risk."

3.3 Timing and clustering of parental depression

Timing of parental depression according to age of offspring appears to cause extensive variation in effect sizes: In their review article, Goodman and Gotlieb (1998) concluded that first exposure to maternal depression at younger age would have a stronger negative impact than later first exposure. On the other hand, the significance of the timing of parental depression has also been questioned in a study by Hammen & Brennan (2003) according to which depressive symptoms at age 15 years are similarly predicted by an exposure to maternal depression at any of the ages between 0 and 10. Instead, studies conducted later have deemed the prenatal (Hay et al. 2010) and postnatal periods to be (Bureau et al. 2009) particularly sensitive when maternal depression is concerned. Some studies imply that exposures at kindergarten and school age are more clearly associated with offspring externalizing than internalizing problems (Essex et al. 2001). A Finnish study found no statistically significant relationships between the initial exposure to maternal depressive symptoms at age 8–9 years and adolescent psychosocial functioning; an exposure at age 16–17 was associated with externalizing but not internalizing problems (Korhonen et al. 2014). Not many studies have directly examined the effects of an exposure during late childhood or early adolescence and compared them to the impact of earlier exposures.

Timing is also linked to the recurrence of parental depression, albeit these two are difficult to disentangle analytically as most children with parents suffering from depression are exposed to parental depression several times and for long periods due to the relapsing nature of the disorder (Korhonen et al. 2014). A study by Halligan et al. (2007) indicated that maternal pre- and postnatal depression was only related to offspring depression in adolescence if there were also later exposures present. In addition, examinations by Hay et al. (2008) and Pawlby et al. (2009) suggested that prenatal maternal depression is related to adolescent depression and girls' emotional problems only if combined with later exposures.

Research evidence suggests that recent parental depression is associated with an increased risk for offspring psychiatric disorder and depression symptoms in adolescents, and that most children who experienced a major depressive episode did so in close proximity to maternal depression (Hammen et al. 1991; Mars et al. 2012). For instance, a longitudinal study by Wickramaratne & Weissman (1998) perceived an 8-fold risk of childhood-onset

major depression and 5-fold risk of early-adult-onset depression in offspring having at least one depressed parent in the beginning of the ten-year follow-up. Conversely, risk for adolescent-onset depression did not increase at all, which the authors interpreted to be catalyzed by the fact that much of the psychopathology in offspring of non-depressed parents occurred in adolescence, resulting in a dilution of the effect of parental depression on adolescent-onset psychopathology. (Wickramaratne & Weissman 1998.) The importance of proximity in time and place is, correspondingly, emphasized by the fact that variation in maternal depression remission, and successful treatment of parental depression seems to diminish, albeit not abolish, the risk of offspring psychopathology (Gunlicks & Weissman 2008). Similar findings have been made in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study in the United States where a decrease in maternal depression symptoms was related to a decrease in offspring internalizing and externalizing symptoms, whereas offspring of parents who did not remit and had more severe depression suffered from more symptoms (Foster et al. 2008; Garber et al. 2011; Pilowsky et al. 2008; Weissman et al. 2006).

These results are supported by studies that have examined the modifying effect of child's age, although it is difficult to disentangle whether their results reflect the effects of proximity to parental depression or the actual age of a child. In any case, Connell and Goodman (2002) perceived that the effect sizes for the association between maternal depression and children's internalizing problems were negatively correlated with children's age ($r = -.29$), and also a more recent meta-analysis observed decreasing effect sizes as studies examined older children and adolescents (Goodman et al. 2011). These more recent results are in line with the findings by Weissman et al. (1984) suggesting that around 60% of individuals who develop depression before age 20 have first degree relatives with affective disorders, compared with merely 30% of individuals experiencing their first episode at a later age.

Timing of parental depression is also at stake when maternal depression and paternal depression become clustered. Here, clustering of parental depression refers to a situation in which a child becomes exposed to both maternal and paternal depression during the same stage of life. Research on assortative mating has shown that persons having suffered from depression tend to choose as partners and have children with such persons who themselves or whose close relatives have a history of psychiatric disorders (Merikangas

1982; Merikangas et al. 1988), although one study indicated assortative mating to be particularly common between depressed females and antisocial males (Marmorstein et al. 2014). Assortative mating puts children of depressed parents at an increased risk of depressive symptoms by entailing both an increased genetic vulnerability and a stressful family environment (Merikangas et al. 1988). Based on these sets of findings, it has been hypothesized that maternal and paternal depression might have an additive effect on the risk of child psychopathology when they occur together (Brennan et al. 2002; Marmorstein et al. 2014). Inversely, one healthy parent in a household might also act as a buffer that protects the child from harmful effects (Tannenbaum & Forehand 1994). Some empirical studies support the assumption that the effects sum up (Foley et al. 2001; Merikangas et al. 1998), but more research is needed to draw solid conclusions. For instance, Dierker et al. (1999) did not find a significant additive effect in parental concordance of anxiety and affective disorders compared with the effect of an exposure to parental depression in one parent only. Also Brennan et al. (2002) observed that an independent exposure to either maternal depression or paternal depression increased the risk for youth depressive symptoms to the same extent as an exposure to both of them. Because of such ambiguity, Connell & Goodman (2002) urge researchers to take account of psychopathology in both parents when studying the risk of intergenerational transmission and examine the interaction between them.

3.4 Socioeconomic circumstances

3.4.1 Socioeconomic status and depressive symptoms

A vast and ever-growing evidence has shown that socioeconomic status (SES) is a strong predictor for most health outcomes: On average, the more advantaged the individuals are, the better their health (Marmot 2011; Adler & Ostrove 1999). In the same vein, low socioeconomic status, as measured through educational level, occupational grade or income, is consistently associated with higher prevalence of depression (Mojtabal & Olfson 2004), although the social gradient seems to be steeper for long-term and recurrent depression than for the incidence of a new episode (Melchior et al. 2013; Lorant et al. 2003). It has also been shown that 1-year increases in material hardship such as financial

strain, deprivation, and poverty lead to an increase in risk of depressive symptoms (Lorant et al. 2007), which implies that the observed associations are not solely caused by selection. Similarly, according to a Danish register-based study, the first-time purchases of antidepressants follow an inverse social gradient, that is, the lower the socioeconomic status, the higher the number of first-time users (Hansen et al. 2004). In a cross-national comparison, income was more strongly related to the risk of a major depressive episode in high-income countries than in low-to-middle-income countries. Such difference was not found when studying education, but in China and Japan, the association was reverse so that those having the lowest educations also had the lowest risk of major depression. (Bromet et al. 2011.)

Life course studies have widened the scientific perspective from individual's own to parental socioeconomic characteristics. According to studies based on retrospective assessments of childhood SES and lifetime depressive symptoms, socioeconomic status in childhood predicts the lifetime risk for major depression even after adjustment for adult socioeconomic status (Kim et al. 2013; McLaughlin et al. 2011; Gilman et al. 2002), albeit a recent Japanese study hinted that this association might be applicable to women only (Ochi et al. 2014). A Finnish longitudinal study emphasized that the effect of childhood SES on depressive symptoms diminishes over time, but a higher level of, and especially faster decline of, depressive symptoms predicts the adulthood occupational SES gradient (Elovainio et al. 2012), implying reverse causation.

Further evidence has suggested that parental socioeconomic status predicts not only adult- but also child- and adolescent-onset depression (Gilman et al. 2003; Meltzer et al. 2003), although a longitudinal study by Miech et al. (1999) did not find any relation between SES and depression before age 21. For the general childhood mental health among a population aged 4 to 15 years, measured using the parents' version of the Strengths and Difficulties Questionnaire, a Spanish study found a social gradient according to both the maternal education level and family social class (Barriuso-Lapresa et al. 2012). Goodman et al. (2003) estimated the population attributable risk (PAR), which represents the proportion of disease that would be prevented if the exposure were removed and if the entire population achieved the disease prevalence in the previously unexposed group, for adolescent depression in the United States: The PAR, adjusted for gender and

race/ethnicity, was 26% for lower income and 40% for lower parental education (Goodman et al. 2003). On the other hand, in a Norwegian population-based study all indicators of low SES, apart from parents' education, were related to higher rates of antidepressant prescription (von Soest et al. 2012), which is not completely in line with the estimates from the United States where parental education seemed to account for the largest impact. What is more, already over two decades ago, another American study highlighted that only girls seem to be directly affected by low parental education and that this association remains largely unaffected after controlling for life-stress and available social support (Gore et al. 1992).

A somewhat different perspective was taken by a Hungarian study which emphasized the role of subjectively determined socioeconomic status as the most significant and consistent of all SES measures in explaining adolescent health inequalities: Those evaluating themselves as middle or lower class (as compared with those from upper/upper-middle classes) reported a higher likelihood of depressive and psychosomatic symptoms, even though among "objective" SES indicators, mothers' lower level of education (but not father's) remained a risk factor for their children's depressive and psychosomatic symptoms (Piko & Fitzpatrick 2007). In addition, a study among Korean middle and high school students found no association between maternal education or family affluence (measured through Family Affluence Scale) and depressive symptoms, but observed a significant inverse association between subjective household economic status and psychological health (Jeon et al. 2013). On the basis of these results, it may be asked whether adolescents are always fully aware of their "objective" SES (i.e. their parents' education, income, and occupational status), and whether the "subjective" and "objective" measures of SES encompass to some extent different risk factors of adolescent psychopathology. Goodman et al. (2002) found stronger correlations between the subjectively determined social standing and father's education among adolescents 15 years of age or older (.83) compared with those younger than 15 years (.68). The authors hypothesized the difference between the age groups to be caused by cognitive maturing which leads to better ability to think abstractly, e.g. understand social stratification. (Goodman et al. 2002.)

Above mentioned, for some part contradictory, results from previous studies on SES and adolescent depression could possibly be explained by country-specific cultural differences,

dissimilar measurements of socioeconomic status and depressive symptoms (depression scores vs. treatment), and cohort effects. Mediators of the relation between socioeconomic conditions and depression are understood even less well, but the availability of social support appears to be one of the key mechanisms. According to the stress-buffering model, individuals gaining strong social support are less likely to become depressed by stressful life events (Cohen & Willis 1985). Strong evidence suggests that socioeconomic factors mediate the association between family structure, especially concerning single-parent households, and adolescent depression (Barrett & Turner 2005), whereas the correlation between lower socioeconomic status and depression is mediated by weaker parental social support, particularly maternal support, and optimism during the socialization process (Piko et al. 2013). On top of that, maternal depression and anxiety mediate the relations between economic pressure and sensitive parenting behaviors (Newland et al. 2013). However, according to a meta-analysis of 46 observational studies by Lovejoy et al. (2000), the relation between socioeconomic status and parenting is a two-way street: Socioeconomic status also moderated the relation so that the harmful effects of maternal depression on positive parenting behaviors were the strongest among families of low socioeconomic status. Some studies have indicated that low socioeconomic status might even heighten the risk of child and adolescent psychopathology by alternating brain development and affecting the functioning of the stress response system (Kishiyana et al. 2009; Tomarken et al. 2004).

Going beyond the mere description of disparities, a recent Swedish register-based study scrutinized the role of clustering adverse childhood experiences in socioeconomic differences of young adult psychopathology. When taking several adverse childhood experiences, e.g. criminality among parents, parental alcohol and drug abuse, and parental separation, into account, the risk of psychotropic medication was the same for all educational groups (highest attained parental education level), although this could partially reflect disparities in access to and utilization of the health care system, as the authors themselves noted. (Björkestam et al. 2013.)

The latter is an important reservation to keep in mind when interpreting the results of a register-based — as well as any other treatment-based — study because, at least among working-age adults, people from higher socioeconomic positions tend to be more prone to utilize antidepressant treatment, even though there is an increased prevalence of depression

in the lower occupational and educational groups (Kivimäki et al. 2007). In a similar way, poor people tend to seek mental health treatment more sparsely (Howard 1995) and, at least in the context of the United States, less frequently receive treatment from mental health specialists (Gallo et al. 1995, Leaf et al. 1998). Among teens, socioeconomic status predicts utilization of medical care, but it seems more ambiguous whether it is associated with seeking mental health services more actively, as well (Goodman & Huang 2001).

3.4.2 Socioeconomic status and intergenerational transmission

It is possible to name at least two mechanisms through which socioeconomic status might interplay with the intergenerational transmission of depressive symptoms. First, as already mentioned, lower socioeconomic status is a potential risk factor for both adult-onset and childhood-onset depression; therefore, correlation between parental and offspring depressive symptoms might be partially explained by a long-term exposure to similar disadvantaged socioeconomic conditions (Ramchandani & Psychogiuo 2009; Barker et al. 2012). Studying depressive symptoms among mothers, Sperlich et al. (2011) indicated that low income was the most important socioeconomic risk factor for high depression scores after controlling for age at first birth and family structure, the effect of job position and years of education remaining non-significant. For a few decades, researchers have made similar findings on associations between low income–high social risk and maternal depression (see Feder et al. 2009, Graham & Easterbrooks 2000; Huston et al. 1994). Barker et al. (2012) approximated that at least 37% of the association between maternal depression and child internalizing disorders (at 7.5 years) is explained by exposure to similar environmental, familial, and lifestyle-related risk factors. The prevalence of childhood and adolescent mental health problems is typically larger in studies sampling low-income families regardless of the prevalence of parental depressive symptoms (Feder et al. 2009). In the United States, children from families with annual incomes below $10,000 have been found to experience more internalizing symptoms (Xue et al. 2005). According to Ramchandani & Psychogiuo (2009), few studies have controlled for parental income and education when studying the relation between parental and offspring depression.

