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A Biopsychosocial and Long Term Perspective on Child Behavioral Problems - Impact of Risk and Resilience

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ABSTRACT

Mental health has become a prominent issue in society. Yet, much remains unknown about the etiology of psychiatric disorders. The aim of the present thesis was to investigate the association between biological, psychological and social factors of risk and resilience and behavioral problems in a birth cohort of Swedish children. 1723 mothers and their children were followed from birth to the age of 12 as part of the South East Sweden Birth Cohort Study (the SESBiC study). Information was gathered through register data, standardized questionnaires and DNA samples.

In study I, stability of maternal symptoms of depression and the impact on child behavior at age 12 were investigated. The prevalence of depressive symptoms was found to be 12.0 % postpartum. Symptoms of postpartum depression significantly increased the risk for subsequent depressive symptoms 12 years later in women. Children whose mothers reported concurrent symptoms of depression and anxiety had an increased risk for both internalizing and externalizing problems at age 12, but no long term effect on child behavior was seen for postpartum depressive symptoms. The greatest risk was seen for children whose mothers reported symptoms of depression on both occasions. In study II, the impact of gene-environment interaction of *5*-HTTLPR and *BDNF* Val66Met and experience of life events together with symptoms of maternal depression and anxiety on child behavior at age 12 was studied. A main effect of *5*-HTTLPR was noticed, but no gene-environment effects were shown. Similarly to study I, concurrent symptoms of maternal depression and anxiety were an important predictor of child behavioral problems. A high degree of psychosocial stress around childbirth was found to have long lasting detrimental effects on child behavior, increasing the risk for internalizing problems at age 12. Study III investigated the impact of gene-environment interactions of *5*-HTTLPR and *BDNF* Val66Met and life events together with symptoms of maternal depression and birth characteristics on behavioral problems at age 3. Symptoms of postpartum depression were found to predict internalizing as well as externalizing problems in children three years later. Child experience of life events was a stable predictor of behavioral problems across the scales similar to sociodemographic factors such as parental immigration status and unemployment. No gene-environment interaction effects of *5*-HTTLPR or *BDNF* Val66Met were shown. Study IV used the risk factors identified in studies I-III to investigate factors of resilience to behavioral problems at age 12. The l/l genotype of *5*-HTTLPR was associated with a lower risk for behavioral problems at age 12, especially for children facing low adversity. Good social functioning was found to be a general resource factor, independent of the level of risk, while an easy temperament

was associated with resilience for children with a high degree of adversity. However, effect sizes were small.

In summary, the results from the present thesis emphasize the importance of maternal mental health and sociodemographic factors for child mental health at ages 3 and 12, which must be taken into account in clinical settings. Moreover, it adds to the null-findings of the gene-environment effect of *5*-HTTLPR and *BDNF* Val66Met on behavioral problems in children, but indicates a main effect of *5*-HTTLPR on internalizing symptoms at age 12.

SVENSK SAMMANFATTNING

Psykisk ohälsa är ett betydande problem i samhället. Trots detta finns kunskapsluckor om hur biologiska och miljömässiga faktorer samspelar vid utvecklingen av psykiska sjukdomar. Syftet med den föreliggande avhandlingen var att undersöka sambandet mellan biologiska, psykologiska och sociala faktorer, samt beteendeproblem i en födelsekohort av svenska barn. Både riskfaktorer och salutogena faktorer har beaktats. 1723 mödrar och deras barn följdes från födseln till 12 års ålder, och den information som samlades in bestod av såväl registerdata som standardiserade frågeformulär och DNA prov.

I studie I undersöktes stabiliteten av depressiva symptom hos mödrar, och dess påverkan på barns beteende vid 12 års ålder. Prevalensen av depressiva symptom befanns vara 12.0 % postpartum. Förekomst av depressiva symptom postpartum ökade risken för symptom på depression och ångest hos mödrar 12 år senare. Barn till mödrar som rapporterade symptom vid 12-årsuppföljningen hade en ökad risk för både internaliserade (inåtvända) och externaliserade (utåtagerande) problem. Depressiva symptom postpartum hade däremot ingen långsiktig påverkan på beteendeproblem hos barn vid 12 års ålder. Den största riskökningen sågs hos barn vars mödrar rapporterade depressiva symptom både postpartum och vid 12-årsuppföljningen. Studie II genomfördes som en replikationsstudie av interaktionen mellan *5*-HTTLPR, *BDNF* Val66Met och traumatiska livshändelser samt effekten av depressiva symptom hos mödrar och dess påverkan på beteendeproblem vid 12 års ålder. *5*-HTTLPR visade sig öka risken för internaliserade symptom, men ingen interaktionseffekt kunde påvisas. I likhet med studie I var samtida symptom på depression och ångest hos mödrar en viktig prediktor av beteendeproblem hos barn. Psykosocial belastning vid födseln hade långvariga effekter på barns beteende, då det ökade risken för internaliserade problem vid 12 års ålder. I studie III undersöktes interaktionen mellan *5*-HTTLPR, *BDNF* Val66Met och livshändelser, samt effekten av depressiva symptom hos mödrar och graviditets- och födelserelaterade faktorer, med utfallet beteendeproblem vid 3 års ålder. Symptom på postpartumdepression ökade risken för både internaliserade och externaliserade problem hos barn vid 3 års ålder. Livshändelser var en stabil prediktor av beteendeproblem, liksom sociodemografiska faktorer som föräldrars invandrarstatus och arbetslöshet. Ingen interaktionseffekt mellan *5*-HTTLPR, *BDNF* Val66Met och livshändelser noterades. I studie IV användes de riskfaktorer som identifierats i studie I-III för att studera salutogena faktorer i förhållande till beteendeproblem hos barn vid 12 års ålder. Individer med två långa alleler av *5*-HTTLPR hade en minskad risk för beteendeproblem vid 12 års ålder, speciellt om de tillhörde gruppen med få

riskfaktorer. God social förmåga befanns vara en generell resurs som minskade risken för beteendeproblem hos alla barn, oavsett risknivå. Ett lätt temperament däremot, var en skyddsfaktor specifik för barn med många riskfaktorer.

Sammanfattningsvis understryker denna avhandling vikten av psykisk hälsa hos mödrar samt av sociodemografiska faktorer för psykisk hälsa hos barn - fynd som bör beaktas i kliniskt arbete. Vidare bidrar resultaten till kunskapsläget om interaktionseffekten mellan *5*-HTTLPR, *BDNF* Val66Met och traumatiska livshändelser på beteendeproblem hos barn. *5*-HTTLPR påverkade risken för internaliserade symptom vid 12 års ålder, men ingen interaktionseffekt påvisades.

LIST OF PAPERS

I. Agnafors S, Sydsjö G, deKeyser L, Svedin CG. (2013). Symptoms of depression postpartum and 12 years later - associations to child mental health at 12 years of age. *Matern Child Health J. Apr;17(3):*405-14

II. Agnafors S, Comasco E, Bladh M, Sydsjö G, deKeyser L, Oreland L, Svedin CG. (2013). Effect of gene, environment and maternal depressive symptoms on pre-adolescence behavior problems - a longitudinal study. *Child Adolesc Psychiatry Ment Health. Mar 22;7(1):*10.

III. Agnafors S, Sydsjö G, Comasco E, Bladh M, Oreland L, Svedin CG. Early predictors of behavioral problems in pre-schoolers – a longitudinal study of constitutional and environmental main and interaction effects. *Under review.*

IV. Agnafors S, Svedin CG, Oreland L, Bladh M, Comasco E, Sydsjö G. A bio-psycho-social approach to risk and resilience in children - a longitudinal study from birth to age 12.

ABBREVIATIONS

5-HTTLPR	Serotonin transporter gene-linked polymorphic region
ADHD	Attention Deficit Hyperactivity Disorder
BDNF	Brain Derived Neurotrophic Factor
CBCL	Child Behavior Checklist
CD	Conduct Disorder
CI	Confidence Interval
CLES-P	Coddington Life Event Scale for Preschoolers
CNS	Central Nervous System
COMT	Catechol-O-Methyl Transferase
CWC	Child Welfare Centers
DNA	Deoxyribonucleic Acid
EPDS	Edinburgh Postnatal Depression Scale
GWAS	Genome Wide Association Studies
LD	Learning Disability
LITE	Life Incidence of Traumatic Events
LSS	Life Stress Score
MAOA	Monoamine Oxidase A
MBR	Medical Birth Register
MDD	Major Depressive Disorder
ODD	Oppositional Defiant Disorder
OR	Odds Ratio
PPD	Postpartum Depression
RNA	Ribonucleic Acid
SCL-25	Symptom Checklist 25
SES	Socio Economic Status
SESBiC	South East Sweden Birth Cohort
SNP	Single Nucelotide Polymorphism
SOC	Sense of Coherence
SSRI	Selective Serotonin Reuptake Inhibitors
VNTR	Variable Number Tandem Repeats

INTRODUCTION

Background to the thesis

Our knowledge and views on mental health are subjects of current debate in both the scientific community and society in general. The since long polarized debate of nature versus nurture of psychiatric illness is facing new challenges as a growing body of gene-environment studies is emerging. Psychiatric categorization and diagnosis are based on symptoms, and thus there is a profound interest in new findings related to the etiology of psychiatric disorders. While gene-environment studies on mental health have come to disparate conclusions, the multifactorial etiology of psychiatric disease, including hereditary influences is commonly recognized. Several years of research have identified a number of factors associated with not only an increased risk of mental health problems, but also factors associated with a protective effect in those experiencing adversities. Increased knowledge on specific resource factors could facilitate the development of prevention programs designed for individuals in adverse environments. Moreover, the continuity of psychiatric symptoms through childhood into adolescence and adult life calls for early identification and intervention in order to prevent dysfunctional development. Therefore, increased knowledge on factors of risk and resilience early in life is of considerable value.

Over the past few decades mental health has become a dominant issue among young people in Sweden (Gustafsson et al., 2010). Swedish studies that follow the development of mental health and family conditions among children growing up are scarce. Therefore, a review of the long-term aspects of early risk factors for behavioral problems is needed. With knowledge of the multifactorial etiology of mental health in children, a multiple-levels perspective in analysis is valuable. As measures of child mental health, internalizing and externalizing behavioral problems are commonly assessed. However, while some risk factors are common for these problems, others are specific for each type. Moreover, there is a considerable overlap between internalizing and externalizing symptoms during childhood and adolescence, giving rise to theories about comorbidity and the accuracy of psychiatric diagnostics in childhood.

Child behavioral problems

Internalizing problems

Internalizing problems includes states of anxiety and depression, or in a more colloquial language – disorders of mood or emotion. These symptoms are often referred to as invisible, as they are not as evident to parents or teachers as are externalizing problems. Likewise, internalizing problems in small children can be more difficult to detect due to the child's limited verbal skills. Internalizing problems have been associated with impaired cognitive functioning (Wagner, Müller, Helmreich, Huss, & Tadić, 2015) and suicidality (Sunderland and Slade, 2015). However, grouped together as internalizing conditions, the common conceptual and nosological basis between anxiety and depression is debated (Roza et al., 2003). While symptoms in small children are not always clearly differentiated, studies indicate differences between anxiety and mood conditions (Sterba et al., 2007; Tandon et al., 2009). Moreover, preschool children have been shown to exhibit more sophisticated emotions than previously believed (Shonkoff and Phillips, 2000).

Externalizing problems

Externalizing behavior comprises symptoms of dysregulated and disruptive behavior, and the term "behavioral disorder" is often used synonymously. Diagnoses such as Oppositional Defiant Disorder (ODD), Conduct Disorder (CD) and Attention Deficit Hyperactivity Disorder (ADHD) are found in this group. Aggressive and delinquent behaviors are common symptoms, and these types of problems often become obvious in the school environment where children are expected to sit still and concentrate. Referral of children for neuropsychiatric examination has increased markedly over the last years in Sweden, however, according to a recent review, no dramatic increased prevalence in externalizing disorders has been observed (Bor et al., 2014).

Course and comorbidity

There is support for a distinction between internalizing and externalizing problems as early as infancy (Briggs-Gowan et al., 2006; Keenan et al., 1998). A considerable stability of symptoms during childhood has been shown (Costello et al., 2003; Mesman et al., 2001), indicating homotypic stability, that is, a continuity of pattern over time. A large epidemiological study known as the Dunedin study showed stability of internalizing symptoms in girls between ages 11 and 15; in boys, however, both internalizing and externalizing problems were shown to predict later externalizing problems (McGee et al., 1992). The change of symptom pattern, called heterotypic stability, has been shown in numerous studies. For example, externalizing problems in childhood have been found to predict anxiety disorders (Roza et al., 2003), and anxiety in childhood has been found to predict conduct disorder in

adolescence (Costello et al., 2003). A complex pattern of psychopathological trajectories has been shown in a prospective longitudinal study (Pihlakoski et al., 2006). Several studies have demonstrated an increased risk for adult psychopathology in individuals with mental health problems in childhood (Caspi et al., 1996; Reef et al., 2009). Externalizing problems in childhood also have been found to predict other problems such as adult alcohol problems (Edwards et al., 2015), and adult criminality (Satterfield et al., 2007). Early detection and intervention is thus crucial to prevent negative development.

The development of internalizing and externalizing symptoms is known to occur during different stages of childhood. The incidence of anxiety increases during early childhood, externalizing problems become more prevalent during the middle of childhood, and the incidence of mood disorders takes a leap during adolescence (Costello et al., 2003). The prevalence of anxiety conditions has been found to be close to 10 % in preschoolers, while the prevalence of depression varies between 0.5-2 % (Egger and Angold, 2006). The prevalence of depression in adolescents has been shown to be around 9.5 % (Wagner et al., 2015). A recent meta-analysis found a prevalence of ADHD just above 7 % in children (Thomas, Sanders, Doust, Beller, & Glasziou, 2015). Sex differences also become more distinct during middle childhood and adolescence. Internalizing problems are more prevalent among girls, while boys exhibit externalizing problems to a greater extent (Angold et al., 2002; Keenan and Shaw, 1997; Thapar et al., 2012).

Moreover, subthreshold symptoms of depression have been shown to increase the risk of later Major Depressive Disorder (MDD) (Fergusson et al., 2005), indicating the importance of including symptom ratings rather than focusing solely on clinical diagnoses. A dimensional view on psychiatric illness, as opposed to the since long prevailing categorical diagnostic approach, has been discussed and was initially proposed for the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (American Psychiatric Association, 2013). Advocates of the dimensional paradigm points to both the increased importance of patients self-reports for the clinical process in such an approach and the advantage of a more informative diagnosis (Narrow and Kuhl, 2011).

There is support for a considerable comorbidity between different childhood mental health problems (Angold et al., 1999; Keiley et al., 2003). The intersecting patterns of behavioral and emotional problems renders a question about whether comorbidity could be an artefact of overlapping symptoms (Kovacs and Devlin, 1998). There has been a debate about the accuracy of psychiatric diagnostics in early childhood, which questions whether or not preschoolers should be diagnosed (Egger and Angold, 2006).

Could comorbidity be an actual disease pattern, a true phenomenon, rather than co-occurring conditions? Hypotheses have been raised regarding differing etiological origin of adolescent onset depression compared to adult onset depression, since the former phenotype is more sensitive to environmental influences, and has a higher comorbidity with externalizing conditions (Hill et al., 2004; Jaffee et al., 2002; Laucht et al., 2009). Moreover, the extensive comorbidity has also given rise to questions about whether particular risk factors for specific disorders could actually be seen as general risk factors for a broader predisposition of mental health problems (Kessler et al., 2011). Nevertheless, both homotypic and heterotypic stability indicates the long-term consequences of childhood internalizing and externalizing problems and the importance of early prevention and treatment. Therefore, it is important to consider both internalizing and externalizing problems when examining mental health in childhood, especially in small children, and to consider the possibility of an overlap of symptoms.

In the present thesis, the term "behavioral problems" is used as an overarching concept for both internalizing and externalizing problems. This approach is common in child psychology and psychiatric research; however, behavioral problems can also refer to externalizing type of problems, such as CD and ODD. In the following paragraphs, both well-known and hypothetical risk and resilience factors for child behavioral problems will be presented.

Early adversity

Birth characteristics

Improvements in health care during the last decades have resulted in increased survival rates in children born preterm or with other birth related complications. The risk for serious sequelae has decreased; however, the awareness of an augmented risk for more subtle problems such as later behavioral difficulties has increased. The early environment is of tremendous importance for child development due to the marked developmental processes of the brain that takes part both during pregnancy and the first years of life (Kundakovic and Champagne, 2015; Vela, 2014). Pregnancy and birth related complications thus may lead to an increased vulnerability due to altered brain functions during this very sensitive period in life. Previous studies on perinatal factors in relation to mental health in childhood, however, have come to different conclusions (Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Wagner, Schmidt, Lemery-Chalfant, Leavitt, & Goldsmith, 2009). For example, preterm birth has been shown to increase the risk for Attention Deficit Hyperactivity Disorder (ADHD) (Marceau et al., 2013), but there are studies demonstrating the opposite (Heinonen et

al., 2010). A low birthweight has been shown to increase the risk for both internalizing and externalizing problems reported by parents (Dahl et al., 2006), whereas another study found no association between birthweight and ADHD (Silva et al., 2014). To be born small for gestational age (SGA) has been associated with an increased risk for ADHD (Heinonen et al., 2010) and for later hospitalization due to psychiatric morbidity (Gustafsson et al., 2009). Tobacco smoking during pregnancy has been shown to increase the risk both for ADHD (Silva et al., 2014) and criminal behavior (Brennan et al., 1999). A low 5 minute Apgar score was not shown to increase the risk for ADHD (Silva et al., 2014).

Life events

Early experience of adversity is associated with a number of negative health outcomes later in life, where mental health problems are a prominent risk (Chan, 2013; Chapman et al., 2004; Kessler et al., 2010). Definitions of early adversity have differed between studies. Physical, sexual or emotional abuse, divorce or separation of parents, incarceration of a parent, or domestic violence towards a parent are usually included, and these events have been shown to increase the risk for behavior problems and adult depression (Briggs-Gowan et al., 2010; Carter et al., 2010; Chapman et al., 2004). The experience of trauma such as war, sexual or violent physical assault, severe car accidents, natural disasters et c. has a well-known impact on mental health (Javidi and Yadollahie, 2012). The prevalence of Post-Traumatic Stress Disorder (PTSD) varies between 0.5-6 % in studies, while the lifetime cumulative incidence of around 60 % for men and 50 % for women have been found (Javidi and Yadollahie, 2012). While many studies focused on experience of childhood maltreatment, there is also support for the impact of cumulative life transitions on child well-being, such as residential mobility and school transitions (Simmons et al., 1987). Various childhood adversities are often co-occurring (Masten and Coatsworth, 1998), and studies show that cumulative life adversities exert the greatest risk for negative outcomes (Sameroff and Rosenblum, 2006), a notion in line with the stress-vulnerability hypothesis.

Sociodemographic risk

Sociodemographic factors are known to increase the risk for negative behavioral and mental health outcomes. A recent review indicated an increased risk for mental health problems among children and adolescents growing up under disadvantaged socioeconomic conditions (Reiss, 2013). More specifically, parental unemployment is associated with negative consequences for families (Ström, 2003), and preschool-aged children of immigrants have been shown to exhibit increased risk for behavioral problems (Jansen et al., 2010). In a review of health inequalities in children and adolescents in Sweden, the author concludes that social factors explain a considerable proportion of health inequalities (Bremberg, 2011). Stability of adequate social and

economic conditions is of importance for good health. Bradley and Corwyn (2002) discuss the importance of socioeconomic status (SES) in the framework of the stress-vulnerability model, and how socioeconomic factors interact with individual and environmental characteristics in the process of child development. Moreover, they conclude that SES impacts child wellbeing and development at multiple levels, including family and neighborhood. The specific pathways through which SES impacts child wellbeing are not fully understood, as adversities tend to coexist.

Maternal depression and depressive symptoms

The prevalence of postpartum depression is approximately 10-19 % (Josefsson et al., 2001; Munk-Olsen et al., 2006; O'Hara and McCabe, 2013; Rubertsson et al., 2005). Childbirth predisposes women to potentially develop postpartum depression as a result of both the hormonal changes occurring postpartum, and the psychological adjustments of becoming a mother (Bloch et al., 2003; Payne, 2003). The risk of subsequent episodes of depression increases for women with a history of PPD; a relapse rate of 80 % has been reported (Halligan et al., 2007). Another study showed a six-fold increased risk for depression four years after childbirth (Josefsson & Sydsjö, 2007). The prevalence of depression in women of childbearing age has been reported to be around 20 % (Civic and Holt, 2000).

Maternal depression affects both the woman herself and her children. Numerous studies have addressed an increased risk of behavioral problems in children of depressed mothers (Araya et al., 2009; Brennan et al., 2000; Campbell et al., 2009; Civic and Holt, 2000; Conners-Burrow et al., 2015; Fihrer et al., 2009; Josefsson and Sydsjö, 2007; Korhonen et al., 2014). A meta-analysis of 193 studies found an increased risk for internalizing and externalizing problems as well as general psychopathology in children of depressed mothers, although effects were small (Goodman et al., 2011). Maternal depression during the first year of life has been found to be associated with frontal electroencephalogram EEG asymmetry in the offspring, which has been associated with negative affect, emotional dysregulation, withdrawal behavior and lack of empathy (Field and Diego, 2008; Jones et al., 2009).

Whether or not the timing of maternal depression is of importance has been debated (Korhonen et al., 2014). Maternal depression during the first year has been shown to increase the risk for infant avoidant and disorganized attachment patterns (Martins and Gaffan, 2000), violent behavior (Hay et al., 2003) and poor academic performance (Murray et al., 2010). Studies demonstrate that the postnatal period is especially susceptible to adverse effects of maternal depressive symptoms (Bagner, Pettit,

Lewinsohn, & Seeley, 2010; Bureau, Easterbrooks, & Lyons-Ruth, 2009; Dale F. Hay, Pawlby, Waters, & Sharp, 2008; Murray et al., 2010). Since the recurrence rate of depression is high, many children will be exposed to maternal depression repeatedly during childhood and adolescence. Exposure over a long period of time has been shown to predict various types of childhood adjustment problems including a lower vocabulary score and behavioral problems (Brennan et al., 2000) as well as decreased social competence (Luoma et al., 2001). Finally, studies argue also that ongoing maternal symptoms of depression have the greatest impact on concurrent child behavior problems (Brennan et al., 2000; Josefsson and Sydsjö, 2007).

Whether or not the severity of maternal depression impacts child development and behavior has also been discussed. While many studies have focused on clinically diagnosed depression, a recent study indicated that even subclinical levels of maternal depressive symptoms have a negative effect on child behavior (Conners-Burrow et al., 2015).

The pathway from maternal depressive symptoms to child behavioral problems is probably multifactorial. Hereditary factors such as a biological predisposition as well as the social consequences of growing up with a depressed parent are likely to contribute. Maternal depression has been shown to increase the risk for insecure attachment (Cicchetti et al., 1998; Forman et al., 2007; Martins and Gaffan, 2000), which also has been associated with both internalizing and externalizing problems (Cicchetti et al., 1998). Attachment could possibly act as a moderator of the effect of maternal depression on child behavioral problems later during childhood (Milan et al., 2009).

Genetic influences on behavior

Molecular genetics

DNA is the primary genetic molecule carrying information on human biology. DNA is constituted of two complementary nucleotide strands coiled around each other forming a double helix. The strands hold four types of nucleotides: cytosine, guanine, adenine and thymine. The combination of nucleotides constitutes the code for, among other things, synthesis of amino acids which in turn constitute the base of proteins. Within the cell, DNA is packed together with proteins in compact structures forming chromosomes. Each chromosome holds between 50 (Y chromosome) and 2000 genes, that is, a DNA locus coding a specific protein or RNA product. Humans have two sets of chromosomes; one set inherited from each parent.

Variation of DNA at a genetic locus is called allelic variation. An allelic variant in the DNA which has at least two forms at the locus and a prevalence of at least 1 % in the population is called genetic polymorphism. The most common type of polymorphism is a single base substitution (Single Nucleotide Polymorphism, SNP). If both alleles at a genetic locus are identical, then the individual is homozygous for that genotype; if the alleles are different, the individual is heterozygous. Allelic variation can results, for example, in how much protein is synthesized. A short variant of an allele can be related to lower expression of the gene, and thus, homozygotes for a short allele might have the lowest protein production. Another form of variability of the genetic make-up is Variable Number of Tandem Repeats (VNTR). VNTR comprises repeated tandem sequences of DNA directly adjacent to each other and can affect the transcriptional activity of a gene.

Most human traits are influenced by the interaction between multiple genes and the environment (gene-environment interaction). Moreover, the human genome is adaptable to renewal and alteration, a process which is crucial for evolution. Allelic variation is caused by mutations that are either normally occurring (wild type) or damaging and can potentially lead to abolished gene function. The relationship between genes and the environment is however not unidimensional as previously thought. The notion of gene-environment correlations is based upon the assumption that there are genetic influences on the exposure to different environments. Epigenetic mechanisms, without altering the DNA sequence, modulate the accessibility of the genetic make-up in an environment-sensitive way (Petronis, 2010). More precisely, genetic variation can have an impact on behavior, which in turn can shape or select different environments (Rutter, 2006). Conversely, gene expression is affected by the environment. By epigenetic processes, alteration of gene expression can occur, and thus environmental effects on DNA become manifest (Rutter, 2006).

Neuronal transmission

Emotions and behavior are affected by several brain structures and systems. Research has identified specific neurotransmitters and associated substrates that influence internalizing and externalizing behaviors, respectively. In the 1960s, the monoamine theory of depression was developed, suggesting that depression is a result of deficiencies in monoaminergic (serotonin and/or noradrenalin) transmission in the Central Nervous System (CNS). Subsequent studies failed to fully support the theory, however, the therapeutic effects of serotonergic and noradrenergic drugs in treating depression are well documented. Thus, the interest in other mediators that affect the monoaminergic systems has increased. The serotonin system is studied extensively and plays a role in several functions, including sleep and wakefulness, mood and

behavioral changes. Additionally, the availability of serotonin in the synaptic cleft has been associated with mood in animal studies (Murphy et al., 2008).

Gene-environment interaction

The nature versus nurture question is no longer central in the debate on the origin of human behaviors and mental illness; however the extent to which genetic and environmental influences contribute to behavior and mental illness is essential in the discussion. Complex diseases, such as psychiatric conditions, are plausibly caused by an interaction of multiple genetic and environmental factors (Duncan and Keller, 2011). Gene-environment interaction is defined as *different effect of environmental factors on the risk of disease in individuals with different genotypes* (Ottman, 1996). Rather than simply an additive combination of various risk factors, a multiplicative model might better suit the gene-environment model for candidate genes in the nosology of mental health (Ottman, 1996). Following the groundbreaking gene-environment model of an interaction effect between the *5*-HTTLPR and experience of stressful life events increasing the risk for depression by Caspi et al (2003), the gene-environment studies on behavior have flourished. However, discordant findings have led to a polarized debate about the relevance of further exploration of candidate genes and mental health (Munafò et al., 2014). Others argue that methodological differences are the cause of the disparate findings and call for well-powered direct replication studies using validated measures (Duncan and Keller, 2011).

Moreover, the polygenic model of inheritance, suggesting a multi-genetic etiology of behavior and mental health, allows for more complex patterns of gene-environment interactions. Kaufman et al (2006) found a gene-gene-environment interaction effect of *5*-HTTLPR, *BDNF*Val66Met and childhood adversity on depression (Kaufman et al., 2006), and to our knowledge, a handful of studies have attempted replication of this three-way interaction effect (Aguilera et al., 2009; Comasco et al., 2013; Grabe et al., 2012; Nederhof et al., 2010; Wichers et al., 2008). The findings are discordant regarding both the presence of a three-way interaction effect and the risk genetic variants in the presence of childhood adversity. Both positive (Comasco et al., 2013; Grabe et al., 2012; Wichers et al., 2008) and negative findings (Aguilera et al., 2009; Nederhof et al., 2010) have been reported.

5HTT

The serotonin transporter gene (*5-HTT)* includes a functional polymorphism, the serotonin transporter gene-linked polymorphic region (5-HTTLPR) which consists of two common alleles; short (s) and long (l). Carriers of the s-allele have been shown to exhibit less effective serotonin expression and availability compared to individuals homozygous for the l-allele (Lesch et al., 1996). The interaction effect between the *5*-

HTTLPR and experience of stressful life events found by Caspi and colleagues (Caspi et al., 2003) has been subjected to numerous attempts at replication. Some researchers have been able to reproduce the results partially or completely (Cervilla et al., 2007; Eley et al., 2004; Grabe et al., 2005; Kaufman et al., 2004; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005; Taylor et al., 2006; Wilhelm et al., 2006), whereas others have not (Chipman et al., 2007; Chorbov et al., 2007; Gillespie et al., 2005; Surtees et al., 2006). Likewise, meta-analyses of the *5*-HTTLPR have arrived at different conclusions (Karg et al., 2011; Munafò et al., 2009; Risch et al., 2009). However, between-study heterogeneity must be considered (Duncan and Keller, 2011).

5-HTTLPR gene-environment studies including children are sparser, and the results have been diverging. In a study involving seven-year-olds, Araya et al. found no association between *5*-HTTLPR and emotional symptoms (Araya et al., 2009), while associations have been shown by other researchers although on smaller study samples (Eley et al., 2004; Hankin et al., 2011; Kaufman et al., 2004; Nobile et al., 2009). Furthermore, a number of studies noted a main effect of *5*-HTTLPR on depression (Cervilla et al., 2006; Clarke, Flint, Attwood, & Munafó, 2010; Hoefgen et al., 2005; Kiyohara & Yoshimasu, 2010; Lesch et al., 1996).

BDNF

Brain Derived Neurotrophic Factor (BDNF) is a protein involved in reparation, plasticity and neurogenesis in the brain. The neurotrophin hypothesis suggests that BDNF plays a critical role in the development of depression. Decreased serum levels of BDNF have been found in individuals suffering from MDD (Sen et al., 2008). In addition, BDNF and serotonin systems have previously been shown to act in synergy (Martinowich and Lu, 2008). A SNP G/A (Val66Met) in the *BDNF* gene has been shown to affect levels of BDNF in the brain (Egan et al., 2003). Discordant results of *BDNF* Val66Met gene-environment effects on depression have been found. Many studies noted an interaction effect (Hwang et al., 2006; Strauss et al., 2005), and these results were confirmed by a recent meta-analysis (Hosang et al., 2014). However, results have also been contradicting (Surtees et al., 2007).

MAOA

Monoamine oxidase A (MAOA) is a mitochondrial enzyme involved in the oxidative deamination of serotonin, dopamine and norepinephrine. The gene coding for MAOA is located on the X chromosome and holds a variable number tandem repeat (VNTR) 30bp upstream in the promoter region (*MAOA*-uVNTR). The polymorphism consists of either 2, 3, 3.5, 4 or 5 repeats and has been shown to affect the transcriptional activity of the *MAOA* gene promoter (Sabol et al., 1998). Research shows that the longer alleles (with 3.5 or 4 repeats of the sequence) exhibit more efficient

transcription process compared to alleles with 3 repeats (Deckert et al., 1999; Sabol et al., 1998). Gene-environment studies on (*MAOA*-uVNTR) have demonstrated that a genotype related to low monoamine oxidase activity is associated with antisocial behavior in the presence of childhood maltreatment (Caspi et al., 2002). An interaction effect between MAOA and childhood adversities on depression have also been noted (Cicchetti, Rogosch, & Sturge-Apple, 2007; Melas et al., 2013).