Second, childhood socioeconomic factors have been suggested to be a possibly significant modifier of the risk for the intergenerational transmission of depressive symptoms (Sellers

2012). Theorizing socioeconomic status as a potential modifier of the risk implies that the observed link between parental and offspring depressive symptoms may differ between socioeconomic groups or even pertain, for instance, only to those families with low income. The reason for why this might happen is that exposure to multiple adversities weakens resilience in the face of stress and other negative life events (Rutter 2005). Some studies of maternal depression have found that children of depressed mothers are at increased risk for cognitive and intellectual problems only if they live in disadvantaged socioeconomic conditions (Hay et al. 2001; Sohr-Preston et al. 2006). One twin study has even hinted that the heritability of internalizing problems might be stronger in families with higher income, whereas environmental mechanisms play a larger part in low-income families (South & Krueger 2011).

Previous studies have typically sampled exclusively either middle and upper class families or solely low-income families; therefore, Feder et al. (2009) emphasize, "[f]uture studies should directly compare children of depressed mothers across socioeconomic groups..." Goodman et al. (2011) summarized, likewise, that very few studies, reviewed in their meta-analysis, systematically examined the occurrence of depression in mothers from diverse social and economic backgrounds and the potential impact of such contextual differences, as most studies sampled largely homogeneous, middle- and upper-middle-income families. Due to the limited number of studies with data allowing tests of SES as a moderator, the authors were only able to compare the effects sizes in samples that contain exclusively low-income families to those consisting of middle-to-high SES families. After having assessed the relation between maternal depression and several childhood mental health outcomes, they conclude:

> In terms of family characteristics, consistent with predictions, effect sizes for associations between depression in mothers and children's internalizing and externalizing problems, general psychopathology, and negative and positive affect/behavior were stronger for studies that sampled families in poverty relative to studies of families in higher or mixed-income levels. Thus, poverty seems to be a broad-scale enhancer of risk in relation to depression in mothers, regardless of the aspect of child outcome assessed. (Goodman et al. 2011.)

3.5 Summary

All in all, previous research has elaborately documented the effects of maternal depression on offspring internalizing and depressive symptoms, although there has been slight variation in the observed effect sizes between different studies. Recently, more and more studies have examined the role paternal depression, too, concluding that the association is fairly similar in strength compared to maternal depression. Meanwhile, there has also been a growing attempt to understand the biological and social mechanisms underlying the intergenerational effects, which has stirred research to focus on the mediators, confounders, and modifiers of the risk (Burt et al. 2005). So far, a multitude of questions regarding the mechanisms of transmission remains to be answered.

One of the unresolved questions is the role of gender. For maternal depression, some studies found boys to be at greater risk, others just the opposite, while some did not find a gender difference at all. For paternal depression, most studies implied that boys might be at a greater risk than girls.

Another still open question is the significance of socioeconomic circumstances. The associations between parental psychiatric disorders and child disorders might be, for some part, explained by exposure to similar socioeconomic conditions, but earlier studies have seldom controlled for parental socioeconomic status (Ramchandani & Psychogiuo 2009). Moreover, according to Goodman et al. (2011), very few studies have systematically examined the role of family socioeconomic status as a modifier of the risk. Also Feder et al. (2009) emphasized that future studies should compare the effects of parental depression between children of different socioeconomic groups.

The role of proximity, timing and clustering of parental depression has also remained an understudied issue, and the meager existing evidence is to some extent contradictory. In addition, the studies having addressed these themes have mainly compared exposures during prenatal, postnatal, and kindergarten periods. The paucity of earlier research is probably due to the large data requirements involved: To answer these questions reliably, one needs prospective longitudinal data with several measurement points and a sufficiently long follow-up period, which are difficult to achieve in survey-based studies.

4 Aims of the present study

4.1 Research questions and hypotheses

This study aims to shed light on some of the understudied and most weakly understood mechanisms underlying the intergenerational transmission of depressive symptoms. The primary objective of the study is to examine how certain social mechanisms and life course processes put adolescents at a different risk of developing depressive symptoms. In other words, the study elucidates how gender, socioeconomic circumstances, and timing of exposures modify and/or mediate the transmission of risk, and thereby identify subgroups who face an elevated risk of suffering from depressive symptoms during adolescence and early adulthood. More specifically, the present thesis aims to answer to the following questions that rise from the previous literature:

1. Do children who were exposed to maternal or paternal depression at age 9–14 years have a heightened risk for developing depressive symptoms when they are 15–20 years old?
2. Are there gender differences in the strengths of the associations?
3. Is the relation confounded or modified by family socioeconomic factors such as parental income and education?
4. Are children exposed to both maternal and paternal depression at age 9–14 at an even heightened risk compared to children only exposed to either maternal or paternal depression?
5. Does exposure to maternal or paternal depression at age 0–5 pose a larger risk than exposure at age 9–14 and is the effect even stronger if the exposure occurred during both of these stages of life?

Leaning on the studies reviewed above, we hypothesize that both maternal and paternal depression at age 9–14 are related to offspring depressive symptoms among both girls and boys aged 15–20. Since our analysis rests on treatment data, we await the observed effect sizes to be slightly weaker than in most of the earlier studies based on depression scales and thereby detected untreated and non-clinical depressive symptoms, as well. Nonetheless, we do not expect the difference to be large because the liability to seek treatment is probably

clustered within families: Parents who have received treatment for depression themselves might be more apt to seek psychiatric treatment for their children when needed. Therefore, our results are presumably slightly biased both positively and negatively due to the operationalization of the outcome variable, which is described and discussed more precisely in the next chapter.

Our second hypothesis is that maternal depressive symptoms are an equally significant risk factor for boys and girls while paternal depressive symptoms form a larger risk for boys than girls. Previous studies on maternal depression have produced mixed results; therefore, a conservative hypothesis was chosen. Paternal depressive symptoms are assumed a more important risk factor for boys since the meager available evidence points to that direction (Ramchandani & Psychogiuo 2009). Owing to the exceptionally large sample size, the present study is able to assess the effects of both maternal and paternal depression separately for boys and girls, and consider the magnitude of their interrelation. Here, an interesting question is also whether the possible gender difference in the effects can be interpreted to increase or decrease the gap between men and women in the life course risk of depressive symptoms.

Our third hypothesis is that the association between parental and offspring depression is partially explained by exposure to similar socioeconomic conditions (parental education and income as confounders) and that the lower the family socioeconomic status gets, the more intense is the association (parental education and income as modifiers) because the great bulk of the available evidence points at an inverse SES gradient for both parental and offspring depression, and a few studies have also elucidated the role of low socioeconomic status as an enhancer of the risk. This sort of finding could be interpreted as a manifestation of multiple cumulative exposures to different risk factors. We expect to find an inverse SES gradient; however, no strong assumptions are made about the strength of the interactions.

The fourth hypothesis of the study is that exposure to both maternal and paternal depression at age 9–14 puts the child at an even greater risk if compared to children who were only exposed to maternal or paternal depression. On the basis of the model of cumulative risks and some previous research, this clustered effect might even be stronger than the sum of its parts, i.e. more than additive. We expect to find such more than additive

effects for both boys and girls but do not expect to find interactions that are more than multiplicative (presence of depressive symptoms in one parent heightens the effect of other parent's depressive symptoms) since earlier literature does not support this assumption.

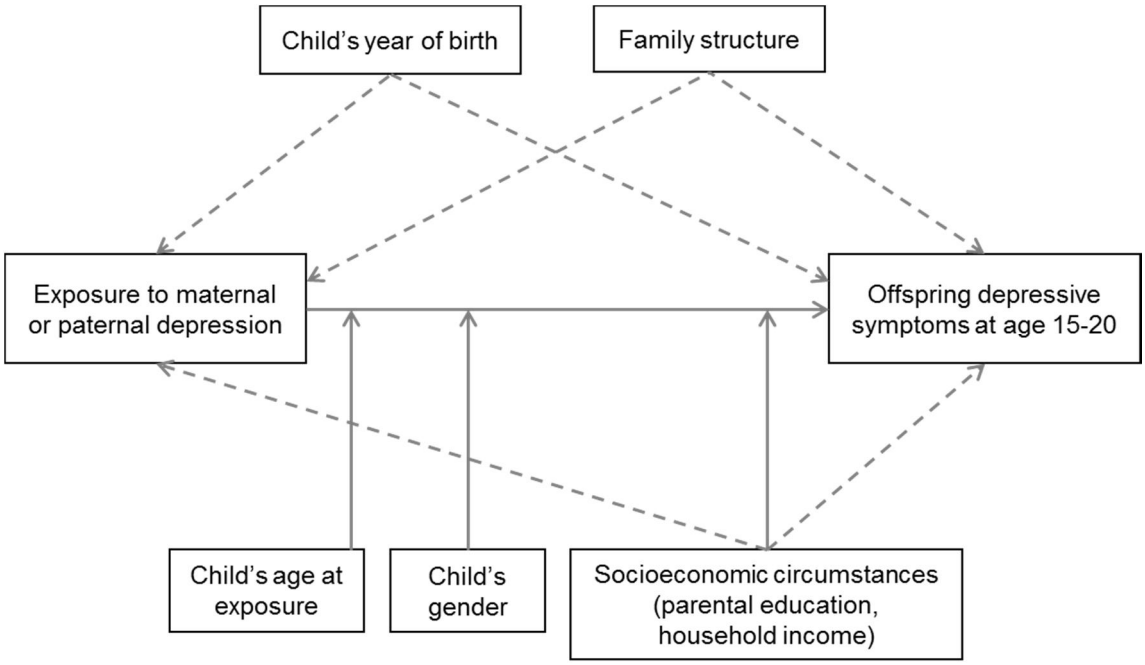
Fifth, as the association between maternal and offspring depressive symptoms was found to be negatively correlated with age (Goodman et al. 2011), we could posit that the association is stronger in those families where the offspring was exposed to parental depression at an earlier age than 9–14 years. On the other hand, few studies have explored the effects of parental depression in early adolescence to offspring depression in late adolescence and early adulthood, which leaves us lacking a viable reference point. Ultimately, we hypothesize the risk of depressive symptoms to be stronger among those exposed only at age 0–5 than in our primary age group (exposed to parental depression at age 9–14), but the strongest among those who were exposed during both of these stages of life. The former assumption rises from the life course model of sensitive periods where early-life adversities and disruptions are typically observed to have especially harmful long-term impacts. On the other hand, some authors have emphasized the importance of proximity to parental depression, which could also support a contrary interpretation (Hammen et al. 1991; Mars et al. 2012). The latter assumption about the effects of recurrent exposures at both stages of life is attached to the pathway model of chains of risk in which an earlier exposure to parental depression increases the risk of later exposures that finally lead to offspring depressive symptoms.

4.2 Study design

Figure 2 summarizes the study design that will be used to answer the above named research questions. The arrows that are drawn in the figure depict only those associations that are of interest in the present analysis and do not imply that there does not exist other kinds of relations between these attributes. The principal question under examination is the association between parental (both maternal and paternal) and offspring depressive symptoms. Those arrows that are marked with dashes represent confounding factors, while those arrows that cut the main association represent moderating factors. Child's year of birth and family structure are considered solely potential confounders on grounds of previous studies and their effects are merely controlled for. Child's age at exposure to

parental depression and child's gender are, instead, considered factors that moderate the association between parental and offspring depressive so that boys and girls as well as those exposed at an earlier and at a later age are expected to face a different risk when exposed to maternal or paternal depressive symptoms. As already mentioned, socioeconomic circumstances are examined both as confounders and modifiers of the risk.

Figure 2 Study design



5 Data and methods

5.1 Study population

5.1.1 Data sources and participants

The present study utilizes internationally unique individual-level data, obtained from the Finnish population register and other administrative registers. Altogether, the EKSY014 data file (Permission TK-53-525-11) includes a 20% random sample of households with at least one child aged 0–14 at the end of 2000 with individual-level information on all household members (n=415,000), supplemented with similar information on all non-coresident biological and adoptive parents of all 0–14-year-olds (n=28,000). The individual-level linkages between different registers, maintained by Statistics Finland, the National Institute for Health and Welfare, and the Finnish Social Insurance Institution, were carried out by Statistics Finland, using unique personal identification numbers. Although the sampling represents the households with children at the end of 2000, the annual measures included make it possible to follow individuals prospectively up to 2012, and retrospectively from year 1970 onwards.

Sociodemographic and labor market characteristics, which are used to assess the role of possible confounders and moderators of risk for transmission of depressive symptoms, were provided by Statistics Finland. Additionally, these data include information on deaths and emigration, which allows us to take account of censoring elaborately, although the benefits of this are arguably mere due to the rarity of these phenomena among Finnish children and adolescents. Emigration has ranged between 0.1% and 0.4% per year in 2000-2012 (Statistics Finland 2013a), but the mortality figures are shadowed by the strong excess mortality among young Finnish men from external causes of death, especially injuries and violence (Remes 2012; Mattila et al. 2008; Koskinen & Martelin 2007). Mortality rate (per 1000) for girls stayed on average below 0.2 for age groups 1-4, 5–9 and 10–14, less than 0.3 for 15–19-year olds, and below 0.4 for 20–29-year olds (Statistics Finland 2013b). For boys, mortality rate stayed averagely below 0.3 for 1–4-year olds, below 0.2 for 5-9 and 10–14 year olds, but more than 1 per 1000 among age groups 20–24 and 25–29. As it seems, the

gender difference is more pronounced towards early adulthood: In 2005–2009, 56% of the deaths occurred for males aged 1–14 years, and 75% for the 15–29 year-olds. (Remes 2012, 12-13). In addition to censoring, information on family type and mortality allows us to identify the children who were exposed to parental divorce or death during their childhood or early adolescence.

5.1.2 Defining the study population

Because of the chosen sampling strategy, the data fully represents only children who were 0–14 years old in 2000, in other words born in 1986-2000. It does not, for instance, contain any singletons born earlier than in 1986 because other persons were only included in the data if they were dwelling in the same household with at least one 0–14-year-old at the end of the year 2000. Therefore, only those who were born in 1986–2000 may be interpreted to nationally represent birth cohorts of their own.