COMT

Catechol-O-Methyl transferase (COMT) is involved in the inactivation of monoamines such as dopamine, epinephrine and norepinephrine. In the gene coding for COMT, a functional SNP results in a substitution of the amino acids valine into methionine at position 158 (Val158Met). The variant including valine is much more efficient in degrading neurotransmitters than the variant including methionine. The substitution thus leads to a marked decrease in COMT enzyme activity, thereby increasing dopamine activity in the brain (Chen et al., 2004). The COMT polymorphism has been associated with, for example, executive functioning (Dickinson and Elvevåg, 2009). Another study found an interaction effect between the *COMT* Val158Met genotype and recent stressful life events on depression onset (Mandelli et al., 2007). However, as with many of the candidate genes, findings from different studies are disparate (Opmeer et al., 2010).

Resilience

The concept of resilience

Albeit a lack of a uniform definition of the concept of resilience, it is usually referred to as a dynamic process of positive adaption within the context of significant adversity (Luthar & Cicchetti, 2000). However, two central conditions have to be achieved: 1) exposure to adversity, and 2) positive adaption in spite of this major challenge (Luthar & Cicchetti, 2000). The interest of resilience was raised in the 1960's, and early research identified a number of personality traits and social factors associated with positive development despite adverse exposures (Werner and Smith, 2001). Since then, the view on resilience has changed, and what was previously seen as a static innate capacity is now considered an acquired ability that can be changed over time (Khanlou and Wray, 2014). Resilience is dynamic to the extent that an individual can be resilient at one time point but not another; likewise, a person may be resilient towards certain exposures but not to others (Cicchetti, 2010; Rutter, 2006). Resilience is thus to be considered as an interactive concept, which changes in relation to experiences and environments (Khanlou & Wray, 2014; Rutter, 2006).

Early research on resilience suggested a number of factors associated with a better-than-expected outcome in children growing up in adverse environments. A broad categorization of these resource factors gives three domains: internal characteristics, family environment, and social environment. *Internal characteristics* represent the child's inner strengths and capacities such as temperament, learning ability, self-esteem and adaptive skills. Temperament has been shown to specifically affect behavior in school-aged children (Prior et al., 2001) and to be associated with resilient outcomes in adults (Kim et al., 2013). *Family factors* found to be associated with resilience are attachment, parenting styles and the parent-child relationship. An association has been found between a high maternal sense of coherence (SOC) and low levels of behavioral problems in preschool children (Huhtala et al., 2014). Moreover, maternal SOC has been shown to influence child attachment style and socioemotional adjustment (Al-Yagon, 2008). The *social environment* encompasses resource factors such as school performance, pro-social adult relations and good friends. The pattern of resource factors has been convincingly replicated since first identified (Masten and Coatsworth, 1998).

A multiple level of analysis

To view resilience as a dynamic concept requires a broad understanding of risk and resource factors as well as the developmental processes of the human being. Current views on resilience encompass a multiple-levels (bio-psycho-social) approach, that is, the incorporation of biological measures in the prevailing psychosocial-environmental perspective (Cicchetti and Blender, 2006). Resilience is thus to be considered as a multilevel construct (Masten, 2007). An increased interest to include a biological approach in human resilience research has been evident during the last decade (Calkins et al., 2007; Carli et al., 2011; Cicchetti and Rogosch, 2012; Kang et al., 2013; Stein et al., 2009).

Longitudinal studies

The advantage of longitudinal studies is the ability to follow the same individuals at several points in time to study the development of a certain phenomenon. Since retrospective studies present a risk for recall bias, prospective studies are usually considered more reliable. A birth cohort is a common target for longitudinal study and has the advantage to follow natural development and variation of normality. Longitudinal studies that follow individuals from birth, or even in utero, can also be used to identify early signs of risk factors and risk behaviors linked to later development of mental health problems.

A few longitudinal studies focusing on mental health from early childhood onwards are currently carried out in the Scandinavian countries. For example, the Behavior Outlook Norwegian Developmental Study (BONDS) is a Norwegian study initiated in 2006 following the development of social competence and behavioral problems in 1159 children (Naerde et al., 2014). The Norwegian Mother and Child Cohort study (MoBa), with a consecutive enrollment between 1999 and 2008 including 111 000 pregnant women and their children, is yet another prospective longitudinal study including aspects of child mental health (Bendiksen et al., 2015). In the Danish Copenhagen Child Cohort (DCCC) including 6090 children followed from birth to preadolescence, prevalence and risk factors for psychiatric disorders have been examined (Elberling et al., 2016). The implementation of contemporary prospective epidemiological studies is important, as society is changing rapidly and generalizable conclusions cannot reliably be drawn from studies from the mid-1900s. Individuals who have grown up during the 21st century experience new and different challenges compared to those who have grown up 30 or 50 years ago.

Growing up in a Swedish context

Sweden has among the lowest rates of infant mortality in the world (Adamson, 2013). Parental leave is provided fulltime up to the child's age 1.5 and most children start daycare before the age of 3. In the end of the 1990s, when the children of the SESBiC study were in preschool age, 80 % of children aged 3 were enrolled in preschools in Sweden (Skolverket, 1999). While child development during the first years depends primarily on the relationship between the child and the primary care giver, quality of preschools and schools is important during early and middle childhood (Broberg et al., 1997). The society of today requires good capacities of flexibility and coping, not just in the school environment, but also for parents (Cederblad, 2003). During the last few decades, Sweden has undergone a considerable change from having had a mainly homogenous population into having a multi-ethnic society in the mid-2010s. While concern has been raised about health discrepancies between Swedish born children and immigrants, self-reports at age 12 from the SESBiC study indicated equal or even better mental health in second generation immigrants (Dekeyser et al., 2011).

Seen internationally, Swedish children and adolescents grow up under comparably good circumstances. A recent report from UNICEF comparing child well-being in rich countries put Sweden in the top five (Adamson, 2013). The report used 5 parameters; material well-being, health and safety, education, behaviors and risks, and housing and environment. A self-report measure was also included, resulting in a markedly lower score indicating discrepancies between objective conditions and subjective

perception. Furthermore, among comparable countries, gender equality is well developed in Sweden.

Theoretical framework

The stress-vulnerability model

It is commonly accepted in clinical practice that an individuals' propensity to develop mental health problems depends on both a predisposition and current stress levels. The stress-vulnerability model was developed in 1977 by Zubin and Spring (Zubin and Spring, 1977) as a model for understanding the development of schizophrenia. According to this model, an individual develops mental health problems when his or her capacity for adaption is overloaded. That is, an individual has a constitutional or acquired predisposition or vulnerability for a certain illness, which becomes manifest when stress levels rise. In individuals with a high level of vulnerability, less stress is required to develop symptoms.

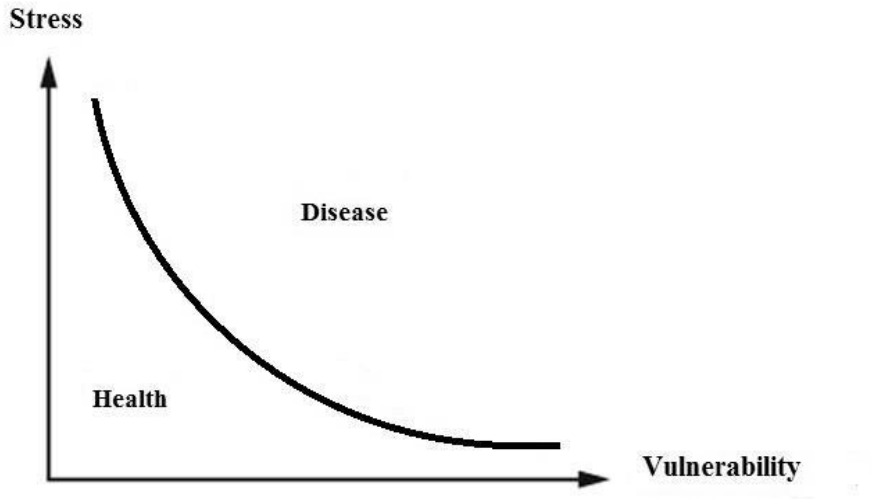

Figure 1. The stress-vulnerability model.

The stress-vulnerability model implies an interaction effect between constitutional and environmental factors. Vulnerability is often defined as genetic predisposition, but this does not exclude biological susceptibility due to, for example, pregnancy or birth-related complications. Genetic predisposition is often referred to as diathesis, which is why the name diathesis-stress model is sometimes used synonymously. Some versions

of the stress-vulnerability model include psychological factors such as attachment styles and temperament. Together with biological susceptibility, these factors can be categorized as personal characteristics as opposed to stressors that are influences of the outside environment (Broberg, Almqvist, & Tjus, 2003). Stress is perceived differently among individuals, but may be caused by, for example, experience of traumatic life events or socioeconomic strain. The gene-environment model as presented by Caspi et al (2003) and repeated by many others can be seen as one example of a stress-vulnerability model. Here, the development of mental health or behavioral problems is seen as a result of an interaction effect between specific genetic variants and the experience of stressful life events. The gene-environment model has been shown to be applicable for many aspects of behavior besides internalizing and externalizing problems, such as temperament and suicidal behavior, for example.

A common point of criticism against the stress-vulnerability model is that it does not allow for a reciprocal relationship between factors of stress and vulnerability. For example, it is plausible to consider alterations in the level of stress that triggers a relapse of depression compared to the first episode. However, the stress-vulnerability model assumes a constant level of constitutional vulnerability that does not change as a result of experience. Quite contradictory to this assumption, the lately increasing interest in epigenetic modifications as a result of environmental influences with indirect effects on behavior does question a static interplay between genes and environment (Feder et al., 2009).

The human ecology model

According to Bronfenbrenner (1979), "…human development is a product of interaction between the growing human organism and its environment." (Bronfenbrenner, 1979, p 16) Bronfenbrenner perceived a marked asymmetry in modern psychology between the assumed weights in this equation which, he thought, placed too much emphasis on the properties of the individual. Rather, he proposed, more focus was to be placed on the different levels of external environment influencing the developing child both directly and indirectly. The human ecology model builds upon the assumption that there is a constant accommodation between the individual and the external environment, as well as between different levels of organization within the environment. The original model includes four ecological levels surrounding the individual. A revision of the model in 2005 resulted in a fifth level: the chronosystem to reflect the time aspect (Bronfenbrenner, 2005).

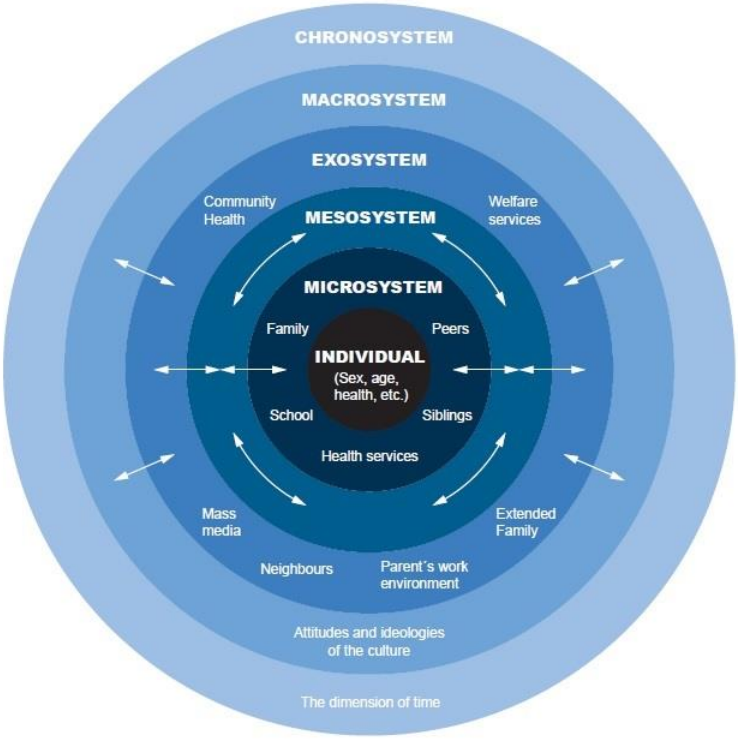

Figure 2. The human ecology model. In Jonsson, (2015). Reprinted with permission from the author.

The developing individual constitutes the center of the model. In later versions of the model, biological factors were included in this dimension. *The microsystem* reflects the various environments immediately surrounding the child, such as the family, preschool and school. The next level, *the mesosystem*, represents the connection between the microsystems, such as parents interacting with teachers, peers interacting with each other and so on. *The exosystem* does not directly involve the individual as an active participant, but constitutes the setting in which the various microsystems are included; thus the individual is indirectly a part of this system. The local community is an evident example of an exosystem. Social and economic factors, as well as the size and setting of the community can be of importance in the exosystem. It is plausible to expect more interaction between inhabitants of a small community, compared to an urban district. Other features of the exosystem important for the child are, for example, accessibility to leisure activities such as sports and other hobbies. *The macrosystem* comprises the overarching consistency regarding culture, ideology, politics and legislation that sets the framework for the lower levels of the model. Child

protection laws have a prominent place in Swedish society, and the UN Convention on the Rights of the Child (The United Nations, 1989) serves as an important guideline for many organizations that work with children. The social security system in Sweden, which allows parents legal rights to full parental leave until the child's age 1.5, and part time parental leave until the child's age 7 also affects living conditions for children growing up in Sweden. *The chronosystem* represents major life transitions such as entering daycare and school, changing place of recidence or experiencing parental divorce. These are all events that plausibly have an impact on the developing individual. The various levels of the model are subjected to constant interaction, and there is a reciprocal relationship between the individual and the external environment. Criticism has been raised on the model's universality, leading to loss of precision (Broberg et al., 2003).

The revised bioecological model has also been used to understand and develop the concept of resilience (Ungar et al., 2013). The authors suggest the bioecological model as a framework to conceptualize resilience research, pointing towards three important principles; equifinality, differential impact and contextual and cultural moderation. Equifinality implies that the development of resilience may take different paths, but ultimately it leads to equally viable aspects of wellbeing. Differential impact implies that different individual resources and exposure to risk have diverse influences on resiliency. Finally, protective processes are not equally important or accessible in all contexts and cultures (Ungar et al., 2013). In the present thesis, the human ecology model is used mainly as a taxonomy to position the studies.

THE EMPIRICAL STUDIES

Overall aim

The overarching aim of the present thesis was to investigate the association between biological, psychological and social factors of risk and resilience, and behavioral problems in a large cohort of children in Sweden.

Aims and hypotheses

Study I
The aim of study I was to examine: 1) If mothers who reported symptoms of PPD were more likely than others to report depressive symptoms 12 years later. 2) Whether symptoms of PPD and/or maternal depression 12 years later were associated with child behavioral problems at age 12.

Study II
The aim of study II was to investigate gene-environment interactions on internalizing and externalizing problems in 12 year old children. We hypothesized to find a gene-environment and possibly gene-gene-environment interaction on internalizing problems including the genetic polymorphisms *5*-HTTLPR and *BDNF* Val66Met, traumatic life events, and maternal symptoms of depression and anxiety.

Study III
The aim of study III was to explore the importance of the early environment and constitutional factors for child behavior at preschool age. In particular, we aimed to examine potential predictive associations between a broad range of risk factors covering pregnancy and birth, genetic polymorphism, experience of multiple life events, psychosocial environment, and child behavior at the age of 3.

Study IV
The aim of study IV was to examine proposed resilience factors at pre-school age and their impact on child behavior at age 12 using a bio-psycho-social model of risk and resilience. More specifically, maternal factors such as sense of coherence as well as individual factors such as temperament, social functioning, and genotype were hypothesized to have a protective effect on child behavior in children exposed to cumulative adversities.

Methods

The SESBiC study

The SESBiC study was initiated in 1995 by the county council of Skåne, with the purpose of early identification of psychosocially burdened children at risk for dysfunctional development. Moreover, the aim was to develop simple screening instruments suitable for routine health care. The present thesis used data from the baseline and from the 3- and 12 year follow-ups of the SESBiC study.

Subjects

All mothers of children reported from the delivery wards to the Child Welfare Clinics (CWC) between May 1st 1995 and December 31st 1996 in Hässleholm and Western Blekinge in the south of Sweden were invited to take part. Mothers of 1723 children (88 %) accepted and were enrolled in the study (Figure 3). In the cohort, 52.8 % were boys, and there were 27 twin pairs.

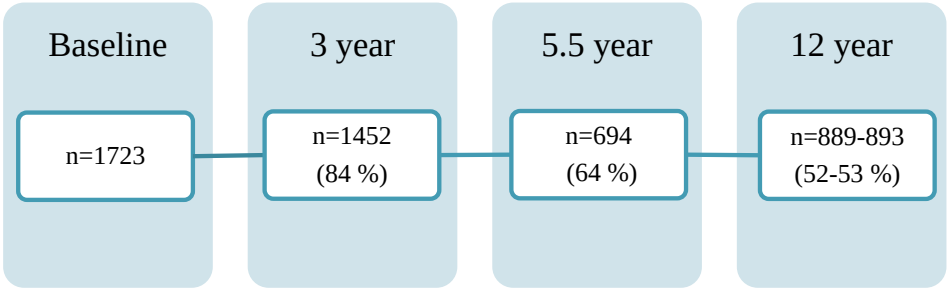

Figure 3. Participants at baseline and follow-ups.

At the 3 year follow-up, one child was deceased. Mothers of 1452 children (84 % of the children in the baseline study) accepted to participate (Figure 3). At age 5.5, another follow-up was made with the children in Hässleholm municipality (no general routine examination was performed at this age in Blekinge). Of the 1090 children living in this area, 694 participated (64 % of the children from Hässleholm municipality in the baseline study). At the 12 year follow-up, two children and four mothers were deceased, ten had moved abroad and 24 were learning disabled. Learning disability was defined by enrollment in schools designed for individuals with intellectual disabilities. For those who did not take part in the 12 year follow-up, notes from the 3- and 5.5 year follow-ups on mental retardation, developmental delay and diagnoses were carefully examined to identify individuals with learning disabilities.

Exclusion criteria were applied depending on which child- and mother measures were used in each study respectively (Table 1).

Table 1. Summary of samples, instruments and measures by study. *n* varies between analyses due to non-response.

	Study I	**Study II**	**Study III**	**Study IV**
Age	12	12	3	12
n	893 (52.3 %)	889 (52.7 %)	1452 (84.3 %)	889 (52.7 %)
Eligibility	2 children, 4 mothers deceased 10 MA	2 children, 4 mothers deceased 10 MA 24 LD	1 child deceased	2 children, 4 mothers deceased 10 MA 24 LD
Eligibility *n*	**1707**	**1683**	**1722**	**1683**
Measures	EPDS LSS SCL-25 CBCL Demographics	EPDS LSS SCL-25 LITE 5HTT BDNF CBCL Demographics	EPDS LSS CLES-P 5HTT BDNF CBCL MBR data Demographics	EPDS LSS CLES-P SOC Difficult Child 5HTT BDNF MAOA COMT CBCL Demographics

Note: MA = Moved Abroad, LD = Learning disability, EDPS = Edinburgh Postnatal Depression Scale, LSS = Life Stress Score, SCL-25 = Symptom Checklist 25, CBCL = Child Behavior Checklist, LITE = Life Incidence of Traumatic Events, 5HTT = Serotonin transporter, BDNF = Brain Derived Neurotrophic Factor, COMT = Catechol-o-methyl transferase, MAOA = Monoamine Oxidase, CLES-P = Coddington Life Event Scale for preschoolers, MBR = Medical Birth Register, SOC = Sense of Coherence.

Procedure

Baseline

The baseline study was conducted at the CWCs in connection with the routine 3 month check-up. Information about participation was given by an attending study psychologist. Mothers were interviewed by one of two study psychologists, and this interview provided the Life Stress Score (LSS). The mothers were also asked to fill out the Edinburgh Postnatal Depression Scale (EPDS).

3 year follow-up

The 3 year follow-up was carried out in connection with the routine 3 year examination at the CWCs. Information about the study and participation was given by the CWC staff. The mothers were asked to complete a series of questionnaires about themselves as well as temperament and behavior of their children. Information was also retrieved from the standardized clinical assessment used by the nurse and doctor.

5.5 year follow-up

The 5.5 year follow-up took place at the CWC in connection with the general investigation at age 5.5. The only data used from the 5.5 year follow up was information on learning disability. Therefore, the 5.5 year follow-up will not be referred to further.

12 year follow-up

Current home addresses for all 1723 children in the baseline study were obtained from the Swedish Tax Offices. Local education offices were contacted in order to obtain information about which school and class each child was attending. Principals were invited to a meeting with the research team where information about the study's aim and design was given. All principals agreed to participation and allowed the survey to be carried out during school hours. Class teachers were contacted via phone by the research assistants to set time and date for the visits, and they were given written as well as verbal information about the project.

Information letters about the study were sent to parents (i.e. legal guardians) of each child. A separate, simplified information letter was enclosed to the child. Enclosed was also a consent form for the parent to complete and return in order to demonstrate that the child was permitted to take part in the study at school. Parents who did not return the consent form in time before the visit to school were contacted by phone and asked whether they wanted to participate or not.

Specially trained research assistants visited the schools and met with the children in groups of 5-20. Only the children whose parents had given written or verbal consent were present in the classroom. The children were given verbal information about the study, and a series of questionnaires were handed out to each child to complete separately, as part of the overarching SESBiC study. Saliva sampling kits were provided to each participant, and verbal information about the procedure was given. The children were allowed to handle the sampling tubes on their own, though supervised by the research assistant. Each session, including questionnaires and saliva sampling, lasted about one hour. The teachers did not attend the session.

Families who had moved out of the original catchment area were contacted by mail and phone in accordance with the regular routine. Those families who agreed to participate received questionnaires and saliva sampling kits by mail. If preferred, the families were visited by a research assistant, and the survey was carried out at the child's home.

Each parent was asked to fill out a series of questionnaires about themselves and their child. The questionnaires were sent to the parents' home addresses with a pre-stamped return envelope to the research team. A reminder was sent after one month.

Instruments

Baseline mother assessment

The Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) is a widely used 10 item self-report questionnaire designed to screen for postnatal depression in community samples. Each item is ranged 0-3 with a total score of 30. The EPDS is not in itself diagnostic, but with a cut-off level of 9/10, the sensitivity of 96 % for MDD and the specificity of 62 % has been noted (Berle et al., 2003). EPDS refers to the 7 days preceding completion of the form and was filled out by the mothers at baseline. Two different cut-offs were used for the EPDS; a screening cut-off of 10 often used in population based samples (Norhayati et al., 2015) (study I-III) and a second cut-off of 13 to capture more severe clinical symptomatology (study II) (Matthey et al., 2006). In study IV, EPDS was used as a continuous variable together with LSS and CLES to create a cumulative adversity score.

The Life Stress Score (LSS) is a 50-item semi-structured interview form addressed to new mothers. The LSS comprises three main domains holding 17 items regarding the mother's social situation (family structure/social network, education, occupation and living conditions), 17 items focusing on medical information (personal maturity, health, workload, pregnancy and health care utilization) and 16 items about psychological information (traumatic experience during childhood and after, pregnancy and child birth and relationship with the child). The LSS has been used previously in a Swedish population based study (Nordberg et al., 1989) and was filled out by a psychologist after interviewing the mothers at baseline. The cut-off was set to the 90^{th} percentile (study I-III). In study IV, the LSS was used as a continuous variable together with EPDS and CLES to create a cumulative adversity score.

3 year follow-up mother assessment

The Sense of Coherence form (SOC) (Antonovsky, 1987) is a widely used form measuring factors associated with strong coping ability. As part of Antonovskys' concept of health, it holds the three main domains: comprehensibility, manageability

and meaningfulness. In this study, the Swedish version of the 13 item SOC was used. Every item is scored on a seven point scale, where 1 corresponds to low agreement and 7 to high agreement. The 13 items are summed to a total score, resulting in the single global factor SOC. The SOC form has been shown to exhibit acceptable validity (Eriksson and Lindström, 2005).

3 year follow-up child assessment

Child temperament was assessed by a global construct "difficult child" based on concepts from studies by Thomas and Chess (Thomas & Chess, 1984). The form holds 11 questions regarding adaptability to altered situations, intensity of emotional reactions and quality of mood. The first nine questions are scored on a five point Likert scale in which the mothers are asked to assess their child's temperament compared to other children. The final two questions are ranged 1-3 and 1-7, respectively, and they were consequently adapted to give equal weight as the other items. Finally, the scores were reversed so that a high score indicated an easy temperament.

The Coddington Life Event Scale (CLES) (Coddington, 1972) is a form used to screen for exposure to different life events. A modified version of the original scale was used, holding virtually the same events as the CLES but evaluating only the occurrence of an event, not the time aspect. It holds 32 specific items and one open item for any events not stated in the list. The CLES is a widely used instrument, and similar versions have been used in Swedish population based studies (Höök et al., 1995).

The Child Behavior Check List/2-3 (CBCL) (Achenbach, 1991) is a well-known 100 item form assessing child behavior during the last two months. The form comprises the two main domains of internalizing and externalizing behavioral problems and six specific subscales. Each item is scored 0-2 from "not a problem" to "often a problem". The CBCL has been used in Scandinavian population based studies, and has proven an effective screening tool for child psychiatric disorders (Bilenberg et al., 2005). The Swedish version of the CBCL 2/3 was filled out by the mothers at the 3 year follow-up.

12 year follow-up mother assessment

The Symptom Checklist (SCL-25), a short version of the SCL-90 (Derogatis et al., 1974), was used to measure symptoms of anxiety and depression during the most recent 14 days. It has been used in population based studies (Herva et al., 2004; Strand et al., 2003) and has been found to have satisfactory validity and reliability (Glass et al., 1978). The form holds 25 items (10 regarding anxiety, 13 depression and 2 somatic symptoms) scoring 1-4 from "not at all" to "extremely". The SCL-25 was

filled out by the mothers at the 12 year follow-up. For the SCL-25 total score, a mean item score of 1.75 was used as cut-off as done previously (Nettelbladt et al., 1993).

12 year follow-up child assessment

To assess potentially traumatic life events experienced by the child, the Swedish version of Life Incidence of Traumatic Experience (LITE) was used (Greenwald and Rubin, 1999; Larsson, 2003). In the 16 item parent-report form (LITE-P), the parent (in this case the mother) reports on traumatic events experienced by the child. The form holds 15 items describing traumatic events and one open item for any upsetting or scaring event not described in the checklist. For each event, the respondent is required to report whether the event occurred, and if so, at what age, the number of occurrences, how distressed/upset the child was at the time, and to what extent the event affects the child presently. In this study, only the incidence of events was used. The LITE-P was filled out by the mothers at the 12 year follow-up. Results on the LITE form were dichotomized into 0-2 events and ≥3 events for which there is support in the literature (Caspi et al., 2003).

The Child Behavior Check List/4-18 (CBCL) is a 113 item form assessing child behavior (Achenbach, 1991). There are eight subscales, and these also form the broadband symptom scales of internalizing and externalizing behavioral problems. The CBCL is used extensively, and it has been shown to exhibit good validity and reliability (Crijnen et al., 1997). The CBCL/4-18 was answered by the mothers at the child's age of 12.

Medical data

Pregnancy and birth related medical data

The Medical Birth Register (MBR) was set up in 1973 by an act of Swedish parliament and covers approximately 98-99 % of all births in Sweden. Missing data mainly represent infants born abroad or infants with invalid or incomplete personal identification numbers. The introduction of standardized medical records used by all delivery units and antenatal care clinics in the country enabled the setup of a national birth register, with the purpose to register information on ante- and perinatal factors and their impact on child health. Routine checks are performed by the Swedish National Board of Health and Welfare, which ensures that the majority of the variables in the MBR are fairly reliable (Centre for Epidemiology, 2003).

From the MBR, information on ante and perinatal birth characteristics was retrieved. The birth characteristics from the MBR were defined as follows: *Small for gestational age (SGA)* was defined as birthweight <-2 SD of the mean weight for the gestational length (Maršál et al., 1996). *Preterm birth* was defined as being born before

gestational week 37, and *Very preterm birth* defined as born before gestational week 32. *Low birth weight* was defined as birthweight below 2500 g, and *Very low birth weight* as below 1500 g. *Apgar score* <7 at five minutes was defined as low in accordance with previous studies (Thorngren-Jerneck and Herbst, 2001). Information on *smoking during pregnancy* was obtained during the first and third trimester. Children of mothers who smoked on one or both of these occasions were compared to children of non-smoking mothers. Infant diagnoses in the MBR were complemented by information on *neonatal illness* retrieved from the child's medical record at the 3 year follow-up. Minor injuries during birth, diagnoses associated with SGA, and mild neonatal distress were not considered, whereas infections, hypoglycemia, anemia and moderate and severe congenital malformations etc. were included. Children with one or more diagnoses were compared to healthy children. The birth and pregnancy characteristics were finally combined to a *Non-optimal birth characteristics* score, in which children with one or more non-optimal birth factors were compared to children with no birth adversity. Information on maternal chronic illness was also retrieved from the MBR (study I).

Sociodemographic measures

SDR score

The SDR-score was used in study I. Socio-environmental data relating to the mother's alcohol consumption, education, employment, country of origin and information on cohabitation (i.e. whether the mother lived together with the child's biological father or not) was gathered when the child was 12 years old. In addition, information about chronic illness was collected from the Medical Birth Register (MBR). These six risk factors were weighted (alcohol consumption and education scoring 0-2, the other items 0-1) and joined together as a separate risk score derived for this study, called Sociodemographic Risk score (SDR score), ranging from 0 to 8. The elements of the SDR score are well known to influence the outcome measures used in this study, and thus, need to be controlled for.

Ethnicity/parental immigration status

Children of whom one or both parents were born abroad were compared to children whose both parents were born in Sweden (study II-IV*)*.

Genetic measures and analysis

The non-invasive and all-in-one Oragene® DNA Collection Kit (DNA Genotek) was used for the collection, stabilization and transportation of saliva samples. DNA was isolated according to the laboratory protocol for manual purification of DNA. Genotyping was carried out as previously described (Comasco et al., 2011). The genotyping call was blind to psychosocial data. In order to estimate the quality-rate of

genotyping errors, a random repetition of ~13 % of the sample was carried out; the comparison indicated no inconsistencies.

The genotypes were in Hardy-Weinberg equilibrium: (*5*-HTTLPR p=0.10; females p=0.51; males p=0.10, *BDNF* Val66Met p=0.77; females p=0.27; males p=0.16, COMT Val158Met p=0.87; females p=0.21; males p=0.320, MAOA-uVNTR females p=0.83). In study IV, dichotomous variables were created for the protective variants and risk variants of each genotype, respectively: *5*-HTTLPR, genotypes with the short allele versus the homozygous for the long allele; *BDNF* Val66Met, genotypes homozygous for the Val-allele versus carriers of the Met-allele; COMT Val158Met, genotypes homozygous for the Val-allele versus carriers of the Met-allele and MAOA uVNTR, carriers of high activity allele (34R and 44R) versus homozygous of the low activity allele (3R).