The need and availability of information on both children and their parents sets even more restrictions to the inclusion of birth cohorts. Data on purchases of antidepressants, forming the core of both the outcome variable and the main explanatory variable of the study, is only available for the time period 1995–2012, which in practice means that for some of the birth cohorts born in 1986–2000 the follow-up of children ends too early, while for some other birth cohorts the follow-up of parents starts too late. In addition, according to our preliminary investigations, depressive symptoms manifest extensively in the data not until the age of 14. To maximize the size of the final study population while still preserving a symmetrical and relevant study design, the solution depicted in Table 1 was chosen.

Table 1 Birth cohorts forming the primary sample (the whole area) and the smaller sub-sample (area in light gray) used in the analysis

Birth year	N	Parental depression detected from age…	Own depression detected until age…
1996	12 026	-1	16
1995	12 711	0	17
1994	12 913	1	18
1993	13 117	2	19
1992	13 080	3	20
1991	13 013	4	21
1990	13 216	5	22
1989	12 711	6	23
1988	12 814	7	24
1987	12 209	8	25
1986	12 218	9	26
Total	140 028		

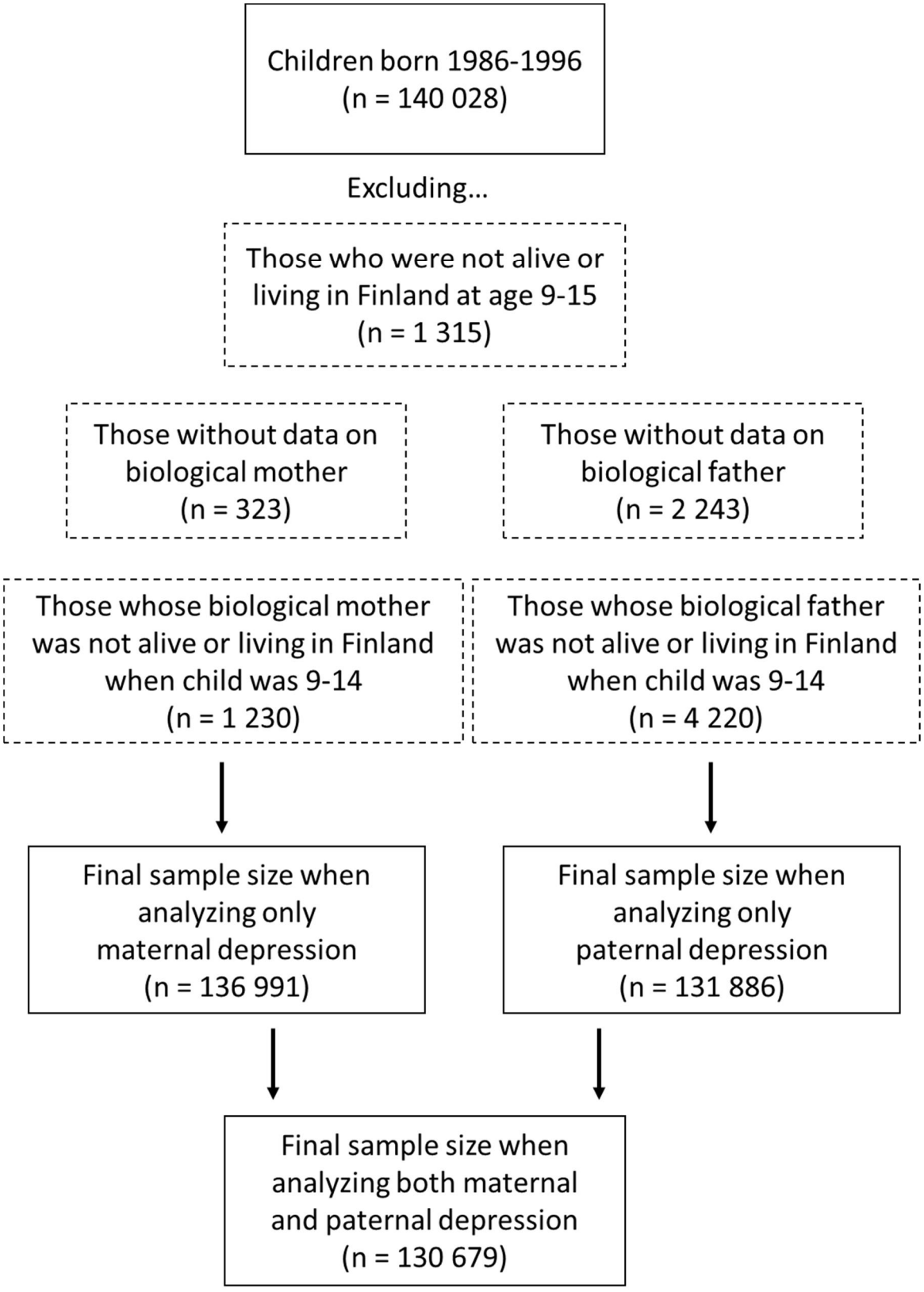
The table shows the birth cohorts that were chosen for the final analysis, including the earliest age when it is possible to detect parental depressive symptoms (i.e. age at the end of 1995) for each birth cohort and the ages of different birth cohorts at the end of 2012 (i.e. at the end of the follow-up). As may be seen in the table, two different sub-samples will be used to answer the study questions. The primary sub-sample, which will be used to answer the study questions from 1–4, consists of children who were born in 1986–1996 (n=140,028). For this group, it is possible to detect parental antidepressant use as well as inpatient and outpatient treatment when the children were 9–14 years and the children's own depressive symptoms starting from the beginning of the year they turned 15 years and ending to the last day of the year they turned 16 or, depending on the birth cohort, up to 26 years. However, since only adolescent depression is at focus in the present study, we end the follow-up of depressive symptoms for all birth cohorts at the latest at the end of the year the person turned 20. Shorter follow-up times than this were allowed for those who were born in 1993–1996.

To be able to answer the fifth study question about the importance of timing of exposure properly, we need to use an even more restricted study group because information on parental depressive symptoms both in early childhood and in early adolescence is necessary. Only those who were born in 1995 or 1996 (n=24,737) meet this requirement

and thereby form the other sub-sample used in the study. As the reader might have noticed, these two birth cohorts also belong to the group whose follow-up ends inevitably earlier than at age 20, which makes the study design somewhat different from the one used with the primary sample. Again, the follow-up of children's own depressive symptoms starts on the first day of the year the child turned 15. Parental depressive symptoms are measured for the five-year age ranges 0–5 and 9–14. The goal of this analysis is to compare the association of an early-life exposure to the association of an exposure at age 9–14 years that is the main interest of the present study. In addition, the examination sheds light on the significance of recurrent exposures to parental depression. Although available, exposure to parental depressive symptoms at age 6–8 is not included in the analysis because, with the smaller sample size, there would not be enough statistical power for reliable statistical inference with so many combinations.

After selecting the birth cohorts to be studied, some other exclusions were also needed to make the analysis as valid as possible. First, we excluded children who had died or emigrated from Finland before the first day of the year they would turn 16 (n=1,315) so that all persons have at least one full year of follow-up. If the person died or emigrated later during follow-up, he or she was included in the study sample and censored on death/emigration. Second, we excluded children for whom there was no information on biological parents in the data (323 individuals had a missing mother and 2,243 a missing father). Those children who were only missing one of their biological parents (or he or she was not included in the data) were included in analyses concerning the non-missing parent only. Third, we excluded children whose biological parents had died or emigrated before the first day of the year the child turned 15 (1,230 had a missing mother and 4,220 a missing father), since these persons were not at risk of becoming exposed to parental depression during the whole age period of 9–14 years. Instead, if the child was dwelling in a different household than the biological parent and both were living in Finland, he or she was included in the sample. Once again, children who had only one deceased or emigrated parent were included in the analysis if it concerned the non-missing parent only. The complete procedure of defining the study population and the final sample sizes in different situations are summarized in Figure 3. The exact sample size varies depending on whether maternal depression and paternal depression are analyzed separately or together.

Figure 3 Exclusions made to the study population and the final sample sizes in different analysis settings



5.2 From measures to variables

5.2.1 Operationalization of depressive symptoms

This kind of register-based study faces somewhat similar challenges as studies using clinical samples: For us to be able to detect any association between parental and offspring depression, parents must first have sought treatment for themselves. Where it differs is that children, whose parents have not sought treatment, are included in the sample, as well, i.e. having a history of parental depression has not been a selection criterion in the sampling process. Therefore, we are able to compare the incidence of depressive symptoms among children of depressed and children of non-depressed parents while controlling for several possible confounders. The specifics of using register-based data and operationalizing "depressive symptoms" as *already having received antidepressant or outpatient treatment* are described in this chapter.

The present study utilizes information on clinical treatment, but differs from most community sample based studies by the fact that research participants are not randomly selected for clinical screening; rather, they first must have sought treatment themselves, or otherwise, they must have been referred to treatment. Using register-based data has not been a common practice in studying intergenerational transmission of psychopathology; nonetheless, with the aforementioned robustness of correlates in mind, we may expect to see somewhat similar or slightly smaller effect sizes as in previous studies.

The outcome variable of the study, i.e. having received treatment for depressive symptoms, consists of data derived from two different sources. First, the Finnish Social Insurance Institution provided information on reimbursement for drug costs, and all purchases of prescription medication, classified by ATC codes. Second, all visits to both inpatient hospital care (1995–2011) and outpatient specialized services (1998–2011) were derived from the Finnish Hospital Discharge Register, maintained by the National institute for Health and Welfare. The register records information on inpatient care in all hospitals and outpatient care in public hospitals, including day of admission and discharge, the medical specialty service, and a main diagnosis and secondary diagnoses according to the ICD-10 (Gyllenberg et al. 2014).

The records obtained from the two data sources were combined into a dichotomous annual indicator of depressive symptoms. Therefore, observations of depressive symptoms could be based on either purchases of antidepressants; visits to inpatient or outpatient care; or both of them. The formation of the indicator went as follows. First, antidepressant medication was identified similarly as in two previous studies on psychiatric disorders, utilizing Finnish register-based data (Joutsenniemi et al. 2013; Joutsenniemi et al. 2011): We included all purchases of antidepressants with ATC code N06A, including combination product N06CA01, but excluding tricyclic medication (N06AA, but not N06AA22 and N06AA24), since they are commonly used for non-psychiatric conditions and thereby poorly reflect psychiatric morbidity (Gardarsdottir et al. 2007; Sihvo et al. 2008). Second, all visits to inpatient hospital care and outpatient specialized services due to depressive symptoms were included. In this case, diagnostic groups were separated by ICD-10 codes of which we included all that encompass depressive symptoms, i.e. F32–F39. We did not include bipolar disorders (F31) because of their strong genetic heritability (85%) compared with e.g. major depression (McGuffin et al. 2003). Only main diagnoses in inpatient and outpatient care were examined since no information on the accuracy and coverage of the secondary diagnoses was at hand. If the subjects had received treatment for depressive symptoms by inpatient or outpatient care criteria or purchased other antidepressant medicines, tricyclic medication was not an exclusion criterion. The same method for identifying depressive symptoms was used for both parents and their offspring.

As discussed in the second chapter of the report, the use of antidepressants among teenagers has recently become more and more common. Since our study design is based on a synthetic cohort formed of several birth cohorts, this might cause a severe bias to our results if not taken into account. Fortunately, the bias would probably cause the effects to be slight underestimates, i.e. more conservative, of the current situation because several older birth cohorts, experiencing lower general prevalence of antidepressant medication, are included in the study population. At any rate, to tackle the possible cohort effect, child's year of birth is added to the multivariate models as a control variable.

The principal explanatory variable of the study, i.e. parental depressive symptoms, was operationalized in a precisely similar way as children's own depressive symptoms. The data would allow the analysis of depressive symptoms of both biological and non-biological

parents, but the decision to include only biological parents was made because they were comprehensively included in the data (apart from the few exceptions mentioned above) even if they never lived in the same household as their children. Non-biological parents, instead, were only included in the data if they were living in the same household at the end of the year 2000. Thus, if they were later replace by a new non-biological parent, we would not observe his or hers depressive symptoms. On the other hand, the examination of exclusively biological parents' depressive symptoms brings out the problem that not all biological parents were living in the same household as their children when the children were 9–14 years old, and we do not even know how often they were meeting their children at that time. Because of this, the results are chiefly reported separately for children who were and who were not dwelling with their biological parents at age 9–14 years.

5.2.2 Measures of socioeconomic status

We use two measures of family socioeconomic status — parental education and household income — to study the confounding and moderating effect of socioeconomic circumstances. Parental educational attainment is measured just before the start of the follow-up, i.e. on the last day of the year the child turned 14, so that most of the parents have achieved their highest educational attainment. To simplify the analysis and keep the sample size fixed (children not living with their fathers of course lack information on paternal education), the role of maternal and paternal education is not analyzed separately; instead, we study the effects of parents' highest educational attainment regardless of whether it is mother's or father's education. The classification of educational attainment in the data follows the Finnish Standard Classification of Education 2007 (Statistics Finland 2007) which is based on the International Standard Classification of Education ISCED 1997. To increase statistical power and the readability of the results, we further classify parental education into four categories:

- Basic education or less
- Secondary education
- Lower or the lowest level tertiary education
- Higher level tertiary education or further

Annual taxable household income is measured as a continuous variable in the data (accuracy: 100 euros). In the analysis, household income will be used both as a continuous and categorical variable depending on the study question concerned. The procedure of dealing with the income measures went as follows: First, the income measures from different years were converted to 2013 euros with the help of the historical currency conversion table upheld by Statistics Finland (Statistics Finland 2014). Second, six-year average household income was counted from the years the children were 9–14 years old to control for potential annual variation in income. Third, the six-year mean income was divided in quintiles across all households for the purpose of studying the moderating effect of income. Finally, a natural logarithm was taken of the mean income to account for the skewness of the association between income and depressive symptoms when studying the confounding effects of income. Before taking the logarithm, one (1 euro) was added as a constant to all income measures because the logarithm of zero is undefined. Such procedure is recommended, for instance, by Osborne (2005).

5.2.3 Control variables

An indicator of family structure and biological relations of the family members will be included to control for the further effects of family type — potentially significant according to previous studies (Barrett & Turner 2005; Joutsenniemi et al. 2013). The variable includes the following classes:

- Two parents, both biological
- Two parents, biological mother
- Two parents, biological father
- Single parent, biological mother
- Single parent, biological father
- Other

In multivariate models, the status of parental depression is reported separately for those who were and who were not living with the biological parent concerned throughout the age range 9–14. Thus, to avoid collinearity, information on biological relations will be excluded when family type is used barely as a control variable. The truncated variable consists of the

classes two parents, single parent, and other. Moreover, the bias caused by child's year of birth will be taken into account with the help of a continuous variable, as mentioned above.

5.3 Statistical methods and the execution of the analysis

To answer the study questions set, the present study utilizes *Cox proportional hazards regression model,* which allows the efficient examination of the effects of several independent variables at the same time. Cox proportional hazards model is a method of *survival analysis* in which longitudinal survival or event history data are used to model event (such as death or disease) rates as a log-linear function of predictor variables, in other words covariates. (Tabachnick & Fidell 2014, 577.) A model with two time-constant variables may be written in the form

$$\log h(t) = a(t) + b_1 x_1 + b_2 x_2$$

where *a*(*t*) can be any function of time and thereby does not have to be specified. Because of this feature, Cox regression is considered a semi-parametric model. The possibility to estimate parameters without knowing *a(t)*, i.e. the underlying *hazard function*, rests on *the proportional hazards condition* which designates that covariates are multiplicatively associated with the hazard and that the ratio of hazards between different subjects is a constant at any point of time. If this assumption is heavily violated, the coefficients cannot be interpreted reliably in the most basic form of Cox regression, but the method may also be extended to permit non-proportional hazards. (Allison 2013, 33.) To test the proportional hazards assumption, Schoenfeld residuals method can be used. If the assumption holds, Schoenfeld residuals should not correlate with time or with any function of time (Allison 2013, 43).

In most data sets, survival times are unknown for a large group of persons included in the study because the outcome has not yet occurred before the end of the study or the persons were for some other reason lost to follow-up. Those cases, whose survival times are unknown, are called *censored*, and *censoring times* refer to those moments of time when the cases are censored. (Tabachnick & Fidell 2014, 578.) In the case of the present study, the follow-up of the person's own depressive symptoms starts from the first day of the year

he or she turned 15 and continues until the last day of the year the person turned 20 except for those born 1993-1996 whose follow-up ends at an earlier age than 20 because they had not yet turned 20 by the end of 2012. Censoring of observations occurs if no depressive symptoms were observed by the end of the follow-up period or if the person dies or emigrates during follow-up.

The estimation of coefficients is based on a method called partial likelihood, which is not affected by the time-scale used for the measures. Instead, it is based on the rank ordering of events that is the only thing that matters when the estimates are calculated. However, there are some days on which several individuals included in the data have received treatment for depressive symptoms. Of the different methods developed for handling tied times, Efron's method was chosen because it has been found to produce the best approximation of coefficients (Hertz-Piccioetto & Rockhill 1997). Moreover, since the data is a household sample and contains siblings living in the same household, the observations are not completely independent of each other. The Huber-White sandwich estimator of variance is chosen as the method of taking account of the family clustering of observations. The sandwich estimator yields unbiased variance estimates, confidence intervals, and p-values for cluster-correlated data (Williams 2000).

The questions about the clustering of parental depressive symptoms and the modifying role of socioeconomic circumstances involved hypotheses about statistical interactions. Under a multiplicative (instead of additive) model such as Cox regression, the statistical tests of interactions test the null hypothesis according to which risks for each exposure combine multiplicatively ($HR_{A\&B} = HR_{A\ only} \times HR_{B\ only}$). In the case of the current analysis, they test whether the association between parental and offspring depressive symptoms differs between groups of SES and whether the association is different if the other parent also had depressive symptoms. Both negative and positive departures from the null hypothesis are statistically significant. Since multiplicativity might be too strong an assumption what comes to parental clustering, we can also count whether the interactions depart from additivity ($RISK_{A\&B} = RISK_{A\ only} + RISK_{B\ only} - RISK_{neither\ A\ nor\ B}$). However, in a normal Cox regression model, a zero hypothesis about additivity cannot be statistically tested. (Zammit et al. 2010.)

Exposure to parental depression is measured when the child is 9–14 years old, i.e. before the beginning of follow-up. Since socioeconomic status and household characteristics are also measured before the start of the follow-up at age 14, all covariates are used as time-constant predictors of survival. The use of fixed covariates yields a clear interpretation for the coefficients and assumedly reduces the chance of reverse causality (e.g. that offspring depression, in fact, heightens the risk of parental depression).

Besides Cox proportional hazards regression, Kaplan-Meier curves will be utilized to illustrate the differences in the cumulative incidence of depressive symptoms according to gender and exposure to parental depressive symptoms. Drawing a plot of Kaplan-Meier estimates allows the visual comparison of estimated survival curves between several groups of interest. These can be interpreted as the cumulative incidence of depressive symptoms at any specific time. The downside of Kaplan-Meier method is that it does not allow controlling for the effects of other covariates as Cox regression does, which makes Cox regression also the best framework for statistically testing the differences in survival curves (Allison 2013, 51). Kaplan-Meier curves can also be used for checking the proportional hazards assumption visually.

The analysis divides into three sections of which the first is a descriptive one and the other two answer to specific study questions. Before conducting the survival analysis, contingency tables will be used to portray the differences in the incidence of antidepressant medication, and inpatient and outpatient care between ages 15 and 20 according to history of parental depression, family socioeconomic factors, and family structure. On the same occasion, single-predictor Cox proportional hazards models are reported according to the same explanatory variables before proceeding to the theme-specific analyses. Contingency tables as well as survival analyses will be presented separately for boys and girls to study the gender-specific effects called for in the previous literature. If a gender difference is observed, it will also be statistically tested. All analyses will be carried out using STATA, version 11.2 (StataCorp, Texas).

6 Results

6.1 Descriptive analysis

Characteristics of the study population are shown in Table 2. As may be expected, girls and boys distribute very similarly according to parental depression and household characteristics. Very few children were not living with their biological mother at age 9–14, and this was only slightly more common for boys (2.3%) than girls (1.5%). Inversely, not living with biological father was generally much more typical than not living with biological mother and slightly more common for girls (17.7%) than boys (16.6%). Overall, two thirds of children were living in households with two biological parents, the second most common form being a household of a single parent biological mother. Less than one tenth of children had parents who had only passed basic education or less, while the most common educational attainment was secondary education.

Instead, clear differences are seen when we look the proportions of girls and boys with depressive symptoms at age 15–20. Overall, during the six-year follow-up girls (11.6%) experienced depressive symptoms more than twice the rate of boys (5.2%), which is well in line with the medication purchase statistics as well as the other studies that were reviewed in the second chapter (e.g. Angold et al. 1998; Torikka et al. 2014). Interestingly, the difference between genders is equally pronounced in children exposed to maternal depressive symptoms, but not that pronounced in children exposed to paternal depressive symptoms: As much as 18.9% of girls exposed to maternal depressive symptoms experience depressive symptoms, whereas the same proportion is 16.4% among girls exposed to paternal depressive symptoms. For boys, maternal and paternal depressive symptoms seem to pose an equally large more than 2-fold risk. However, the largest risk of adolescent depressive symptoms appears to be faced by those who were not living with their depressed biological parents.

All types of family structure that differ from the most typical family of two biological parents seem to be associated with an increased risk of adolescent depression. This phenomenon pertains equally to girls and boys, although living with biological father and without biological mother might be a slightly more significant risk factor for girls than boys. We

may also notice from the table that there is a clear social gradient in adolescent depressive symptoms according to parental education and household income. For instance, if we compare the households of lowest and highest income quintile, the former had almost a 2-fold prevalence of depressive symptoms. Generally speaking, depressive symptoms in adolescence seem to be more common, the lower the parental socioeconomic status.

Table 2 Distribution of the study population and prevalence of depressive symptoms at age 15–20 years according to exposure to parental depression and household characteristics

		GIRLS			BOYS		
		N	%	% with depressive symptoms	N	%	% with depressive symptoms
Depressive symptoms and co-residence of biological mother when child was 9-14	Absent, co-resident	54 971	81.9	9.9	56 922	81.5	4.3
	Absent, non-coresident	683	1.0	16.1	1 018	1.5	5.3
	Present, co-resident	11 086	16.5	18.9	11 424	16.4	9.3
	Present, non-coresident	364	0.5	20.6	523	0.8	10.3
Depressive symptoms and co-residence of biological father when child was 9-14	Absent, co-resident	47 778	74.1	9.5	50 576	75.1	4.0
	Absent, non-coresident	9 378	14.5	15.9	9 240	13.7	7.2
	Present, co-resident	5 317	8.2	16.4	5 615	8.3	9.2
	Present, non-coresident	2 051	3.2	20.0	1 931	2.9	10.3
Family structure and biological relations	Two parents, both biol.	45 373	66.9	9.2	47 674	67.4	4.0
	Two parents, biol. mother	6 393	9.4	16.2	6 073	8.6	7.0
	Two parents, biol. father	911	1.3	17.6	1 271	1.8	6.5
	Single parent biol. mother	12 494	18.4	16.0	12 166	17.2	8.0
	Single parent biol. father	1 849	2.7	16.7	2 607	3.7	5.8
	Other	835	1.2	24.8	913	1.3	15.7
Parents' highest level of education	Higher tertiary	10 270	15.1	9.2	10 777	15.2	4.7
	Lower tertiary	24 421	36.0	10.2	25 088	35.5	4.5
	Secondary	27 279	40.2	12.6	28 598	40.5	5.5
	Basic or unknown	5 885	8.7	16.8	6 241	8.8	7.9
Household income quintile	Highest	13 181	19.4	8.7	13 790	19.5	3.8
	2	13 915	20.5	9.6	14 387	20.4	4.4
	3	14 218	21.0	11.0	14 566	20.6	4.8
	4	13 705	20.2	12.9	14 556	20.6	5.6
	Lowest	12 836	18.9	16.0	13 405	19.0	7.7
TOTAL		67 855	100.0	11.6	70 704	100.0	5.2

Table 3 presents separate Cox proportional hazards models for the same background variables while controlling for the potentially confounding effects of birth year. The basic findings are very similar, but controlling for the effects of birth year appears to be wise since

one-year increase in birth year equals to a 4%-6% increase in the hazard of depressive symptoms.

The effects of the principal explanatory factors, i.e. maternal and paternal depression, are at a level that could have been expected on the grounds of previous research. Girls, who were exposed to maternal depression at age 9–14, face a 2.12-fold hazard of depressive symptoms at age 15–20. For boys, the same hazard ratio is even larger (2.33), although the gender difference falls just behind the 0.05 significance level. As we already observed from the previous table, an even larger risk of depressive symptoms concerns children who do not live with their biological parents suffering from depressive symptoms.

More clear gender differences are seen when we look at the effects of paternal depression. At any point of time, boys who were living in the same household with their biological father and whose father had depressive symptoms experience a 2.47-fold hazard ratio of depressive symptoms between ages 15 and 20 compared to those whose father did not have depression. Girls, instead, face a seemingly smaller 1.88-fold risk, and this difference is also statistically significant at the 0.001 level. Thus, paternal depression seems to pose a larger risk for boys than girls, whereas the difference is less evident for maternal depression. It is also less clear whether paternal depression is an even greater risk factor for boys than maternal depression since the effect sizes are quite close to each other and confidence intervals overlap.

The effects of parental depression are, for the most part, more severe than the effects of household and socioeconomic characteristics. Hazard ratio between the ones living with two biological parents and those living in any other type of household where there is at least one biological parent present is slightly less than two. Living with a single parent biological mother pertains to a greater hazard of depressive symptoms per unit time in boys than in girls, whereas with single parent biological fathers the situation is just the opposite. Nevertheless, depressive symptoms are most common among adolescents who were living with neither of their biological parents at age 14.