Data analysis

Study I

On the CBCL subscales, the 90th percentile was set as a cut-off. For the SDR score, the 88th percentile was set as a cut-off due to data distribution. Statistical significance was defined as (two-sided) $p \leq 0.05$. Pearson correlations were used to test for correlations between all of the questionnaires. To evaluate the stability of maternal symptoms of depression, bivariate analysis of EPDS and SCL-25 was performed. The corresponding Odds Ratio (OR) and Chi Square were used in data presentation. To examine differences in child behavior in relation to maternal depression, logistic regression was performed with CBCL scores as dependent variables. The independent variables were as follows: maternal symptoms of depression at 3 months (EPDS), at 12 years (SCL-25), or on both occasions (if applicable), the sex of the child, as well as background factors at baseline (LSS) and at the 12 year follow-up (SDR score). Data was presented with corresponding Odds Ratios (OR) and 95 % Confidence Intervals (CI). All statistical analyses were performed using IBM SPSS version 19 (IBM Corporation, Armonk, NY).

Study II

On the CBCL scales, the 90th percentile was set as a cut-off. Bivariate logistic regression analyses between genetic markers (*5*-HTTLPR and *BDNF* Val66Met) and psychological scales (EPDS, SCL-25, CBCL), as well as between scales, were performed. Multivariate analyses were also performed with CBCL scales as dependent variables and psychological scales, socio-environmental variables (LSS) and genetic markers as independent variables. Ethnic background (both parents born in Sweden, compared to one or both parents born abroad) and sex of the child were also controlled for. The multivariate analysis consisted of

conditional stepwise logistic regression considering full factorial models. However, since this procedure may choose models containing interactions without corresponding main effects, the models have been corrected for this, further evaluated, and reduced to include models with significant main effects and appropriate corresponding interactions. Results are presented with corresponding OR and 95% CI. All statistical analyses were performed using IBM SPSS version 19 (IBM Corporation, Armonk, NY).

Study III

On the LSS, Life Event and CBCL scales, the 90th percentile was set as a cut-off. Bivariate analyses between genetic markers (*5*-HTTLPR and *BDNF* Val66Met), psychological scale (EPDS), medical data (MBR), socio-environmental variables (LSS and parental unemployment) and life events, were performed using logistic regression. CBCL subscales were used as outcome variables, and each subscale was modelled separately. Multivariate analyses were also performed with CBCL scales as dependent variables and other scales as independent variables. Ethnic background and sex of the child were also controlled for. The multivariate analysis consisted of conditional stepwise logistic regression considering full factorial models. The procedure allows for models containing interactions without corresponding main effects. Therefore, the models have been corrected for this, further evaluated, and reduced to include models with either significant main effects and appropriate corresponding interactions or significant interactions and the corresponding main effects, though the main effects may not be statistically significant. Results are presented with corresponding OR and 95 % CI. A *p*-value <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS version 22 (IBM Corporation, Armonk, NY).

Study IV

A cumulative early life adversity index was calculated by combining the LSS, the EPDS and the CLES. Bivariate linear regression indicated somewhat similar effect sizes for the LSS, EPDS and CLES on internalizing and externalizing problems (β = 0.196-0.436), all 95 % confidence intervals overlapped (i.e. no statistically significant differences between the coefficients were present), and thus, they were all given equal weight. Multicollinearity was also tested for and was found to be weak to moderate (0.15-0.30) though not expected to have significant effect on the estimates. Therefore, no further adjustments were made. The scores on each instrument were standardized to allow summation.

Different statistical methodologies were used to examine resilience to behavioral problems at age 12, as previously done by Miller-Lewis et al. (2013). All three

methodologies examined internalizing and externalizing behavior problems separately. Initially, bivariate analyses were conducted in order to examine both proposed risk- and resilience factors. Only factors that were significantly associated with internalizing or externalizing behavior problems at age 12 were included in further analysis. This was done in order to avoid saturated models, especially with the interaction models.

The first model consisted of hierarchical multiple linear regression including statistical interactions between proposed risk- and resilience variables. In this model, significant interaction effects would possibly indicate a protective effect in the context of adversity. At step one, ethnicity and sex were entered as covariates. At step two, cumulative adversity was entered, and at step three proposed resilience factors were added. At the final step, interaction terms between cumulative adversity and all proposed resilience factors were entered.

The second model utilized linear regression to compute resilience residual variables. This was done by regressing the level of behavioral problems on the risk score (cumulative early life adversity). The residual scores were reverse-coded whereby higher scores indicated greater resilience with respect to behavioral problems (Miller-Lewis et al., 2013). Consequently, children who scored above the fitted regression line (that is, a "better-than-expected" outcome) were considered resilient, whereas children who scored below the fitted regression line (a "worse-than-expected" outcome) were assumed to be more vulnerable. The residuals were subsequently used as outcome variables in a following regression with proposed resilience factors entered as predictor variables. Covariates (ethnicity and sex) and proposed resilience factors were entered simultaneously into the model. Multivariate analyses were then run separately for the lowest and highest third of cumulative risk scores, allowing for comparison of effect sizes between children facing low and high adversity.

The third model used a person centered approach. Risk scores and behavioral problem scores were divided into thirds, enabling the formation of four groups as used initially by Masten et al. (1999): *resilient* group with a top third adversity score and a lowest third behavioral problem score, *maladaptive* group with a top third score of both adversity and behavioral problems, *competent* group scoring in the lowest third on both adversity and behavioral problems, and *highly vulnerable* group with a score in the lowest third on adversity but in the highest third on behavioral problems. The categorization was done for internalizing and externalizing problems, respectively. The middle third on either variable was not included in further analysis. This approach reduces the risk for non-distinct groups, as can be the case with a median split (Miller-Lewis et al., 2013). Next, comparison of groups was performed to examine whether

proposed resilience factors had different effects in children of low versus high adversity with high versus low functioning. All statistical analyses were performed using IBM SPSS version 22 (IBM Corporation, Armonk, NY).

Ethical considerations

The study outline was approved by the Ethics committee at the University of Lund in 1994 and 1998 and by The Regional Ethical Review Board in Linköping 2007 (Dnr M51-07). For the 12 year follow-up, written information was sent to all mothers, and a simplified information letter was enclosed to the child. The voluntary nature and the possibility to terminate participation at any time were stated. Participation took place only after informed consent was obtained, either written or verbal. The children were also informed verbally about the study and voluntary nature of their participation. Participating families received two movie tickets as a symbolic reward.

The following elements can afflict the integrity of study participants and were therefore carefully considered:

-The use of biological samples and genetic analyses. Saliva samples received a code upon collection and were handled and stored according to Act (2002:297) on biobanks in health care.

-Informed consent. An information letter was sent to the parents, and enclosed was a simplified information letter to the child. Participants could choose not to take part in all aspects of the project (for example, by not providing saliva for the genetic sample). They were also informed that they could end participation in the study at any time.

-Questionnaires regarding mental health and behavior. A research assistant was present in the classroom during the entire session, and the children were encouraged to ask questions if any aspects were unclear. All questionnaires have been used previously. Questionnaires were coded before data analysis and stored in a research archive.

-Research on children. The question was raised whether the parent as the legal guardian could gain access to the child's questionnaire. Participating children were guaranteed anonymity, and parents asking for detailed information on their child got the choice not to take part in the study. Results have only been presented on group level to avoid identification of individuals.

The results emanating from a longitudinal prospective study such as the SESBiC study adds valuable knowledge about risk and resiliency for behavioral problems in children and pre-adolescents. The importance of increased knowledge on psychosocial health in youths needs to be weighed against the possible inconvenience of participation.

Results and discussion

Study I

Prevalence and stability of maternal depressive symptoms

Prevalence rates of depressive symptoms at baseline and symptoms of depression and anxiety at the 12 year follow-up are found in Table 2. In bivariate analysis, symptoms of postpartum depression increased the risk for symptoms of depression and anxiety in mothers at the 12 year follow-up by three-fold. The prevalence of postnatal depression symptoms ranged between 10.4-12.0 %, which is in accordance with other Swedish population based studies (Rubertsson et al., 2005). At the 12 year follow-up, 18.2 % scored above the cut-off for symptoms of depression and anxiety. The risk for recurrent symptoms was doubled in women with symptoms of postpartum depression compared to women without depressive symptoms at baseline. An increased risk for subsequent depressive symptoms has been noted earlier (Josefsson and Sydsjö, 2007). The number of women who reported symptoms both postpartum and at follow-up was only 3.5 %; however a skewed dropout resulted in fewer women with symptoms of PPD taking part in the follow-up.

Table 2. Prevalence of depressive symptoms in mothers

Depressive symptoms	**N**
Baseline	204 (12.0 %)
Baseline (who took part in follow-up)	92 (10.4 %)
12-year follow-up (depression and anxiety)	161 (18.2 %)
Baseline and 12-year follow-up	31 (3.5 %)
No depressive symptoms	660 (75.2 %)

Note: Depressive symptoms at baseline measured by EPDS (Edinburgh Postnatal Depression Scale). Symptoms of depression and anxiety at follow-up measured by SCL-25 (Symptom Checklist 25).

Effects of maternal depressive symptoms

Correlations between maternal depressive symptoms and child behavioral problems were generally weak, ranging from r=0.064-0.334 (Pearson's r). The strongest correlation was found between SCL-25 and externalizing problems in boys and SCL-25 and internalizing problems in girls. In multivariate analysis, the mother's symptoms of depression and anxiety at the 12 year follow-up increased the risk for both internalizing type of problems, externalizing and total problems in the children four to five times (Table 3). This finding is in line with previous

studies (Araya et al., 2009; Brennan et al., 2000). It is plausible to consider that a depressed or anxious parent has difficulty providing adequate support for his or her child. Hereditary influences that increase the risk for child mental health problems must also be taken into consideration. However, as the reports on child behavior were provided by the mothers, there is an apparent risk for overestimation of child problems. Previous studies have indicated that depressed mothers tend to overestimate behavioral problems in their children (De and Kazdin, 2005; Van Der Toorn et al., 2010), but these discrepancies do not imply a major bias to the results (Van Der Toorn et al., 2010).

Table 3. Multivariate logistic regression predicting behavioral problems at age 12, study I.

	OR	95 % CI
Internalizing problems ≥ 90th percentile		
SCL-25	5.17	3.00- 8.91
LSS med	4.03	1.78-9.13
Sex	1.77	1.04-3.03
Anxious depressed ≥ 90th percentile		
SCL-25	4.13	2.45-6.99
LSS med	3.39	1.50-7.64
LSS psych	3.24	1.39-7.55
Sex	1.88	1.13-3.14
Withdrawn ≥ 90th percentile		
SCL-25	3.99	2.40-6.63
LSS med	2.45	1.07-5.63
Externalizing problems ≥ 90th percentile		
SCL-25	4.35	2.62-7.21
LSS psych	4.34	1.98 9.52
Sex	0.50	0.30 0.82
Total problems ≥ 90th percentile		
SCL-25	4.75	2.85 7.93
LSS med	3.18	1.41 7.30
LSS psych	2.77	1.20-6.40

Note: SCL-25 = Symptom Checklist 25, LSS = Life Stress Score.
Logistic regression. Dependent variable: Child Behavior Checklist. Independent variables (0 is used as a reference level): SCL-25 (0=mean score <1.75, 1=mean score>1.75), LSS (0<90 percentile, 1≥90 percentile), sex (boy=0, girl=1). Only significant factors are shown (p<0.05).

Symptoms of postpartum depression did not increase the risk for internalizing or externalizing problems in any of the models. This results is inconsistent with many previous studies, that have seen a persistent effect in children of mothers who suffered from postpartum depression (Hay et al., 2003;Murray et al., 1999). However, Josefsson & Sydsjö, (2007) did not find long term consequences for children whose mothers were depressed postpartum.

Effects of recurrent maternal depressive symptoms

The mothers were divided into four groups based on occurrence of depressive symptoms: "no depressive symptoms", "depressive symptoms at baseline", "depressive symptoms at follow-up" and "depressive symptoms on both occasions". Multivariate analysis showed an eight-fold increased risk for internalizing problems in children whose mothers reported symptoms of depression both at baseline and follow-up. Correspondingly, there was an increased risk for both externalizing and total problems. This finding indicates that children of mothers experiencing subsequent or concurrent depression are in need of support, and this need to be taken into account in clinical practice. The results adhere to the present literature showing the greater impact on child wellbeing of subsequent maternal depression or symptoms that persist over a long period of time (Brennan et al., 2000; Luoma et al., 2001).

Effects of socio-environment and sex

A high score on the medical subscale of the LSS increased the risk for both internalizing type of problems and total problems in the children (Table 3). A high score on the LSS psychological subscale at baseline increased the risk for externalizing, total and anxious depressive problems. However, social factors of the LSS, and SDR score, did not influence the risk for child behavioral problems in any of the models. The LSS social subscale contains information on education, work, living conditions and family, which are factors that may have changed during the 11.5 year period between baseline and follow-up. Thus, a more extensive form than the SDR-score would have been valuable to control for social factors at the 12 year follow-up.

Girls had an increased risk for internalizing problems compared to boys while boys had significantly more externalizing problems than girls (Table 3). This result was expected, and has been shown previously (Achenbach et al., 1991). In a review by Goodman et al (2011), the same magnitude was found between maternal depressive symptoms and internalizing problems in girls and externalizing problems in boys respectively (Goodman et al., 2011).

Study II

Effects of maternal symptoms of depression and anxiety

In bivariate analysis, maternal symptoms of depression and anxiety at the 12-year follow up increased the risk for both internalizing type of problems and externalizing problems by fivefold. With the screening cut-off of 10 on EPDS, there was an increased risk for externalizing and withdrawn depressive symptoms in the children. However, no effect was seen for either internalizing problems or the subscale anxious depressed. The higher cut-off of 13 reduced the number of EPDS positive mothers from 92 to 35. Moreover, using the clinical cut-off of 13 on the EPDS strengthened the association between maternal depressive symptoms postpartum and all CBCL scales.

In the stepwise multivariate analysis using a cut-off of 10 on EPDS, maternal symptoms of depression and anxiety at the child's age of 12 increased the risk for both internalizing and externalizing problems in the children (Table 4). When using a cut-off of 13 on EPDS an effect was seen also on the subscale anxious depressed. No separate significant effect was seen for EPDS using either of the two cut offs. A large body of research exists on the importance of maternal mental health for child development and wellbeing (Goodman et al., 2011). However, we have no information on the course of maternal depressive symptoms, and subsequent or persistent conditions could expose the child for more stress compared to a single depressive episode. Neither the screening cut-off nor the clinical cut-off resulted in an effect of postpartum depressive symptoms on child behavior at age 12. Studies on the impact of maternal depression on child behavior have used both clinical diagnoses and screening instruments like the EPDS and SCL-25 (Goodman et al., 2011). For the EPDS, different cut-offs have been used, and there is a concern about the specificity for MDD when the lower cut-offs are applied (Matthey et al., 2006). However, even lower levels of depressive symptoms have been shown to increase the risk for child behavioral problems (Conners-Burrow et al., 2015).