Table 3 Non-adjusted single-predictor Cox models predicting depressive symptoms at age 15–20 years with hazard ratios and 95% confidence intervals by gender and p-values of gender differences

		Girls		Boys		P of sex
		HR	95% CI	HR	95% CI	difference
Birth year		1.04	1.03 – 1.05	1.06	1.04 – 1.07	0.637
Depressive symptoms and co-residence of biological mother when child was 9-14*	Absent, co-resident	1.00		1.00		
	Absent, non-coresident	1.68	1.39 – 2.04	1.22	0.93 – 1.61	0.057
	Present, co-resident	2.12	2.01 – 2.23	2.33	2.17 – 2.51	0.051
	Present, non-coresident	2.38	1.88 – 3.01	2.58	1.96 – 3.40	0.690
Depressive symptoms and co-residence of biological father when child was 9-14*	Absent, co-resident	1.00		1.00		
	Absent, non-coresident	1.78	1.67 – 1.89	1.88	1.72 – 2.05	0.350
	Present, co-resident	1.88	1.75 – 2.02	2.47	2.24 – 2.73	<0.001
	Present, non-coresident	2.40	2.17 – 2.67	2.81	2.42 – 3.25	0.110
Family structure and biological relations	Two parents, both biol.	1.00		1.00		
	Two parents, biol. mother	1.88	1.75 – 2.01	1.79	1.61 – 1.99	0.410
	Two parents, biol. father	2.09	1.78 – 2.46	1.64	1.31 – 2.06	0.076
	Single parent biol. mother	1.84	1.74 – 1.94	2.04	1.89 – 2.21	0.037
	Single parent biol. father	1.94	1.73 – 2.19	1.45	1.22 – 1.71	0.004
	Other	3.14	2.71 – 3.62	4.32	3.63 – 5.14	0.006
Parents' highest level of education	Higher tertiary	1.00		1.00		
	Lower tertiary	1.07	0.99 – 1.16	0.94	0.84 – 1.04	0.047
	Secondary	1.32	1.23 – 1.43	1.13	1.02 – 1.25	0.016
	Basic or unknown	1.77	1.62 – 1.94	1.60	1.41 – 1.82	0.234
Household income quintile	Highest	1.00		1.00		
	2	1.05	0.97 – 1.14	1.11	0.99 – 1.25	0.428
	3	1.18	1.09 – 1.28	1.17	1.04 – 1.31	0.971
	4	1.38	1.28 – 1.49	1.32	1.18 – 1.48	0.701
	Lowest	1.74	1.61 – 1.87	1.81	1.63 – 2.02	0.377
Log of household income		0.74	0.71 – 0.77	0.75	0.72 – 0.78	0.632

*If the biological mother/father was alive and living in Finland when the child was 9-14 years old

Parental education forms a clear social gradient when comparing tertiary, secondary, and basic education, but higher tertiary and lower tertiary degrees do not differ significantly from each other. The relation between household income and adolescent depressive symptoms is positively skewed in the way that the groups from middle to highest income quintile differ very little from each other and more distinct effects are seen among groups of lowest and second lowest income. Thus, there is clear rationale for using a logarithm of income for a better model fit when controlling for the confounding effects of

socioeconomic status in the next analysis. An increase of one unit in log income translates to a 36% lower risk of depressive symptoms.

6.2 The role of socioeconomic circumstances

In this chapter, we examine whether parental educational attainment and household income confound or moderate the association between parental depression and offspring depression that was perceived in the previous chapter. From Table 3, we saw that parental socioeconomic status is associated with adolescent depressive symptoms. Moreover, a separate analysis revealed that parental socioeconomic status is also inversely associated with the risk of exposure to parental depressive symptoms (see Appendix A: Table A-1). Table 4 presents a four-phase analysis where the socioeconomic factors and household characteristics are added to a Cox proportional hazards model one at a time while observing the change in the strength of the effect of maternal and paternal depression on offspring depression. The first model controls only for birth year, the second model introduces parental education, the third model log of household income and the fourth model family type. The potential confounders are added in this order because educational attainment is the most stable indicator of SES and may be thought to precede income temporally. Family type is added to the model last to examine what happens to the difference between coresident and non-coresident parents when controlling for socioeconomic factors as well as the residence of another parent (either biological or social). No later than at this point, it could be expected that depression of a coresident parent should have a stronger effect on a child than depression of a non-coresident parent.

Overall, very little change in the associations is seen among those living with their biological parents when the sociodemographic factors are controlled for. For example among girls, the effect of maternal depression when mother is co-resident decreases first from 2.09 to 2.06 when parental education is controlled for and then to 2.02 when controlling for household income. A slightly larger decrease to a hazard ratio of 1.94 occurs when information on family type is added to the model. The situation is pretty much the same for boys, as well as with paternal depression: Controlling for parental education and household income decreases the strength of the association in all cases, but the size of decrease is next to none. Family type plays a slightly larger role, but the impact may still be

considered meager. Even the confidence intervals remain relatively narrow in the fourth model.

Table 4 also tells us that even though depressive symptoms of a non-coresident parent seem to have a stronger impact in the first place, the association diminishes substantially when socioeconomic traits and especially family structure are controlled for. In fact, the effects of depression of a coresident and non-coresident parent turn upside down in the last model, as was anticipated above. On the other hand, all effects of non-coresident parents remain statistically significant at the 5% level even in the fourth model, emphasizing the robustness of the relation between parental and offspring depressive symptoms. A sensitivity analysis was conducted using the decile of household income (divided by the number of consumption units) instead of logarithm, but the decreases in coefficients were only slightly (0.01–0.03) smaller than the ones seen in Table 4. Coefficients for the other covariates included in the fourth model are presented in Table A-2 and Table A-3 in Appendix A. Schoenfeld residuals showed no violation of the proportional hazards assumption for the variables indicating parental depressive symptoms in any of the four models.

Table 4 Change in the effect of maternal and paternal depressive symptoms on the hazard of offspring depressive symptoms at age 15–20 years when parental education, household income, and family type are controlled for

			Model I		Model II		Model III		Model IV	
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Biological mother had depressive symptoms when child was 9-14 (1)	Mother co-resident	Girls	**2.09**	1.99 – 2.20	**2.06**	1.95 – 2.16	**2.02**	1.92 – 2.13	**1.94**	1.84 – 2.04
		Boys	**2.30**	2.13 – 2.47	**2.25**	2.09 – 2.42	**2.21**	2.05 – 2.38	**2.08**	1.93 – 2.24
	Mother not co-resident	Girls	**2.33**	1.84 – 2.95	**2.07**	1.63 – 2.62	**2.07**	1.64 – 2.63	**1.73**	1.35 – 2.21
		Boys	**2.55**	1.93 – 3.36	**2.28**	1.73 – 3.01	**2.09**	1.56 – 2.80	**1.58**	1.17 – 2.11
Biological father had depressive symptoms when child was 9-14 (2)	Father co-resident	Girls	**1.86**	1.73 – 2.00	**1.84**	1.71 – 1.98	**1.81**	1.68 – 1.95	**1.76**	1.63 – 1.90
		Boys	**2.43**	2.20 – 2.68	**2.40**	2.17 – 2.65	**2.36**	2.14 – 2.61	**2.27**	2.05 – 2.51
	Father not co-resident	Girls	**2.36**	2.12 – 2.62	**2.22**	2.00 – 2.47	**2.07**	1.86 – 2.31	**1.86**	1.66 – 2.08
		Boys	**2.75**	2.38 – 3.19	**2.61**	2.25 – 3.02	**2.43**	2.09 – 2.82	**2.10**	1.79 – 2.47

(1) Reference group: biological mother co-resident and did not have depressive symptoms

(2) Reference group: biological father co-resident and did not have depressive symptoms

Model I: Birth year

Model II: Model I + parents' highest level of education

Model III: Model II + logarithm of six year average household income

Model IV: Model III + family type (two parents / single parent / other)

After examining the confounding role of socioeconomic status, attention is turned to the modifying role of socioeconomic circumstances. Since there would not be enough cases nor clear interpretation for the moderating effect of SES among those who were not dwelling with their depressed parent, the analysis was only conducted for those who were living with the parent concerned at age 9–14 years. The results of interaction models are reported in Table 5 with higher tertiary education and highest income quintile as reference categories. Hazard ratios describe the effect of parental depression in different groups of SES, and p-values help to judge whether the differences observed between the reference category and the other categories are statistically significant. The results are reported both for the whole study group (adjusting for gender) and for girls and boys separately.

Table 5 Interactive effects of socioeconomic factors and parental depression on adolescent depressive symptoms at age 15–20 years (hazard ratios and p-values) adjusted for birth year

		Maternal depression						Paternal depression					
		Girls		Boys		Both**		Girls		Boys		Both**	
		HR	p	HR	p	HR	p	HR	p	HR	p	HR	p
Parents' highest level of education	Higher tertiary*	**1.99**		**2.11**		**2.02**		**1.93**		**2.12**		**1.98**	
	Lower tertiary	2.08	0.62	2.39	0.31	2.17	0.35	1.81	0.59	2.57	0.22	2.02	0.85
	Secondary	2.06	0.70	2.18	0.77	2.09	0.64	1.80	0.54	2.52	0.25	2.00	0.92
	Basic or unknown	2.03	0.86	2.29	0.57	2.10	0.65	2.02	0.75	1.96	0.71	1.99	0.98
Household income quintile	Highest*	**2.04**		**2.44**		**2.17**		**1.66**		**2.40**		**1.89**	
	2	2.06	0.94	2.17	0.39	2.10	0.69	1.79	0.58	1.91	0.20	1.83	0.78
	3	2.10	0.79	2.09	0.25	2.10	0.68	1.79	0.56	2.48	0.84	2.02	0.51
	4	1.91	0.44	2.22	0.47	2.01	0.31	1.82	0.48	2.27	0.74	1.96	0.72
	Lowest	2.03	0.95	2.21	0.42	2.10	0.63	1.94	0.22	2.69	0.48	2.19	0.14

*Reference category **Adjusting for gender

The table shows that no statistically significant multiplicative interactions were found. In effect, even without looking at statistical significance, it is difficult to spot any clear tendency or direction in the coefficients. For instance, if we look at education, the highest hazard ratios are among children whose parents have lower tertiary education, except for girls exposed to paternal depression. On the other hand, there is no strong evidence for an indirect relationship either. With income, the differences are equally arbitrary. For example, if we look at the coefficients of maternal depression when both boys and girls are included in the analysis (the situation when there is the largest number of cases at use), the

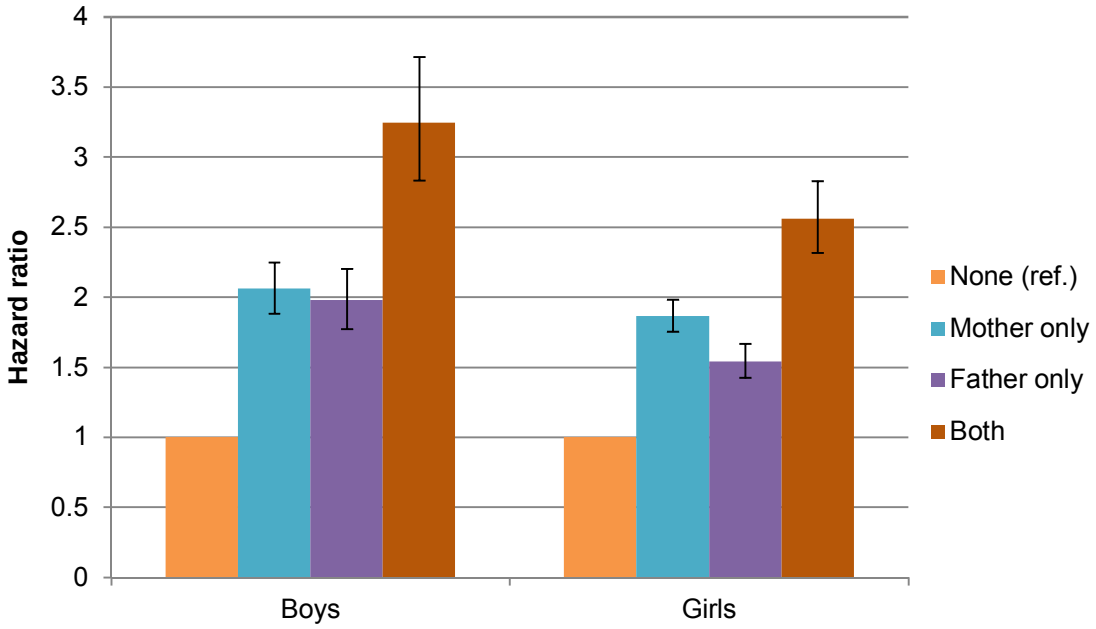
hazard ratio is the largest among those belonging to highest income quintile and the weakest among those who belong to the second lowest quintile. The income analysis was also conducted using the continuous logarithm of household income and an alternative categorized variable where the highest and lowest 10% constituted separate classes, but in both cases, the interactions remained small and non-significant. Overall, the analysis provides no support for the hypothesis that education and income moderate the effect of parental depression on offspring depression in the manner of an inverse social gradient.

6.3 Clustering, timing, and recurrence of parental depression

Finally, we look at the effects of timing and clustering of parental depression. Timing of parental depression refers to the stage of life in which a child was exposed to parental depression, while clustering refers to the situation in which a child becomes exposed to both maternal and paternal depression during the same stage of life. The latter may be partially caused by the fact that maternal depression and paternal depression are reciprocally associated with each other, forming a cumulative risk to the child. In the same vein, timing is linked to the recurrence of depression, which may cause a chain of risk to the child. Therefore, it is interesting to compare children with only one exposure to children with several exposures in both of these situations.

Figure 4 depicts the hazard ratios of those who were only exposed to either maternal or paternal depression and those who were exposed to both of them between ages 9 and 14. This analysis only includes children whose both biological parents were alive and living in Finland throughout the whole measurement period and controls for family structure and biological relations. The figure clearly demonstrates that exposure to both maternal and paternal depression puts the child at greatest risk. The other interesting observation that can be made is that the clustering of parental depression seems to be a more severe risk factor for boys than girls: The effect of a combined exposure is more than additive for both boys ($HR>3.1$) and girls ($HR>2.4$), but also less than multiplicative for both genders ($HR<4.1$ for boys and $HR<2.9$ for girls), though only for boys statistically significantly ($p=0.011$).

Figure 4 The effects of exposure to maternal depression, paternal depression and both of them at age 9–14 years on the hazard of depressive symptoms between ages 15 and 20, adjusting for birth year and family type



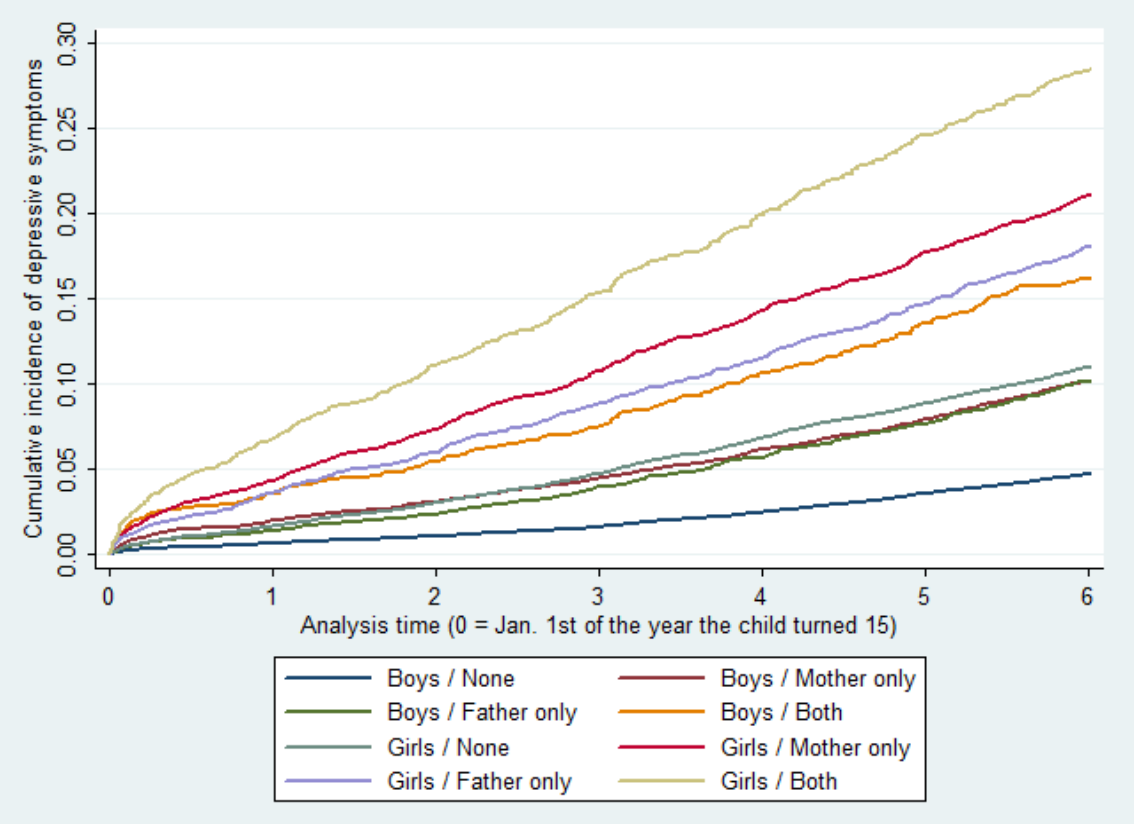
Significance of the interactions: boys (p=0.011), girls (p=0.081)
Significance of the gender interaction: mother only (p=0.099), father only (p<0.001), both (p=0.005)

Figure 4 is also the first one that separates the effects of maternal and paternal depression. In the former analyses presented, depressive symptoms of the other parent may have, for some part, confounded the association between parental and offspring depression so that, for example, some children who were exposed to paternal depression were, in fact, also exposed to maternal depression. Despite this, the earlier results hold: Maternal and paternal depression pose an equally large risk for boys, while paternal depression is a weaker risk factor for girls than boys. Maternal depression is a similarly large risk factor for boys and girls.

In Figure 5, the same results are illustrated with Kaplan-Meier failure curves that show the cumulative incidence of depressive symptoms between ages 15 and 20 by gender and exposure to parental depression. The one group that most seemingly separates from the others are girls who were exposed to both maternal and paternal depression between ages 9 and 14. On the other hand, as we saw from Figure 4, the clustering of parental depression poses a larger relative risk for boys than girls, which merely demonstrates the difference

between absolute and relative risks. Overall, almost 30% of girls who were exposed to both maternal and paternal depression exhibit depressive symptoms themselves, whereas approximately 15% of such boys develop depressive symptoms. What is more, the cumulative incidence of depressive symptoms is approximately similar among those girls who were not exposed to parental depression as among those boys who were exposed to either maternal or paternal depression.

Figure 5 Kaplan-Meier failure curves for the six-year follow-up of depressive symptoms between ages 15 and 20 years according to child's gender and exposure to parental depression



From Figure 5, we may also see that some of the curves cross, which might imply a violation of the proportional hazards assumption. We also tested the assumption using Schoenfeld residuals that showed a very small but statistically significant correlation (<0.03) with time for classes "mother only" and "both" among both boys and girls. We tried adding an interaction term of time and parental depressive symptoms to the model as recommended

by Allison (2013, 45), but this had very little impact to the coefficients probably because the correlations with time were this small.

The last analysis of the study is reported in Table 6. It explores the effects of timing and recurrence of parental depression in a smaller sub-sample consisting solely of children born in 1995 and 1996. The table also reports the numbers of cases of depressive symptoms according to history of parental depressive symptoms as such information was not provided in the descriptive section for this sub-group. Hazard ratios are compared between those who were exposed to maternal or paternal depression at age 0–5 and 9–14 as well as at both of these ages. This time, no violation of the proportional hazards assumption was observed.

Some apparent tendencies may be noticed in the associations. First of all, recurrent parental depression seems to be a more significant risk factor than an exposure at one of these stages. Second, the effect of an exposure at age 9–14 appears to be mainly stronger than the effect of an early-life exposure. Third, there is even some evidence that recurrent or long-term parental depression poses a larger risk for boys than girls.

Most of the differences, though fairly consistent, are not statistically significant because of the small sample size. The only clear statistically significant differences (at the 0.05 level) are seen in maternal depression where recurrent depression seems to pose a larger risk than an exposure to maternal depression solely during one of these stages of life. The same observation can also be made in the analysis where maternal depression and paternal depression are pooled together. Even though there is an apparent tendency that later exposures have stronger associations, none of these differs statistically significantly from the associations of early-life exposures. On the other hand, all situations where there has been any kind of exposure to parental depression (apart from girls exposed to only paternal depression at age 0–5) differ significantly from the situation where there has not been any exposure. Above all, it is possible to conclude that a more proximate exposure to parental depressive symptoms at age 9–14 years is at least as strong a predictor as an exposure at age 0–5 — and probably even stronger.

Table 6 The effects of different timing and recurrence of paternal depression on offspring depressive symptoms at age 15–17 years in a sub-sample consisting of children born in 1995–1996*

	Child's age**		GIRLS			BOYS			BOTH***		
	0-5	9-14	n of cases	HR	95% CI	n of cases	HR	95% CI	n of cases	HR	95% CI
Biological mother had depressive symptoms	-	-	425	1.00		146	1.00		571	1.00	
	x	-	35	2.04	1.44 – 2.87	12	1.97	1.09 – 3.55	47	2.02	1.50 – 2.71
	-	x	163	2.12	1.77 – 2.55	75	2.64	2.00 – 3.49	238	2.26	1.94 – 2.63
	x	x	98	3.01	2.41 – 3.76	58	5.14	3.79 – 6.98	156	3.56	2.97 – 4.26
Biological father had depressive symptoms	-	-	501	1.00		184	1.00		685	1.00	
	x	-	23	1.40	0.91 – 2.16	16	2.55	1.53 – 4.24	39	1.72	1.24 – 2.39
	-	x	120	2.13	1.74 – 2.61	51	2.47	1.81 – 3.36	171	2.22	1.88 – 2.63
	x	x	48	2.10	1.57 – 2.82	25	3.22	2.12 – 4.89	73	2.39	1.87 – 3.05
One of the biological parents had depressive symptoms	-	-	324	1.00		132	1.00		431	1.00	
	x	-	51	2.10	1.56 – 2.83	20	2.41	1.50 – 3.88	71	2.18	1.69 – 2.81
	-	x	230	2.37	2.00 – 2.81	95	2.79	2.12 – 3.67	325	2.48	2.14 – 2.86
	x	x	131	2.98	2.43 – 3.66	72	4.95	3.68 – 6.67	203	3.47	2.93 – 4.11

* Includes only those whose biological parent(s) was/were alive and lived in Finland when child was 0-5 and 9-14

** x = exposure, - = no exposure

*** Adjusting for gender

7 Discussion

7.1 Evaluation of the results on the basis of earlier empirical evidence

Although being one of the first to examine the intergenerational transmission of depressive symptoms with a large register-based data set, the current study found fairly similar associations between parental depressive symptoms and offspring depressive symptoms as the great pile of earlier research on the subject. Thanks to the exceptionally large sample size, the study was able to assess the effects of both maternal and paternal depressive separately for both boys and girls as parts of the same analysis, which has not been that common a practice in the research field that has traditionally been characterized by small clinical samples focusing mainly on mothers. The present study also offered novel insight by studying depressive symptoms in adolescents aged 15–20 years instead of in children and by measuring maternal and paternal depressive symptoms when the person was 9–14 years old instead of during early childhood.

For boys, maternal and paternal depressive symptoms posed a uniform 2-fold risk when the other biological parent did not suffer from depressive symptoms. For girls, maternal depressive symptoms posed a similar 2-fold risk, while paternal depressive symptoms posed a 1.5-fold risk that differed statistically significantly from the one of boys. Overall, these effect sizes are at an expected level based on the previous studies: As was hypothesized, they neither belong to the strongest (more than 3-fold) nor the weakest (less than 1.5-fold) that have been observed. Generally speaking, studies that have found effects markedly larger than 2-fold have typically sampled younger children and used clinical high-risk samples; studies that have spotted weaker effects were mostly based on retrospective self-reports of parental and offspring symptoms (see Goodman et. al 2011; Mendes et al. 2012).

We hypothesized that maternal depressive symptoms would pose an equally large risk for boys and girls and paternal depressive symptoms a larger risk for boys. Our hypothesis was fully realized in the analysis with precise and robust parameter estimates. The finding that an exposure to maternal depression puts boys and girls at a similar risk is also in line with the study of Bureau et al. (2009) that measured maternal depressive symptoms in infancy,

at age 8 and at age 19, and child depressive symptoms at ages 8 and 19 using an extensive self-report scale but a relatively small sample size. The study did not find support for the moderating effect of gender at any of these ages. On the other hand, a study by Burt et al. (2005) found girls to be at greater risk when exposed to maternal depressive symptoms, while Essex (2003) and Carter et al. (2001) argued just the other way around. What comes to the studies by Essex et al. (2003) and Carter et al. (2001), they both measured child depressive symptoms already before the age of five, which makes them difficult to compare with the present study. Specifically, Burt et al. (2005) clarified that mother's depressive symptoms at ages 4 and 16 might be more directly correlated with psychopathology in girls than boys at age 17.5, whereas among boys, the effect was largely mediated by parenting and family environmental factors. The present study was not able to measure the quality of child-parent relationship, but it supports the notion that maternal depressive symptoms are a similarly important risk factor for boys and girls when depressive symptoms are measured during adolescence. Based on these as well as previous results, maternal depression may be a more severe risk factor for boys than girls only at a very young age.

One of the robust results of the study is that paternal depression poses a larger risk for boys than girls in adolescence. This observation is also supported by earlier evidence, although it has focused more on the early developmental effects of paternal depressive symptoms (Ramchandani et al. 2005, Ramchandani & Psychogiou 2009). Ramchandani et al. (2005) observed that paternal depressive symptoms during postnatal period were associated with an increased risk of emotional and behavioral problems between ages 3 and 5 years in boys but not in girls, albeit this tendency was more pronounced for conduct and hyperactivity problems than for emotional symptoms. Scientific literature has speculated on the possibility that the moderating effect of gender might differ according to the developmental phase of the child, as it has not been clear whether the gender differences persist during adolescence (Bureau et al. 2009; Ramchandani & Psychogiou 2009). The results of the current study gave support to the idea that, in adolescence, gender still modifies the effect of paternal depressive symptoms but not the effect of maternal depressive symptoms. One potential explanation for the gender difference in the effects of paternal depression is that fathers may spend less time with their daughters than their sons (Ramchandani & Psychogiuo 2009). At least in the United States, the ratio of maternal and paternal

involvement with their children tends to become more even as children become older (Yeung et al. 2001). These reasons together could in part explain why paternal depressive symptoms pose a larger risk for boys than girls even during adolescence.

As an interesting fact, the adoption study of Tully et al. (2008) did not find any association between depressive symptoms in fathers and psychopathology in their non-biological children. For biological children, they found an association but it was not statistically significant because of the small sample size. Unfortunately, the study did not assess psychopathology in adolescents separately for boys and girls, which makes comparison with the present study difficult. As a reason for why the adoption study found no effects for paternal depression, the authors speculated with the possibility that the transmission of risk from depressed fathers might involve a stronger genetic component (Tully et al. 2008). This assumption is supported by the findings of Klein and colleagues (2005), suggesting that paternal depression is only associated with adolescent and young adult depression that is at least moderate in severity. Also the present study was only able to observe clinical depressive symptoms, i.e. fairly severe, which might explain why the observed associations between paternal and adolescent depressive symptoms were strong as this.

The confounding role of socioeconomic status was explored by controlling for the effects of parents' highest educational attainment and household income. Adding these indicators of socioeconomic circumstances to the model attenuated the associations between parental and offspring depressive symptoms very little among those individuals who were living in the same household with the depressed parent at age 9–14, and we expected to encounter somewhat larger reductions than these. The final model also included family type (two parents / single parent / other), but the association was reduced only slightly more than with socioeconomic factors. The theoretical interpretation of this result is that even though parental education and household income are both distinctly associated with both parental and offspring depressive symptoms, the relation between parental and offspring depressive symptoms itself is largely independent of these factors. As exposure to parental depressive symptoms and family socioeconomic factors were both measured during the same stage of life, we cannot judge anything about the direction of the association between socioeconomic factors and parental depressive symptoms (see Appendix A: Table A-1). For instance,

parental depressive symptoms might as well lead to lower household income, but this would not affect our answer to the study question.