Effects of 5-HTTLPR and BDNF Val66Met

In bivariate analysis, the s/s genotype of the *5*-HTTLPR was associated with more internalizing type of problems at age 12 compared to l/l homozygotes. The same applied for externalizing problems. Differences between s/l and l/l carriers were not significant. In the multivariate analysis, s/s carriers were again at greater risk for internalizing problems (Table 4), but the effect on externalizing problems disappeared. Main effects of the *5*-HTTLPR on depression have been found previously (Cervilla et al., 2006; Clarke et al., 2010; Hoefgen et al., 2005; Kiyohara & Yoshimasu, 2010; Lesch et al., 1996), though most studies did not show any main effects (Eley et al., 2004; Kaufman et al., 2004; Kendler et al., 2005). There was no evidence for either

gene-environment interactions, or gene-gene-environment interactions in the present study. No effect was seen for *BDNF* Val66Met genotype on child behavioral problems in any of the models. The discrepancies between findings of gene-environment studies have been attributed to methodological differences between studies (Duncan and Keller, 2011).

Table 4. Multivariate logistic regression predicting behavioral problems at age 12, study II.

	OR	95 % CI
Internalizing problems ≥ 90th percentile		
SCL-25	5.72	3.30-9.91
5-HTTLPR	4.73	2.14-10.48
LSS	3.42	1.43-8.21
Anxious depressed ≥ 90th percentile		
5-HTTLPR	2.41	1.25-4.62
LSS	3.91	1.81-8.44
Withdrawn ≥ 90th percentile		
SCL-25	4.27	2.57-7.10
5-HTTLPR	2.30	1.18-4.51
Externalizing problems ≥ 90th percentile		
SCL-25	5.47	3.40-8.78
Sex	1.84	1.14-2.97

Note: SCL-25 = Symptom Checklist 25, *5*-HTTLPR = serotonin transporter gene-linked polymorphic region, LSS = Life Stress Score. Logistic regression. Dependent variable: Child Behavior Checklist. Independent variables (0 is used as a reference level): SCL-25 (0=mean score<1.75, 1=mean score>1.75), LSS (0<90 percentile, 1≥90 percentile), *5*-HTTLPR (s/s=0, l/l=1), sex (boy=0, girl=1). Only significant factors are shown (p<0.05).

Effects of life events

In bivariate analysis, traumatic life events increased the risk for internalizing and externalizing problems in the children. Similarly, an effect was seen for anxious depressed but not for withdrawn problems. No effect was seen for life events in any of the multivariate models. This indicates that in the present study population, the experience of traumatic life events did not explain as much of the variance as the other factors included in the models. Adverse life events have a well-documented impact on the risk for developing mental health problems (Chapman et al., 2004). Therefore, the absence of an effect on child internalizing and externalizing problems in the present study was not expected. Child experience of adverse life events was reported by the

mothers, in order to gain a more accurate estimate of early childhood events compared to self-reports. However, there are studies indicating discrepancies between childrens' and parents' self-reports on exposure to violence (Thomson et al., 2002). Parent-child discrepancies on reports of life incidence of traumatic events by the child's age of 12 have been shown in the SESBiC study (Tingskull et al., 2013). While the primary caregiver would have the best knowledge on the early life of children, it is possible that 12 year olds experience for example intrapersonal events outside of their parents' awareness.

Effects of socio-environment and sex

In both bivariate and multivariate analysis, maternal life stress at baseline increased the risk for internalizing type of problems in the children but not for externalizing problems (Table 4). Previous studies have shown effects of socio-environmental factors on both internalizing and externalizing problems (Amone-P'Olak et al., 2009; Vollebergh et al., 2006). However, the LSS includes a broader spectrum of factors like somatic and mental health problems which may possibly impact child behavior differently. In bivariate analysis, second generation immigrants had an increased risk for both internalizing and externalizing problems compared to children with a Swedish background, but this association did not remain in multivariate analysis. In a study using self-reports as well as reports from parents and teachers on the SESBiC population, second generation immigrants were found to have similar mental health statuses compared to children of Swedish-born parents (deKeyser et al., 2014). However, parental divorce and educational level were associated with behavioral problems in children regardless of parental immigration status. The results are in line with previous studies finding no discrepancies between second generation immigrants and children born in the host country (Alati et al., 2003).

In bivariate analysis, boys had an increased risk for externalizing problems compared to girls, whereas girls had an increased risk on the subscale anxious depressed. The effect for externalizing problems remained present in multivariate analysis, but not for anxious depressive problems (Table 4). Previous studies including adolescents have shown sex differences in prevalence rates of internalizing and externalizing problems (Angold et al., 2002; Keenan & Shaw, 1997).

Study III

Effects of maternal depression

Symptoms of postpartum depression stably predicted internalizing and externalizing problems in children both in bivariate and multivariate analysis. In multivariate analysis, maternal symptoms of postpartum depression more than doubled the risk of internalizing problems, while the effect for aggressive problems disappeared (Table

5). The present study showed an effect of postpartum depression three years after birth, indicating not only immediate effects, but also more persistent consequences. Previously published results on the participants of the SESBiC-study showed no effect of postpartum depression on behavior in preadolescence (Agnafors, Sydsjö, Dekeyser, & Svedin, 2013a). Since no assessment of maternal depressive symptoms at the 3 year follow-up was used, there is no way to discriminate between depressive symptoms demarcated to the postpartum period and recurrent conditions. Children of mothers experiencing subsequent depressive episodes presumably experience greater strain compared to children of mothers with single episode depression. However, these findings may indicate a strong chance for child recovery.

Effects of 5-HTTLPR and BDNF Val66Met

In bivariate analysis, carriers of the Val/Met genotype of the *BDNF* Val66Met showed an increased risk of problems on the anxious depressive subscale compared to Val/Val carriers. This finding is in accordance with previous studies, that have shown an association between the Met-allele of the *BDNF* Val66Met and an increased risk for depression (Aguilera et al., 2009). No other effects of the *5*-HTTLPR or *BDNF* Val66Met polymorphisms were seen. For the externalizing scales, there were no influences from either *5*-HTTLPR or *BDNF* Val66Met polymorphisms. In multivariate analysis, no genetic main effects or gene-(gene)-environment effects remained. Moreover, Pearson's correlations were run in order to rule out effects due to gene-environment correlations, but no such associations were found.

To our knowledge, previous studies on the *5*-HTTLPR and *BDNF* Val66Met gene-environment interaction have not examined internalizing and externalizing problems in children as young as age 3. Studies have been conducted on infants and preschool children assessing either *5*-HTTLPR or *BDNF* Val66Met polymorphisms separately or with outcomes other than behavioral problems (Cicchetti et al., 2011; Luijk et al., 2011; Luthar et al., 2000; Willoughby et al., 2013). However there is no substantial body of research on *5*-HTTLPR and *BDNF* Val66Met effects on small children.

Moreover, the type of adversities used in the interaction models might impact the results. The experience of adverse life events is limited at the young age of 3, which possibly affects the presence of gene-environment interactions at this age. Methodological differences have been claimed as one of the major reasons for discrepant results in the field (Duncan and Keller, 2011). In particular, Hosang et al (2014) posit that the interaction between BDNF and childhood adversity might be developmentally sensitive, and thus not evident during childhood and adolescence (Hosang et al., 2014). In summary, the present study adds to the null-findings on gene-environment interactions of *5*-HTTLPR and *BDNF* Val66Met.

Table 5. Multivariate logistic regression predicting behavioral problems at age 3, study III.

	OR	95.0 % CI
Internalizing ≥ 90th percentile		
EPDS	2.93	1.60-5.39
Life events	2.26	1.03-4.98
Parental unemployment	2.19	1.21-3.99
Parental immigration status	2.17	1.15-4.10
Anxious depressed ≥ 90th percentile		
EPDS	2.63	1.32-5.23
Life events	3.80	1.77-8.19
Parental immigration status	3.05	1.57-5.91
Withdrawn ≥ 90th percentile		
EPDS	2.75	1.41-5.36
Life events	3.56	1.66-7.63
Parental immigration status	2.79	1.45-5.38
Externalizing ≥ 90th percentile		
EPDS	2.60	1.39-4.84
Life events	4.02	1.99-8.12
Parental unemployment	0.32	0.18-0.56
Aggressive ≥ 90th percentile		
Life events	3.52	1.70-7.29
Parental unemployment	0.36	0.20-0.65
Destructive ≥ 90th percentile		
EPDS	2.79	1.49-5.23
Life events	2.47	1.14-5.38
Parental unemployment	0.32	0.18-0.56
Sex	1.99	1.18-3.38
Apgar	8.54	1.92-37.95

Note: EPDS = Edinburgh Postnatal Depression Scale. Multiple logistic regression. Dependent variables: Child Behavior Checklist. Independent variables (0 is used as a reference level): EPDS (0≤9, 1≥10), Life Events and LSS (0<90th percentile, 1≥90th percentile), Parental unemployment (0=both parents employed, 1=one or both parents unemployed), Parental immigration status (0=both parents born in Sweden, 1=one or both parents born abroad), sex (0=girls, 1=boys). Only significant factors are shown (p<005).

Effects of life events

In bivariate analysis, experience of life events was found to be a stable predictor of internalizing as well as externalizing problems both for the broadband scales and for the subscales. In multivariate analysis, experience of multiple life events was the strongest predictor of internalizing problems, giving almost four times the risk of anxious depressive problems (Table 5). Experience of multiple life events was also significantly associated with externalizing problems, increasing the risk up to four times. While most gene-environment studies assess only more severe adversities or life events (Caspi et al., 2003), the present study included a broader spectrum of events such as changing place of residence or entering day-care which could impact the interaction effect. Experience of life events early in childhood most likely impacts the whole family. Thus it is plausible to consider both main effects and the involvement of mediating factors in the association between early experience of life events and behavioral problems.

Effects of pregnancy and birth related factors

No effect was seen for prenatal or birth related factors on internalizing problems at age 3 in either bivariate or multivariate analysis. Both non-optimal birth characteristics and a low Apgar score at birth carried a slight increased risk of destructive problems in bivariate analysis, but no other effect was seen for the other pregnancy and birth related variables. In multivariate analysis, the effect remained present for a low Apgar score on destructive problems; however the groups were small in size and the result must thus be interpreted cautiously (Table 5). Pregnancy and birth-related factors were hypothesized to have a more pronounced impact on behavioral problems at age 3. The present finding was in line with studies by Silva et al (2014) and Wagner et al (2009) showing limited effects of obstetrical and neonatal complications on externalizing problems (Silva et al., 2014; Wagner et al., 2009). At the same time, many studies have found support for developmental and behavioral consequences of pregnancy and birth complications (Bhutta et al., 2002; Marceau et al., 2013). Moreover, the SESBiC-study includes 88 % of the children born in the catchment area, and there is no information on the 12 % that chose not to take part. Mothers who experienced recent pregnancy or birth related complications might feel reluctant to engage as a study participant. Moreover, children who suffered from pregnancy or birth related complications could belong to the group excluded from the study due to learning disabilities.

Effects of socio-environment and sex

Maternal life stress at baseline increased the risk for internalizing and anxious depressive problems in bivariate analysis, but results were not significant for withdrawn problems. The same applied for externalizing problems, where an

increased risk was seen for externalizing and destructive problems but not for aggressive problems. No effect was seen for early life stress score in multivariate analysis. Parental unemployment increased the risk for internalizing as well as externalizing type of problems in bivariate analysis. In multivariate analysis, children with one or both parents unemployed had an increased risk of internalizing problems, though significance was not reached for the subscales. For externalizing problems parental unemployment increased also the risk for the subscales (Table 5). Unemployment have been shown to be associated with many negative circumstances for families (Ström, 2003). More specifically, unemployment might lead to social and financial adversities, and socioeconomic disadvantage has been shown to impact child well-being and socioemotional development (Bradley and Corwyn, 2002).

In bivariate analysis, children of immigrants had an increased risk of internalizing problems apparent also on both subscales (Table 5). Likewise, parental immigration status was significantly linked to externalizing and destructive problems, but not aggressive problems. In multivariate analysis, children of immigrants were at greater risk of internalizing problems compared to children of non-immigrants. Thus, a clear pattern emerged in multivariate analysis which showed an effect of parental immigration status on internalizing problems, but not on externalizing problems. An increased prevalence of behavioral problems has been observed in preschool aged children of immigrants (Jansen et al., 2010); however, most studies in this field includes refugees but not second generation immigrants.

Boys showed an increased risk of destructive problems compared to girls, but no other sex differences were detected (Table 5). No sex differences were found for internalizing problems. Previous studies have shown minimal differences in psychological adjustment between the sexes during infancy, with different patterns emerging during the preschool ages (Prior et al., 1993). At preschool ages, boys showed less motor and language skills compared to girls, whereas differences in behavioral and adjustment problems became evident during the early school years (Prior et al., 1993). Age 3 could thus be too early to detect behavioral differences between boys and girls.

Study IV

Variable centered models

Initially, bivariate analyses were run in order to examine both proposed risk- and resilience factors. Only factors that were significantly associated with internalizing or externalizing behavioral problems at age 12 were included in further analysis. This was done in order to avoid saturated models, especially with the interaction models. The cumulative adversity index increased the risk for both internalizing and

externalizing problems as expected. No effect was seen for *BDNF* Val66Met, MAOA-uVNTR or COMT Val158Met and thus they were not included in further analysis. The first model used hierarchical multiple regression, performed for internalizing and externalizing problems respectively. Effect sizes for all interactions were very small and thus not likely to be of clinical significance. The second model used resilience residuals, created by regressing the level of behavioral problems on the risk score (cumulative early life adversity). Regarding internalizing problems 553 children (62.2 %) had better outcomes than expected, that is, a positive residual. Correspondingly, for externalizing problems 560 children (63.0 %) had a better-than-expected outcome. This result is in line with previous studies that have noted levels around 60 % (Miller-Lewis et al., 2013). Next, the residuals were used as outcome variables in a following regression with proposed resilience variables entered as predictor variables. Multivariate analyses were then run separately for the lowest and highest third of cumulative risk scores.

Effects of internal characteristics

In the interaction models, the l/l genotype of the *5*-HTTLPR was associated with a lower risk for both internalizing and externalizing problems. Good social capacity in children predicted lower internalizing and externalizing problems. An easy temperament decreased the risk for externalizing problems, and an interaction effect was seen between temperament and cumulative life adversities on internalizing as well as externalizing problems. In the residual models, the l/l genotype of the *5*-HTTLPR was associated with lower residual scores for internalizing problems both in the total sample and in the low adversity group. For externalizing problems, the l/l genotype was associated with lower problems in the total group. Good social functioning in children had a protective effect in all three groups for both internalizing and externalizing residual scores. An easy temperament implied a small positive effect, both for internalizing and externalizing problems in the total sample and in the high adversity group. The results of the interaction and residual models are found in Table 6.

Quite unexpectedly, the l/l genotype of the *5*-HTTLPR was associated with a lower risk for internalizing problems in the whole group and in the low adversity group but this association was not found in the high adversity group. Correspondingly, there was no interaction effect between early life cumulative adversities and the *5*-HTTLPR. This finding is in line with the majority of the existing literature regarding the association between the l-allele and a lower risk for mental health problems as compared to the s-allele (Lesch et al., 1996). The present results indicated a protective effect of the l/l-genotype; however, the association does not seem to be specific for individuals experiencing adversity. Criticism has been put forth for including general

adversity in the gene-environment models rather than testing specific trauma such as childhood maltreatment (Duncan and Keller, 2011). The lack of a gene-environment effect in the present study could be explained by additional experience of stressful life events between ages 3 and 12 that were not considered in the present study. Such an interaction was not, however, present in a previous study on the same population (Agnafors et al., 2013b). The main effect of the 5-HTTLPR on internalizing problems was consistent over all three models, indicating an accountable impact.