This finding carries much weight since the potential confounding role of socioeconomic status in intergenerational transmission of depressive symptoms has been speculated in scientific literature (Barker et al. 2012; Ramchandani & Psychogiuo 2009), but few studies have actually put the hypothesis to the test. Moreover, the assumption makes sense since socioeconomic circumstances have been indicated to be associated with both parental (Sperlich et al. 2011; Graham & Easterbrooks 2000; Huston et al. 1994) and offspring (Gilman et al. 2003; Meltzer et al. 2003; Feder et al. 2009) depressive symptoms in the way that the lower the socioeconomic status, the higher the risk of depressive symptoms. Similar social gradients were also observed in the present study. Of the studies reviewed, only Barker et al. (2012) had directly approached the hypothesis and approximated that at least 37% of the association between maternal depression and child internalizing disorders is explained by exposure to similar environmental, familial and lifestyle-related risk factors of which one was low socioeconomic status. The problem with this study as a reference point is that it uses an index score that includes also several other environmental exposures than income and education and does not give a separate estimate for the effect of socioeconomic status. In addition, the internalizing symptoms were already measured at age 7.5 years. On the other hand, the same tendency that controlling for more environmental risks attenuates the effect of parental depression gradually was also observed in the present research, albeit the decreases were very small.

When studying the effects of parental depressive symptoms among those who did not live in the same household as their depressed parents at age 9–14, controlling for socioeconomic characteristics had a much stronger impact. In unadjusted models, depression of a non-coresident biological parent seemed to be an even more severe risk factor than depression of a coresident parent. However, the difference narrowed immediately when socioeconomic factors were brought into the model and turned upside down when family type was also controlled for. Based on this tendency, non-coresident parents are likely to suffer from a broader range of problems that also affect the child. A vast scientific literature has also documented the negative effects of parental divorce on child and adolescent well-being and mental health mediated by economic hardship,

parental conflict, and family disorganization (Aseltine 1996; Cherlin et al. 1998). Overall, the effect of depression of a non-coresident parent appears to be much more pervasively explained by external confounders than is the case with coresident biological parents, although the unadjusted models might also partially reflect differences in the severity of depressive symptoms between those parents who did and who did not live in the same household with their children. Further analysis could scrutinize this question in more detail. In any event, there is a good reason to assume that direct causal effects of parental depressive symptoms are stronger in those individuals who reside with their parents and thereby have more contact with them. Such notion is also supported by the adoption study of Tully and colleagues (2008), indicating that the association between maternal and offspring psychopathology in adolescence also applies to those families in which mother and child are not biologically related to each other.

The other analysis concerning socioeconomic circumstances examined the moderating role of parental education and household income. This question was also raised by the previous literature, which deemed it an understudied issue (Feder et al. 2009; Goodman et al. 2011). The postulated hypothesis was that the risk of intergenerational transmission becomes gradually higher when moving downwards the social hierarchy because exposure to multiple adversities might weaken resilience in the face of stress (Rutter 2005). However, this assumption was neither supported by the study. On the contrary, the slight differences that were observed between the educational groups and income quintiles were arbitrary and did not have any clear tendency or direction. Some studies of maternal depression have found that children of depressed mothers are at increased risk for cognitive and intellectual problems only if they live in disadvantaged socioeconomic conditions (Hay et al. 2001; Sohr-Preston et al. 2006). Moreover, the effects of parental depression on the risk of offspring internalizing seem to be on average stronger in those studies sampling low-income families compared with those studies sampling middle- and high-income families (Goodman et al. 2011). On the other hand, Gutierrez-Galve et al. (2015) found no moderating effects of paternal education when investigating the association between postnatal paternal depression and offspring behavioral problems at age 7 years.

There are several possible reasons for why no moderating effect was either found in the present study. First, depression was measured using treatment data, and differences in

liability to seek treatment between socioeconomic groups could hamper the inference by leveling the effects. Second, the studies included in the meta-analysis by Goodman et al. (2011) were mostly conducted in the United States and their results might not be applicable to a "universalist" Nordic welfare state like Finland where poverty rates and income differences are smaller than in the United States (see OECD 2015). Third, most previous studies have measured offspring depressive symptoms at a younger age than the current study. Fourth, none of the previous studies that were found have directly compared the relation between parental and offspring depressive symptoms across socioeconomic groups; thus, the results of the present study lack an appropriate reference point and might as well reflect a real non-existence of such interaction. To say the least, this study provides hard evidence that the risk of the intergenerational transmission of depressive symptoms, when measured using treatment data, does not differ across different groups of parental education or income in Finland.

The analysis concerning the clustering of parental depression clearly demonstrated that exposure to both maternal and paternal depression at age 9–14 years puts the child at the highest risk, although the difference between this group and those who were only exposed to either maternal or paternal depression was both for boys and girls only barely as large as was hypothesized, i.e. more than additive. For girls, the hazard ratio of a clustered exposure (compared to no exposure at all) is barely over fifty percentage points higher than the hazard ratio of an exposure to maternal depression only. For boys, the same hazard ratio was more than one hundred percentage points higher than the one of a single exposure. This gender difference is presumably caused by the fact that maternal and paternal depressive symptoms are an equally large risk factor for boys, but for girls, maternal depressive symptoms play a more significant role than paternal depressive symptoms. Therefore, also the sum of parental depressive symptoms is different for boys and girls so that boys are at greater risk than girls when their effects are combined.

Some previous studies scrutinizing the subject used a different definition of an "additive effect" than the statistical term used earlier in this report: The effect is "additive" if, for instance, paternal depression heightens the risk of offspring depressive symptoms even in the presence of maternal depressive symptoms (e.g. Brennan et al. 2002). The effects of concordant parental depression observed in the present study would also be additive in

this, less strict, sense. In this respect, Brennan et al. (2002) made an interesting remark that an independent exposure to either maternal depression or paternal depression increased the risk for youth depressive symptoms as much as an exposure to both of them. A substantial problem with the study is that it used lifetime measures of parental and youth depressive symptoms at age 15; thus, not much can be said about the direction of the effects nor the timing of exposure. Instead, Merikangas et al. (1998) found that the risk of major depression in children and adolescents aged approximately 10–18 years increased by the number of parents with any psychiatric diagnosis. Results of the study of Foley et al. (2001) also revealed such an association among juvenile twins aged 8–17 years; however, the association was stronger for girls than boys, which is in disconcordance with the results of the present study. This could be caused by the fact that the study did not find differences in the effects of a single exposure to maternal or paternal depressive symptoms. The study also used lifetime estimates of parental depressive symptoms, making the comparison complicated.

The final analysis handling the role of timing of exposure should be considered tentative, but it still managed to unveil some notable leanings that were consistent across different groups. Whether we look at maternal or paternal depression, it seems that a single exposure at age 9–14 years poses a larger risk for both boys and girls at age 15–17 years than a single exposure at age 0–5 years (i.e. without an exposure at age 9–14). There was not enough statistical power in the data for significance, but the tendency could clearly be seen in all of the groups. What is more, at greatest risk are offspring exposed to maternal or paternal depressive symptoms at both of these stages of life. For maternal depressive symptoms, the difference was also statistically significant.

The finding that an early-life exposure has a smaller effect than a later exposure does not comport with the hypothesis of the study. The hypothesis was based on some previous studies emphasizing the importance of the first years of life in the later risk of developing depressive symptoms (Hay et al. 2010; Essex et al. 2001; Korhonen et al. 2014). Research has most commonly focused on prenatal and postnatal parental depression (i.e. the first weeks of life), whereas the present study measured early-life parental depressive symptoms during a longer period of time at age 0–5 years. If the sensitive period covers only, for example, the first months of life, this could result in a dilution of the effects. A study by

Essex et al. (2001) implied that exposures at kindergarten and school age were more clearly associated with offspring externalizing than internalizing problems. In addition, a Finnish study by Korhonen et al. (2014) found a statistically significant relation between maternal depressive symptoms and adolescent internalizing when the initial exposure occurred two months postnatally, but no effects were found for initial exposures that occurred later than this. These two observations could explain why the current study was able to perceive signs of an independent association between parental depressive symptoms at age 0–5 and offspring depressive symptoms at age 15–17 as well as why the effect was weaker than the one of a later exposure.

The observation about the particularly strong impact of recurrent maternal depressive symptoms, instead, fits perfectly well into the picture and suits to the hypothesis of the study as well. Korhonen et al. (2014) found recurrent maternal depressive symptoms to be the best predictor of internalizing problems in adolescence, and also several other studies have ended up to the same conclusion (Halligan et al. 2007; Hay et al. 2008; Pawlby et al. 2009). What comes to recurrent paternal depression, the present study hinted that it might only put boys at an even heightened risk, but a larger sample would be needed to consolidate this impression. At the same time, we cannot completely rule out the possibility that the recurrent exposures also reflect the effects of a more severe and more heritable depression.

7.2 Evaluation of the results on the basis of the life course framework

One social epidemiological insight of the study was to associate the research tradition of intergenerational transmission with the life course epidemiological framework. This idea was inherited from Warner & Weissman (2014) as well as Rudenstine (2014). When addressing the aims of the study, we also asked whether the intergenerational transmission of depressive symptoms partially contributes to the gender difference in the life course risk of depressive symptoms. Previous studies have demonstrated that after puberty, girls face an approximately 2-fold risk of depressive symptoms throughout the whole life course (e.g. Angold et al. 1998; Torikka et al. 2014). The same 2:1 ratio was also observed in the six-year follow-up of the present study. However, the analysis did not support the assumption about intergenerational transmission as an explanatory factor for the gender difference

because maternal depressive symptoms were an equally significant risk factor for boys and girls, whereas paternal depressive symptoms were a more significant risk factor for boys.

In the second chapter of the report, we discussed that life course epidemiology separates three different life course processes that are, above all, theoretical and conceptual by nature. These processes included critical and sensitive periods, accumulative influences, and pathway influences, i.e. chains of risk. All of them were attached to at least one of the research questions.

Because of huge data requirements and specific biological hypotheses involved, this study was not able to investigate critical periods, which refer to such stages of early-life when some developmental achievements are vital and the disruption of them, accordingly, irreversible later in life (Pillas et. al. 2014, 305). By contrast, the study did include one hypothesis pertaining to a possible sensitive period during the first years of life. It was hypothesized that an exposure to parental depressive symptoms between ages 0 and 5 would have an even stronger impact than an exposure at age 9–14 because some earlier studies have speculated about the possibility of a sensitive period during infancy (Hay et al. 2010; Essex et al. 2001; Korhonen et al. 2014). Contrary to the assumption, the analysis produced more evidence for the stronger effect of a later exposure. As was already mentioned above, this does still not disprove the existence of a sensitive period because some previous studies have implied that, especially with the risk of offspring depressive symptoms, the sensitive period might only pertain to the first weeks or first months of life (Korhonen et al. 2014). Unfortunately, we were not able to investigate the question further because there would not have been enough statistical power if we had measured parental depressive symptoms, for instance, only in the first year of child's life. However, the fact that an exposure to parental depressive symptoms at age 0–5 years was, after all, clearly associated with an increased risk of offspring depressive symptoms at age 15–17 might also reflect an underlying sensitive period besides genetic predisposition. Moreover, the stronger effect of a later exposure could also be caused by the fact that we observed depressive symptoms more comprehensively for later years because of the increase in the use of antidepressants, discussed in the second chapter.

More than one of the research questions touched the accumulation of risk model, which emphasizes the harmful effects of exposure to several risk factors and adversities. Accumulation of risk may occur if there have been either several exposures to the same risk factor or multiple exposures to different risk factors. (Pillas et al. 2014, 306–308.) An idea about the latter type of accumulation was included in the research question concerning the role of parental socioeconomic status. Precisely, the hypothesis about SES being a confounder of the intergenerational transmission implied that maybe the cumulative harmful effect of SES and parental depressive symptoms is not as large as one could think based on unadjusted models; in other words, the association between parental and offspring depressive symptoms was surmised to be partially caused by exposure to similar socioeconomic circumstances. The second hypothesis concerning the modifying effect of SES predicted that the risk of intergenerational transmission could be higher in families of lower education and income. However, in favor of the confounder hypothesis, there was little evidence in the analysis, whereas in favor of the modifier hypothesis, there was no evidence at all. From the perspective of the accumulation of risks model, these results lead us to the following conclusion: Low socioeconomic status and parental depressive symptoms are for the most part independent risk factors of adolescent depressive symptoms; thus, if an adolescent is exposed to both of them, their negative effects sum up in an additive way. However, the association between parental depressive symptoms and offspring depressive symptoms does not differ across different groups of parental education and income; therefore, no more than multiplicative accumulation of risk occurs.

Finally, recurrent exposure to parental depressive symptoms was attached to the model of pathway influences, which refers to a process where an exposure at one stage of life heightens the risk of an exposure at a later stage, eventually forming a chain of risk that raises the probability of a mental disorder throughout the life course (Pillas et al. 2014, 309-310). Previous studies have indicated that the likelihood of a depressive episode increases by the number of former episodes (Monroe & Harkness 2005); thus, also children whose parents have suffered from depression are at an increased risk of a new exposure. As for maternal depressive symptoms, the study produced clear evidence that such a chain of risk exists: Children exposed to maternal depressive symptoms both at ages 0-5 and 9-14 had the largest risk of exhibiting depressive symptoms at age 15–17 years. As our analysis also

gave support to the independent effects of separate exposures, this chain of risk could be categorized as one where all links of the chain have their own direct influence alongside the fact that they temporally increase the probability of one another. Among boys, such a tendency was also observed in paternal depressive symptoms, even though the effect did not differ statistically significantly from the one of a single exposure at one of these stages of life. Although the chains of risk model was chosen as a theoretical framework to analyze relapsing parental depression, the process might as well be understood as an accumulation of risk, which merely demonstrates the blurriness of the lines between different life course models.