Temperament was found to be specifically protective for children facing high adversity compared to the other factors that were equally beneficial for all children regardless the level of adversity. Although the effects in the present study were small, temperament has shown to be associated robustly with resilient outcomes (Kim et al., 2013; Masten and Coatsworth, 1998). Contrarily, social functioning was found to be more of a general resource factor, which was associated with a lower risk for behavioral problems in both high and low adversity groups.

Effects of family factors

In the interaction models, maternal sense of coherence had a protective effect on child behavioral problems. In the residual models, a high maternal sense of coherence was associated with a lower residual score for both internalizing and externalizing problems in the whole group. No significant effects were seen for SOC either in the low or high adversity groups, possibly because of smaller sample sizes. However, for internalizing problems the p-value approached significance (p=0.053), which could indicate differences between impact for children experiencing high and low adversity.

Effects of ethnicity and sex

Ethnicity was not found to influence either internalizing or externalizing problems in the interaction and residual models. In the interaction models, girls had an increased risk for internalizing problems while boys had an increased risk for externalizing problems. In the residual models, female sex increased the risk for internalizing problems in the whole group and in the high adversity group. Male sex increased the risk for externalizing problems in the whole group and the low risk group. These findings are in line with previous studies on sex differences of behavioral problems during pre-adolescence (Angold et al., 2002; Keenan and Shaw, 1997).

Table 6. Multiple regression predicting behavioral problems at age 12. Interaction models and standardized resilience residuals, variable centered models, study IV.

Internalizing problems				
Interaction models		Resilience residuals		
β Total group (n=889)		**β** Total group (n=889)	**β** Low risk (n=246)	**β** High risk (n=238)
Sex (c)	0.89	0.18	NS.	0.42
SOC (m)	-0.05	-0.01	NS.	NS.
Social functioning (c)	-0.37	-0.08	-0.09	-0.08
Temperament (c)	NS.	-0.02	NS.	-0.04
5-HTTLPR (c)	-0.93	-0.22	-0.23	NS.
CELA x temperament	-0.04		NA.	
Externalizing problems				
Interaction models		Resilience residuals		
β Total group (n=889)		**β** Total group (n=889)	**β** Low risk (n=246)	**β** High risk (n=238)
Sex (c)	-1.01	-0.20	-0.15	NS.
SOC (m)	-0.06	-0.01	NS.	NS.
Social functioning (c)	-0.35	-0.07	-0.05	-0.08
Temperament (c)	-0.14	-0.03	NS.	-0.05
5-HTTLPR (c)	-0.86	-0.17	NS.	NS.
CELA x temperament	-0.06		NA.	

Note: Linear regression models predicting child internalizing and externalizing problems. The residual scores are standardized and therefore effect sizes ranges between -2 and +2. CELA = Cumulative Early Life Adversities, SOC = Sense of Coherence, *5*-HTTLPR = serotonin transporter gene-linked polymorphic region. (m) = maternal variable, (c) = child variable. Dependent variables: CBCL (internalizing and externalizing problems). Independent variables: Maternal SOC, child social functioning, child temperament. Categorical variables: *5*-HTTLPR (0=l/l, 1=s-carriers), Sex (1=boys, 2=girls). Only significant factors are shown (p<0.05).

Person-centered approach

By combining the lowest versus highest tertiles of risk scores and behavioral problems for internalizing and externalizing problems respectively, four groups were generated: *Resilient*, *Maladaptive*, *Competent* and *Highly vulnerable*. Chi-square statistics revealed differences between groups with respect to behavioral problems of both internalizing (χ^2=474.01, p<0.001) and externalizing problems (χ^2=445.18, p<0.001). This results shows that a high level of adversity is associated with a high degree of behavioral problems, and thus resilience in terms of mental health can be considered a "better-than-expected" outcome (Miller-Lewis et al., 2013). Generally, differences

between the four groups were small. The group of competent children scored higher on the majority of proposed protective factors, while the maladaptive group had the lowest scores.

Effects of internal characteristics

For internalizing problems, highly vulnerable children had a significantly larger proportion of s-allele carriers of the 5-HTTLPR compared to resilient and competent children. Regarding externalizing problems, there were no significant differences in genotype distribution between the groups. The easiest temperament was found among competent children, followed by resilient, highly vulnerable and maladaptive children; however, the difference between the resilient and highly vulnerable groups was not significant. This pattern was shared between internalizing and externalizing problems. For internalizing problems, the scores for social functioning were lowest in the maladaptive group. With regard to externalizing problems, maladaptive children had lower scores of social functioning compared to all other groups. Moreover, competent children had significantly higher scores on social functioning compared to highly vulnerable children. Results from the person centered model are found in Table 7.

Effects of family factors

Regarding internalizing problems, the highest scores of sense of coherence was found in mothers of competent children (Table 7). There was no significant difference between resilient and maladaptive children in maternal sense of coherence. For externalizing problems, mothers of competent and highly vulnerable children had significantly higher SOC scores compared to resilient and maladaptive children. This finding is interesting, as a higher sense of coherence was found in competent and highly vulnerable children (the two groups comprising individuals with a low adversity index) in comparison with resilient and maladaptive children (comprising individuals with a high adversity score). Thus, there seem to be an association between the level of adversity and the level of SOC that reflects either a direct association or a reciprocal relationship between negative experiences and sense of coherence. Volanen et al. (2007) found that experience of negative life events can impact SOC levels. Since the present study uses a measure of adversity that includes maternal symptoms of PPD, early life stress and child experience of life events by the age of 3, the joint score could very well be affecting maternal wellbeing. It must be noted, however, that effect sizes for maternal SOC at age 3 were small, indicating limited importance in clinical work.

Table 7. Planned contrast for adaption groups, person centered model, study IV

Adaption groups for internalizing problems			
A n = 106	B n = 124	C n = 159	D n = 87
Resource variable	**Planned contrast** **a/b, a/c, a/d, b/c, b/d, c/d**		
SOC (m)	a/c <0.001, a/d 0.001, b/c <0.001, b/d <0.001, c/d 0.001		
Social functioning (c)	a/b <0.001, b/c <0.001, b/d 0.012, c/d <0.001		
Temperament (c)	a/b <0.001, a/c 0.006, b/c <0.001, b/d 0.001, c/d 0.004		
5-HTTLPR (c)	a/d 0.011, c/d 0.018		
Sex (c)	a/b 0.014, a/c 0.005, a/d 0.002		
Ethnicity (c)	a/c 0.011, a/d 0.001, b/c <0.001, b/d <0.001		
Adaption groups for externalizing problems			
A n = 77	B n = 131	C n = 150	D n = 74
Resource variable	**Planned contrast** **a/b, a/c, a/d, b/c, b/d, c/d**		
SOC (m)	a/c <0.001, a/d 0.002, b/c <0.001, b/d <0.001		
Social functioning (c)	a/b <0.001, b/c <0.001, b/d <0.001, c/d 0.027		
Temperament (c)	a/b <0.001, a/c 0.012, b/c <0.001, b/d 0.001, c/d 0.004		
5-HTTLPR (c)	NS.		
Sex (c)	a/c 0.001, b/c 0.003, c/d 0.029		
Ethnicity (c)	a/c 0.001, a/d 0.022, b/c <0.001, b/d 0.012		

Note: T-test results. Adaption groups: A. Resilient (high risk + low problems), B. Maladaptive (high risk+ high problems), C. Competent (low risk + low problems), D. Highly vulnerable (low risk + high problems). SOC = Sense of Coherence, *5*-HTTLPR = serotonin transporter gene-linked polymorphic region. (m) = maternal variable, (c) = child variable. Categorical variables: *5*-HTTLPR (0=l/l, 1=s-carriers), Sex (1=girls, 2=boys) and Ethnicity (0=one or both parents born abroad, 1= both parents born in Sweden).

Effects of ethnicity and sex

The resilient and maladaptive groups comprised significantly more second generation immigrants compared to the competent and highly vulnerable groups both for internalizing and externalizing problems. It is thus plausible to consider an association between a high degree of early life adversity and ethnicity. The parental length of stay in Sweden could possibly impact the degree to which immigration status is associated with child behavior. Moreover, language difficulties could moderate the risk for child behavioral problems. However, there was no consistent pattern for ethnicity over the models. For internalizing problems, there were a significantly larger proportion of boys in the resilient group compared to the other groups. This indicates that even if boys experience a high degree of childhood adversity, they are less likely to develop internalizing problems than girls. For externalizing problems, there were significantly more girls in the competent group than in the other groups.

Complementary analyses – continuity of behavioral problems

In logistic regressions controlled for sex, continuity of behavioral problems between ages 3 and 12 was examined. Analyses indicated both homotypic and heterotypic continuity of symptoms as measured by CBCL broadband scales. The strongest association was found for homotypic continuity of externalizing problems, where problems at age 3 increased the risk for subsequent problems seven fold (Table 8).

Table 8. Logistic regression. Continuity of behavioral problems from age 3 to 12 measured by CBCL broadband scales.

	OR	95 % CI	*p*
Internalizing problems at age 12 ≥ 90th percentile			
Internalizing problems	4.396	2.280-8.476	<0.001
Sex	0.560	0.323-0.972	0.039
Externalizing problems	5.102	2.661-9.782	<0.001
Sex	0.505	0.289-0.883	0.016
Externalizing problems at age 12 ≥ 90th percentile			
Internalizing problems	4.081	2.163-7.699	<0.001
Sex	1.615	0.975-2.673	0.063
Externalizing problems	7.221	4.007-13.015	<0.001
Sex	1.467	0.876-2.454	0.145

Note: CBCL = Child Behavior Checklist. Logistic regression predicting internalizing and externalizing problems at age 12. Dependent variables: CBCL internalizing and externalizing problems at age 12. Independent variables: CBCL internalizing and externalizing problems at age 3 (0<90th percentile, 1≥90th percentile).

In line with previous studies, the present results indicated homotypic stability of behavioral symptoms during childhood (Costello et al., 2003; Mesman et al., 2001). Moreover, the results indicated heterotypic stability, both for internalizing and externalizing problems; however, co-occurrence of behavioral problems was not controlled for. Heterotypic stability from externalizing to internalizing problems is well-established (Mesman et al., 2001; Pihlakoski et al., 2006; Roza et al., 2003). Anxiety in childhood has been shown to increase the risk for conduct disorder in adolescence (Costello et al., 2003); however, other studies found internalizing problems to have a protective effect on preadolescent externalizing problems (Mesman et al., 2001; Pihlakoski et al., 2006).

GENERAL DISCUSSION

Summary of findings

The main aim of the present thesis was to investigate the association between biological, psychological and social factors of risk and resilience and behavioral problems in a large cohort of children in Sweden. More specifically, the aim was to investigate the impact of both more well-known and less well-established factors of risk and resilience for mental health in children at different ages. Study I focused specifically on stability of maternal depressive symptoms and its impact on child behavior at age 12. Study II investigated the impact of gene-environment interactions of *5*-HTTLPR and *BDNF* Val66Met and experience of life events together with symptoms of maternal depression and anxiety on child behavior at age 12. Study III examined the impact of gene-environment interactions of *5*-HTTLPR and *BDNF* Val66Met and life events together with symptoms of maternal depression and birth characteristics at age 3. Study IV used the risk factors identified in studies I-III to investigate factors of resilience to behavioral problems at age 12.

The present study is strengthened by the longitudinal perspective and prospective design. It combines register data (MBR) with well-known instruments (CBCL, EPDS and SCL-25), structured interviews (LSS) and DNA samples. The size of the study population allows for complex statistical methods without the limitation of restricted statistical power. Moreover, the same informants were used at baseline as well as at the follow-ups.

The main findings are summarized in the following paragraphs. The studies showed that depressive symptoms in mothers increased the risk of both internalizing and externalizing problems in children. Carriers of the s/s genotype of the *5*-HTTLPR were at increased risk for internalizing problems at age 12 compared to l/l carriers. No gene-environment interaction effect between *5*-HTTLPR, *BDNF* Val66Met and experience of life events was seen on internalizing or externalizing problems at either 3 or 12 years of age. Socio-environmental factors such as early life stress, parental immigration status and parental unemployment were important predictors of both internalizing and externalizing problems. As expected, boys had an increased risk for externalizing problems and girls had an increased risk for internalizing problems. Both individual factors, such as genotype and temperament, as well as family factors, such as maternal sense of coherence, were associated with resilient outcomes with regard to behavior at age 12; however, effect sizes were small.

Maternal symptoms of depression

The results from the studies in the present thesis stress the importance of maternal mental health for child wellbeing. In study I it was shown that children, whose mothers reported depressive symptoms both postpartum and 12 years later, were at an eight-fold increased risk of internalizing problems compared to children of mothers without depressive symptoms. We found a five-fold increased risk for behavioral problems in children whose mothers reported symptoms of depression and anxiety at the 12 year follow-up, but no long term effect of postpartum depressive symptoms on child behavior. When looking at the 3 year follow-up, maternal depressive symptoms postpartum increased the risk of internalizing problems confirming that concurrent- or in this case- recent problems exert a substantial risk for behavioral problems. Even though maternal symptoms of depression were a stable predictor of child behavioral problems in the present studies, a few exceptions emerged. In study II, concurrent symptoms of maternal depression and anxiety were not shown to increase the risk for anxious problems in the children. In study III, symptoms of postpartum depression increased the risk for both internalizing and externalizing problems, with the exception of aggressive problems. However, the final model for aggressive problems explained only six percent of the variance, which is low in comparison with the other models. There is a large body of research showing the importance of maternal mental health for child wellbeing and development. Studies have also examined different possible moderators in the association between maternal depression and child behavioral problems (Goodman et al., 2011). Both socioeconomic factors, gender and relational factors such as attachment pattern have been discussed (Goodman et al., 2011; Milan et al., 2009). From a developmental point of view, maternal depression may have different consequences for the children at different ages and stages of development. During the first year of life, the main developmental task of the child is attachment to the caregiver. Maternal sensitivity to the infant, but also other behaviors such as positive attitude and emotional support has been shown to facilitate attachment security (De Wolff and van Ijzendoorn, 1997). A depressed parent might not be able to provide the emotional availability that is required for the development of a secure attachment, increasing the risk for secondary adjustment problems. During preadolescence, the main developmental tasks are to form and maintain relations with friends and to manage school and leisure activities. At this stage, the child is not as dependent on the primary caregiver as the infant, and other adults can provide adequate support that to some extent might act as buffers in an adverse environment (Miller-Lewis et al., 2013). It is thus plausible to consider maternal depression during early life of the child as more harmful with regard to child development. However, in the present thesis, no long term effect of PPD on child behavior was seen. We consider it a promising sign that children of mothers with depressive symptoms only postpartum seem to have developed satisfactorily, and these children are not at a

greater risk of presenting behavioral problems than the children of mothers who did not suffer from postnatal symptoms of depression.

Genotypes

The lack of success by replication studies of the early and promising studies by Caspi et al. has given rise to much criticism. The hope for genetic research elucidating the causes of psychiatric disease has diminished with the lack of replicability. However, given the multifactorial etiology of psychiatric illness, with heritability accounting for around 30-80 % (Kendler, 2013), and the estimation that single genetic polymorphisms account for a very small proportion (less than 0.1 %) of phenotypic variance (Gratten et al., 2014; Munafò et al., 2014), the reality probably concords better with polygenetic and complex interactions between genetic and environmental factors.