7.3 Methodological considerations

In the present study, treatment data were used as a proxy for the incidence of depressive symptoms, which introduces several uncertainties in the analysis. In the case of intergenerational transmission, it may be asked how large a part of the association between parental and offspring depressive symptoms (measured this way) is caused by the fact that parents having a history of depression treatment might also be more liable and prepared to seek treatment for their children if they begin to show symptoms. What is more, there is always the possibility that the severity of symptoms predicts the clinical detection in both parents and their offspring, which could strengthen the association because severe depression is also more heritable (Sullivan et al. 2000). On the other hand, as was discussed earlier, it seems equally possible that the non-detection of sub-clinical depressive symptoms also slightly weakens the associations observed. To say the least, this study was only able to observe cases who had received treatment, which limits the generalization of the results to such cases of depressive symptoms that were severe enough to have received treatment.

What is known better is that the administrative registration of treatment events is inevitably affected by the policies that are effective at the time. The only major reform introduced during the follow-up period of the study was the removal of excess share in the reimbursement of medicines belonging to the basic reimbursement class in 2006 after which inexpensive medicines have been more comprehensively registered in the data file. This may have had a small effect on the registration of more expensive antidepressants, but the change was more significant in sedatives and sleeping pills (Autti-Rämö et al. 2009).

The use of administrative data also arouses suspicion of the validity of the measurements. The validity of measurements may be evaluated in terms of both diagnostic validity (i.e. whether the diagnostic criteria are accurate) and comprehensiveness (i.e. whether we observe the incidence of depressive symptoms extensively) (Byrne et al. 2005). Bock et al. (2009) explored the validity of the diagnosis of a single depressive episode (ICD10: F32–32.9) in Danish registers by conducting a SCAN (Schedules for Clinical Assessment in Neuropsychiatry) interview for a sample of patients with a registered diagnosis. The diagnosis was confirmed in 75.4% of the cases, which the authors interpreted to reflect a rather high validity, albeit the accuracy varied according to the severity of depression: 82.8% of patients with a severe single depressive episode obtained a SCAN diagnosis, while only 65.2% of patients with a mild single depression were diagnosed in the interview. (Bock et al. 2009.) An older study conducted by Sorvaniemi et al. (2001) observed that Finnish clinicians had difficulties in recognizing the recurrence of depression and depressive symptoms of psychotic patients. Since no studies that we are aware of have examined the validity of depression diagnostics among young people in Finland, it can only be presumed that they are approximately as accurate as diagnoses given to adults.

Another concern about validity is raised by the fact that antidepressants are generally used to treat other conditions than solely depression. These include, for instance, sleeping problems, severe headache or pain, panic disorder, social phobia, and post-traumatic stress disorder (Sihvo et al. 2008). Among Finnish adult population, only 59% of antidepressant users had some history of depression (Sihvo et al. 2008), and similar figures were obtained in the Netherlands (Gardarsdottir et al. 2007) and Southern Italy (Trifirò et al. 2007). Thus, Gardarsdottir et al. (2007) emphasize that researchers using antidepressants as a proxy for depressive symptoms always need to be prepared to handle a bias of some extent. Fortunately, the data used in the study made it possible to identify the accurate ATC code of the medicines and thereby exclude older tricyclic medications which are more commonly used to treat other than psychiatric conditions (Gardarsdottir et al. 2007; Sihvo et al. 2008). Moreover, non-psychiatric use of antidepressants is generally known to be less common among younger population (Sihvo et al. 2008), although none of the above mentioned studies sampled adolescents.

Neither do we know much about how generally children and adolescents with depressive symptoms are prescribed antidepressant medication or sent to outpatient or inpatient treatment in Finland. In the United States, adolescent depression has been observed to stay more often unrecognized than depression in adults (Leaf et al 1996). Unfortunately, information on the use of primary care was only available for years 2011 and 2012, and there was a lot of missing information concerning diagnostic criteria — the mere available information probably being regionally biased. Therefore, we were unable observe children and adolescents with depressive symptoms who were not recognized by primary care, and hence not referred to, for instance, specialized outpatient services. Meanwhile, all Finnish school-aged children attend several compulsory health check-ups during the comprehensive school; therefore, the risk of child and early adolescent psychopathology being left completely unnoticed is rather small (Gyllenberg et al. 2014). What is more, when the detection of problems in children's psychosocial functioning is not merely up to parents, socioeconomic and regional differences of seeking treatment should also be diminished. On the other hand, the current study measured adolescent depressive symptoms between ages 15 and 20 when most people do not attend comprehensive school any longer, which might leave some groups of people marginalized from treatment.

Fortunately, there are also several strengths in assessing depressive symptoms via prescription medication and service use. First, we encounter, in principle, no loss of follow-up since all purchases of prescription medication and visits to inpatient and outpatient care are recorded to the respective nationwide administrative registers; thus, we also avoid problems caused by attrition, selective dropout, measurement errors, and small sample sizes, typical of longitudinal survey designs (Wolke et al. 2009; Gustavson 2012). Second, a great deal of previous studies approaching the subject were based on retrospective self-reports, which has been estimated to cause a significant recall bias in the evaluation of age-specific lifetime major depression prevalence (Andrews et al. 1999; Schraedley et al. 2002; Patten 2003). Despite the above-mentioned problems with the data, we have good reason to believe that it relatively accurately and comprehensively contains the treatments that the subjects have received during the follow-up period. Third, prospective studies utilizing surveys and clinical measurements are seldom able to collect data very frequently because of both financial requirements and the convenience of participants. Therefore, the present

study is quite unique in the research field of intergenerational transmission by being able observe treatment annually for an entire period of 18 years.

Most of the above-mentioned benefits also apply to the other variables used in the study. Measures of educational attainment, household income, and family structure contained practically no missing information, and although even registers are not fully free of mistakes, the information can be presumed very accurate. Some previous studies have underlined the importance and different role of subjective SES measures (Jeon et al. 2013; Piko & Fitzpatrick 2007), but the data used in this study was unfortunately restricted to administrative measures of parental education and household income only. Since the present research work was merely able to assess this kind of "objective" SES, the important take-home message here is that the aspects of the socioeconomic risk for adolescent psychopathology may have only been partially captured via the indicators used.

Some authors have called for genetically informed study designs (Goodman et al. 2011; Sellers 2012), and there is, in fact, strong evidence for the genetic heritability of clinical depression (Sullivan et al. 2000). Because of this, it is critical to emphasize that the study design used in this thesis was neither able to separate the genetic, environmental and social causes nor evaluate the amount to which the correlation between parental and offspring depressive symptoms may have been accounted for either "nature or nurture". What is more, despite using annual prospective data, the present study may still be considered a "correlational study", not providing evidence for causality: Even though we were able to clarify the temporal order of events, we still cannot be sure that we have controlled for all significant confounders (Buka & Lacy 2014, 14). On the other hand, the main goal of the study was to investigate the life course mechanisms that underlie the associations, identifying sub-groups who are at greatest risk of developing depressive symptoms and should thereby be the principal targets of preventive actions. Without other evidence, we can arguably assume that the genetic risk of inheriting depression is relatively similar across the groups compared. Even the findings that the heritability of clinical depression might be higher in women (42%) than in men (29%), (Kendler et al. 2006) and that the heritability of internalizing problems is higher in families with higher income (South & Krueger 2011) do not affect the interpretations made about the results of the present study. In addition, since the covariates of interest (parental depressive symptoms, child's gender, and parental

socioeconomic status) are mostly independent of the actions of the individuals belonging to the study population, we may presume selection bias — one of the greatest perils of observational studies (Buka & Lacy 2014, 14) — relatively meager.

7.4 Conclusion

The current study managed to shed light on some of the seldom-studied mechanisms of the intergenerational transmission of depressive symptoms. First, the results revealed that maternal depressive symptoms are an equally severe risk factor for adolescent girls and boys but paternal depressive symptoms, instead, pose a somewhat larger risk for boys. Second, the investigation implied that socioeconomic factors might not play such a significant role as has been hypothesized in scientific literature. Third, the study showed that a history of concurrent exposure to both maternal and paternal depressive symptoms puts adolescents at greatest risk. Finally, the analysis indicated that adolescents exposed to maternal depressive symptoms during both the early childhood (ages 0-5) and the late childhood (ages 9-14) form a particular risk group compared with adolescents who experienced maternal depressive symptoms during the late childhood only.

Besides these significant contributions, the study also raised some open questions that further research could approach in more detail. First, the study was only able to make benefit of the large sample size when analyzing the relation between parental depressive symptoms at age 9–14 years and offspring depressive symptoms at age 15–20 years. It would be interesting to explore whether the results concerning gender differences and socioeconomic factors would stay the same if parental depressive symptoms were measured at an earlier stage of life. Second, the preliminary results on early-life effects should be investigated further using a larger sample and measuring parental depressive symptoms separately for the first year of life. Third, the present study only examined the effects of depressive symptoms in biological parents. For a more elaborate understanding of the social and environmental mechanisms involved, it would be beneficial to see what would happen to the associations if they were studied using non-biological parents.

Alongside research, the study also left a few take-home messages for public health policy. The results clearly indicate that the accumulation and chaining of risk factors gradually increase the risk of adolescent depressive symptoms. Especially children exposed to both

maternal and paternal depressive symptoms could benefit from early preventive actions that seek to prevent depressive symptoms by considering the familial context. What is more, another source of severely increased risk is exposure to recurrent long-term parental depressive symptoms, putting children under a continuous stress that may finally lead them to develop depressive symptoms themselves. Fortunately, there are many possibilities to break this chain of risk by building up protective factors and resilience through therapy, education, and public campaigns, and providing financial and social support to high-risk families (Pillas et al. 313). Instead, the result implying an unexpectedly meager effect of socioeconomic circumstances should not be interpreted in the way that socioeconomic status is not important. On the contrary, the study revealed that the negative effects of low socioeconomic status and parental depressive symptoms are mostly independent of each other; thus, when combined together, their effects sum up and put children at an elevated risk. Overall, the results advocate a more holistic approach to the prevention of adolescent depressive symptoms, beginning from the identification of familial risk and leading to actions that target all members of the family. This is also the starting point of a life course approach to mental health policy (Pillas et al. 314).

8 Literature

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Appendix A. Supplementary tables

Table A-1 Prevalence of parental depressive symptoms when child was 9–14 years old according to parents' highest level of education and household income quintile

		Biological mother had depressive symptoms (%)*	Biological father had depressive symptoms (%)*
Parents' highest level of education	Higher tertiary	16.0	10.8
	Lower tertiary	15.8	10.2
	Secondary	17.3	11.6
	Basic or unknown	23.5	15.6
Household income quintile	Highest	15.5	9.4
	2	15.1	9.4
	3	16.0	10.7
	4	17.4	12.3
	Lowest	21.8	15.3

*If the biological mother/father was alive and living in Finland when the child was 9-14 years old

>> All tables statistically significant (p<0.001) according to chi-squared test

Table A-2 Cox regression model predicting the hazard of depressive symptoms at age 15–20 years with birth year, maternal depressive symptoms, socioeconomic factors, and family type as covariates (hazard ratios and 95% confidence intervals)

		Girls		Boys	
		HR	95% CI	HR	95% CI
Birth year		1.04	1.03 – 1.05	1.05	1.04 – 1.06
Depressive symptoms and co-residence of biological mother when child was 9-14*	Absent, co-resident	1.00		1.00	
	Absent, non-coresident	1.37	1.12 – 1.67	0.89	0.67 – 1.18
	Present, co-resident	1.94	1.84 – 2.04	2.08	1.93 – 2.24
	Present, non-coresident	1.73	1.35 – 2.21	1.58	1.17 – 2.11
Parents' highest level of education	Higher tertiary	1.00		1.00	
	Lower tertiary	1.02	0.94 – 1.10	0.88	0.79 – 0.98
	Secondary	1.15	1.06 – 1.24	0.97	0.87 – 1.08
	Basic or unknown	1.20	1.08 – 1.34	0.94	0.81 – 1.09
Log of household income		0.83	0.80 – 0.87	0.84	0.80 – 0.88
Family type	Two parents	1.00		1.00	
	Single parent	1.32	1.24 – 1.39	1.46	1.35 – 1.58
	Other	2.02	1.65 – 2.46	3.54	2.78 – 4.49

*If the biological mother was alive and living in Finland when the child was 9-14 years old

Table A-3 Cox regression model predicting the hazard of depressive symptoms at age 15–20 years with birth year, paternal depressive symptoms, socioeconomic factors, and family type as covariates (hazard ratios and 95% confidence intervals)

		Girls		Boys	
		HR	95% CI	HR	95% CI
Birth year		1.04	1.03 – 1.05	1.05	1.04 – 1.07
Depressive symptoms and co-residence of biological father when child was 9-14*	Absent, co-resident	1.00		1.00	
	Absent, non-coresident	1.41	1.31 – 1.51	1.45	1.30 – 1.61
	Present, co-resident	1.76	1.63 – 1.90	2.27	2.05 – 2.51
	Present, non-coresident	1.86	1.66 – 2.08	2.10	1.79 – 2.47
Parents' highest level of education	Higher tertiary	1.00		1.00	
	Lower tertiary	1.00	0.92 – 1.08	0.88	0.79 – 0.99
	Secondary	1.15	1.06 – 1.24	0.95	0.85 – 1.06
	Basic or unknown	1.17	1.05 – 1.31	0.94	0.81 – 1.10
Log of household income		0.86	0.82 – 0.90	0.85	0.81 – 0.90
Family type	Two parents	1.00		1.00	
	Single parent	1.25	1.17 – 1.33	1.31	1.19 – 1.44
	Other	2.19	1.78 – 2.69	3.13	2.44 – 4.01

*If the biological father was alive and living in Finland when the child was 9-14 years old