Both Munafó et al (2009) and Duncan and Keller (2010), point to the risk of false positive results (type I-errors) in the gene-environment studies in psychiatry due to the large possible number of statistical tests when interaction terms are included in the analyses (Duncan and Keller, 2011; Munafò and Flint, 2009). Moreover, as stated by Duncan and Keller, there is an apparent risk for publication bias, as the incentives to publish null findings are much lower among both authors and editors. Nonetheless, in their review of 103 candidate gene-environment interaction studies in psychiatry, Duncan and Keller conclude that gene-environment effects are most likely common, and important to understand the etiology of psychiatric disorders. However, to separate the wheat from the chaff, there is a call for well-powered direct replication studies (Duncan and Keller, 2011). The SESBiC study used a large population based sample and virtually the same set up as previous studies with regard to phenotypic variables, genetic polymorphisms, statistical model, environmental moderator and inclusion of both sexes. The results should thus be useful in future meta-analytical compilations.

A main effect of the *5*-HTTLPR on internalizing symptoms was found in study II. However, no interaction effect was seen at either 3 or 12 years of age. The non-relation to experience of life events became even clearer in study IV, where the l/l genotype was associated with resilience to internalizing problems in the whole sample and in the low risk group, but this association was not seen in children facing a high degree of early adversity. Similar results with genotype predicting resilient outcomes for non-maltreated children, but not for maltreated children has been found (Cicchetti and Rogosch, 2012), however these results are not in accordance with the typical gene-environment interaction studies in psychopathology. The results thus do not adhere to the proposed diathesis-stress model. Two important concerns can be raised

from these findings. First: there is concern about the reliability of the measure of life events, which will be discussed further in the following paragraph. Secondly: there is concern about the age at investigation of life events. At the age of 3, the number of life events experienced is generally limited. Additionally, the finding raises the question as to whether the gene-environment interaction effect of *5*-HTTLPR and *BDNF* Val66Met varies across life time and calls for replication studies specifically in children.

Differential susceptibility versus diathesis-stress

The present thesis builds upon the gene-environment interaction as proposed in the diathesis-stress model. However, the differential susceptibility hypothesis assume that rather than predisposing for an increased vulnerability, the genetic polymorphisms work as plasticity agents (Belsky, 1997; Belsky & Pluess, 2009). This means that they do not only convey an increased risk, but also bring about an increased probability for positive adaption in the context of a positive environment (Belsky & Pluess, 2009). Similarly, Boyce and Ellis (2005) proposition of biological sensitivity to context suggests that it is environmental rather that genetic influences that impact individuals' sensitivity to context in a developmental perspective (Boyce and Ellis, 2005). Integrating different models of gene-environment interplay is important to promote the understanding of the complex nature of mental health and behavior.

While the candidate gene-environment model is a hypothesis-based approach to understanding the genetic influences on mental health, another approach is Genome Wide Association Studies (GWAS). GWAS searches the genome for a large number of common genetic variants (SNPs) that are related to a specific phenotype. These studies have rendered important information on candidate genes for psychiatric disorders, but just like gene-environment interaction studies, results are not consistent (Collins and Sullivan, 2013).

Life events

Experience of life events at age 12 did not increase the risk for behavioral problems to the expected extent. There is consensus on the potentially deleterious effects of stressful or adverse life events on child mental health and behavior (Chan, 2013; Chapman et al., 2004). In the present study, mothers reported on child experience of traumatic events. At the age of 12, there could be a risk for discrepancies in the agreement on these types of reports, as parents might not be aware of especially inter-personal events experienced by the child. In fact, a comparison between parental reports and self-reports on life incidence of traumatic events by age 12 in the SESBiC cohort, showed low to moderate agreement (Tingskull et al., 2013). The use of child reports might thus have rendered other results. However, we expected mothers'

reports to be more accurate on the experiences from early childhood, during which time the children are too young to remember. Also, only the actual occurrence of an event was investigated even though the form assesses both how much the event upset the child at the time it occurred and to what degree it bothered the child at the time the form was completed. As individuals respond differently to traumatic events (in accordance with the diathesis-stress model), this information could be important to assess the degree of impairment caused by the occurrence of an event. At age 3, experience of life events, as reported by the mothers, resulted in an increased risk for both internalizing and externalizing problems. The absence of a gene-environment effect at age 3 is possibly related to the use of more general events and common life transitions, whereas the majority of positive gene-environment studies on *5*-HTTLPR and *BDNF* Val66Met used more severe experiences such as childhood maltreatment (Caspi et al., 2003).

Factors of resilience

In general, the effects of the proposed resilience factors were small. However, some of the factors were consistently associated with better outcomes over the models despite the time elapsed. At pre-school age when the resilience factors were assessed, the main developmental tasks for the child are the development of symbol language, differentiating the self from the outer world, exploring the outer world, and learning how to cooperate. Maternal resource factors, such as sense of coherence, could be of importance in order to meet the emotional needs of the child and help the child to cope with difficulties. Individual factors such as temperament and social abilities could facilitate interpersonal skills. Targeting resilience factors with an impact on child mental health and wellbeing could facilitate the understanding of the developmental mechanisms, in particular in individuals exposed to risk.

As the fourth wave of research on resilience arises, there is a call for integrating past theory and findings with genetic data in multiple levels models (Davydov, Stewart, Ritchie, & Chaudieu, 2010; Luthar et al., 2000; Masten, 2007). Moreover, given the knowledge on the number of factors which influence mental health and wellbeing, varied pathways to resilient outcomes (equifinality) are to be expected. Including factors of the exosystem, in particular, would likely lead to a better understanding of the possible developmental paths to resilience.

Sociodemographic factors

Sociodemographic factors increased the risk for behavioral problems in all studies. Interestingly, while a few factors were common for internalizing and externalizing problems in study III, some factors were more specific for each broadband scale. While unemployment mainly had an impact on externalizing problems, parental

immigration status increased the risk for internalizing problems. Previous studies reported a stronger association between SES and externalizing problems than internalizing problems (Amone-P'Olak et al., 2009), however other studies reported the opposite association (Vollebergh et al., 2006). In a meta-analysis, Reiss et al concludes that low SES increases the risk particularly for externalizing problems, which is possibly explained by a greater endogenous etiology of internalizing disorders (Reiss, 2013). Moreover, they concluded a low household income to be one of the strongest socioeconomic risk factors for mental health problems among children and adolescents. However, mediating factors such as maternal depression have been suggested.

The present study found an increased risk for internalizing problems at age 3 in children of immigrants. An Australian study on internalizing and externalizing problems showed no differences between children of immigrants and their Australian counterparts (Alati et al., 2003). However, cultural differences in reporting of behavioral problems also need to be considered regarding differences between children of immigrants and Swedish born parents. With regard to the human ecology model elaborated by Ungar et al (2013), it is plausible to consider that immigrants might not have access to the same resources as Swedish-born individuals (e.g. social network, language etc.) which can impede adjustment and thereby increase the risk for mental health problems. In summary, the findings of the present thesis are important, not only because of restricted social mobility for socially disadvantaged individuals and the transmission of poverty over generations, but also in the light of increasing socioeconomic inequalities in society. The impact of sociodemographic factors on childhood and adolescent mental health thus needs to be recognized.

Comorbidity and continuity

In general, the mothers reported low frequencies of behavioral problems both at age 3 and age 12. The low frequency at age 12 was confirmed in self-reports (Strenghts and Difficulties Questionnaire) by the children. This finding is in line with previous studies, which point to the lowest prevalence of depression at age 12 (0.4 %) when mental health was examined in ages 9-16 (Costello et al., 2003). At age 3, we found a prevalence of 8 % for internalizing problems and 9 % for externalizing problems which is somewhat lower compared to previous studies (Tick et al., 2007).

Previous studies have shown a high degree of comorbidity between internalizing and externalizing problems in children and adolescents (Angold et al., 1999; Laucht et al., 2009). While the risk factor pattern was similar for the subtypes of internalizing problems (anxious depressed and withdrawn depressed), different factors came out significant for internalizing and externalizing problems both at age 3 and 12. At age 3,

parental immigration status was associated with internalizing problems, while parental unemployment was associated with externalizing problems. At age 12, early life stress increased the risk for internalizing problems, but not for externalizing problems. Maternal mental health, sociodemographic risk and familial adversity are all well-known risk factors for both internalizing and externalizing problems. Of the risk factors included in the present study, pregnancy and birth characteristics are studied more with regard to externalizing problems. Consistently, a low Apgar score was shown to increase the risk for destructive problems at age 3, while no effect was seen on internalizing problems. Likewise, there is a large body of literature investigating the association between *5*-HTTLPR, stressful life events and internalizing/depressive symptomatology, but there are not as many studies examining the association with externalizing problems. Accordingly, a main effect of *5*-HTTLPR was found on internalizing problems at age 12.

When the stability of symptoms between ages 3 and 12 was investigated, both homotypic and heterotypic continuity was indicated. However, one must take into consideration that co-existence of behavioral problems was not controlled for. The most prominent association was found between externalizing problems at ages 3 and 12, with a seven-fold increased risk for subsequent problems of the same type. However, externalizing problems at age 3 also increased the risk for internalizing problems at age 12 by fivefold, indicating that externalizing problems at preschool age is a more influential risk factor for preadolescent behavioral problems than internalizing problems (Table 8). The findings are in line with previous studies (Loth et al., 2014; Mesman et al., 2001; Pihlakoski et al., 2006); however, Mesman et al (2001) and Pihlakoski et al (2006) found internalizing problems at pre-school ages to be protective against preadolescent externalizing problems. It would have been interesting to follow behavioral trajectories in children with co-existing symptoms of internalizing and externalizing problems at age 3 to further evaluate the effects of comorbidity. Furthermore, information on co-occurring symptoms may differentiate between pure hetero- and homotypic pathways and comorbidity. Nevertheless, the results illuminate the complex patterns of mental health trajectories during childhood.

Conclusions

The present thesis confirms a multifactorial pattern of risk and resilience associated with internalizing as well as externalizing problems. The results emphasize the importance of maternal mental health and sociodemographic factors for child mental health at ages 3 and 12. The hypotheses were based on the diathesis-stress model, but no gene-environment effect of *5*-HTTLPR and *BDNF* Val66Met on behavioral problems in children at age 3 or 12 was found. No firm conclusions about flaws in the diathesis-stress model can be drawn from the results of the present study; however, the

null-results could indicate a more bidirectional relationship between genes and environment. This suggests that future studies based on the different susceptibility hypothesis or studies which examine epigenetic mechanisms should be conducted. Moreover, while Bronfenbrenners' bioecological model was used mostly to position the models of the current thesis, the low degree of variance explained in many of the multivariate models could indicate a multifactorial etiology including variables related to other levels in the bioecological model than solely the individual and micro system. Factors of the exo- and mesosystems, such as quality of preschool and school, relations with friends and teachers, and additional individual factors that were not included in the present study are all likely to contribute to the development of behavior and mental health in children and adolescents.

Despite the lack of gene-environment effects, the results from the present thesis indicates a main effect of *5*-HTTLPR on internalizing symptoms at age 12. Future studies examining main and interaction effects specifically in children could be useful to help draw clearer conclusions regarding the influence of candidate genes on mental health during childhood and adolescence. The studies included in the present thesis are strengthened by the longitudinal and prospective design, combining register data with well-known instruments, structured interviews and genetic samples. However, there are some methodological considerations and limitations that need to be considered.

Methodological considerations

The use of questionnaires

Information on maternal and child mental health and experiences was collected mainly through single informant (mothers) questionnaires. Clinical interviews or diagnoses would most likely have rendered a more precise definition and specification of diagnoses. However, most of the questionnaires used are well-established instruments for measuring symptoms of depression and anxiety (EPDS, SCL-25), child behavioral problems (CBCL) and experience of traumatic life events (LITE). Moreover, psychosocial impairment has been shown to be of similar magnitudes between clinically diagnosed patients and sub-clinically depressed individuals (Gotlib et al., 1995). The use of clinical interviews in a large longitudinal cohort study like the SESBiC study would be considerably more time and resource consuming.

The SCL-25 measures symptoms of both depression and anxiety; however, when results from the SCL-25 are presented and discussed in the present thesis, anxiety

is not always mentioned. Likewise, in the discussion the focus is on depression. Less is known about the impact of maternal anxiety during childhood, however maternal panic disorder has been shown to increase the risk for anxiety and inhibition in children (Weinberg and Tronick, 1998). The comorbidity between depression and anxiety is considerable, and no separate analyses for anxiety and depression subscales of the SCL-25 were conducted. However, especially at the 12 year follow-up when the SCL-25 was used, the influence of anxiety symptoms should be considered.

Continuity and recurrence of maternal depressive symptoms

Since symptoms of depression in mothers were found to be an important predictor of child behavioral problems, an assessment of maternal depression at the 3 year follow-up would have been of great value. The current data does not provide information on depressive symptoms during the 11.5 year period between baseline and the 12 year follow-up. Whether mothers suffered from subsequent depressive episodes or whether treatment, personal or family therapy by any reason was in question is therefore not known. Moreover, the present thesis did not include measures of mental health in the fathers or control for whether the mother had sole custody of the child. The involvement of fathers has been suggested to moderate the effect of maternal depression on child behavior (Goodman and Gotlib, 1999).

Genetic analyses

In paper II and III, we choose to analyze the genetic variables in three levels, that is, each genotype separately. In paper IV dichotomous variables were created, comparing high risk allele carriers (the s-allele of *5*-HTTLPR and the Met-allele of *BDNF* Val66Met) with individuals homozygous for the presumed low-risk allele. Both methods have been used in previous studies (Risch et al., 2009). We argue that analyzing the alleles separately better represents the data, and this is possible due to the large sample size. However, the number of Met/Met carriers was only 39, resulting in very small groups when interaction terms were included. Thus, dichotomous variables might have yielded more reliable results. In study III, complementary analyses were run with genetic markers as dichotomous variables comparing Met-carriers with Val/Val homozygotes and s-carriers with l/l homozygotes. No differences emerged in the results for the internalizing scales. For externalizing problems, an interaction effect between *BDNF* and sex appeared; however, the significance was not strong (p=0.044). With this background, the multivariate models were also run separately for boys and girls (data not included in the paper), but no gene-environment effects emerged. In study IV, we choose to use dichotomous variables as more complex statistical methods were used, rendering smaller groups for comparison.

The use of the same risk factors and outcome variables across the studies

It was a conscious methodological choice to include maternal symptoms of depression in the second and third paper after finding significant effects on child behavioral problems in study I. Our aim was to test the impact of different factors of risk and resilience on child behavioral problems at various ages. Behavior and mental health are complex traits, to which multiple factors contribute. Using multivariate logistic regression, only the factors explaining the greatest amount of the variance will be significant in the final models. Thus, which factors are included in the models is of great importance. To exclude a variable that was known to increase the risk for the outcome variable of internalizing and externalizing problems in children could be seen as ignoring the known effect of this factor. However, using in part the same variables in subsequent publications requires the outermost clarity and transparency of which results have been published before and what is new about the study. This could have been clearer between the studies.

Limitations

Attrition rate

The 12 year follow-up of the SESBiC study was laden with a dropout rate of between 47.2 % (study II and IV) and 47.7 % (study I) depending on the measures used. Previous studies have noted similar magnitudes of attrition in longitudinal studies (Deng et al., 2013). However, selective attrition might be problematic for the generalizability of the results. Individuals of socioeconomic disadvantage, ethnic minorities and those in poor health, for example, are more prone to non-response in studies (Bergman et al., 2010; Patel et al., 2003). In the present study, dropouts differed from participants regarding PPD (study I), ethnicity/parental immigrating status (study II-IV) and experience of early life stress (study II-IV). The extent to which a skewed dropout actually biases the results is debated. Some researchers did see an effect of selective attrition (Scott, 2004) while others did not (Bergman et al., 2010). Different strategies to minimize the attrition rate have been proposed and evaluated. In a systematic review, Booker et al. (2011) showed that incentives, reminder calls or letters and offering alternate locations or modes of data collection all increased the retention rates between 5-24 %. The present study used many of these strategies, which possibly increased the retention rate somewhat. The issue of DNA sampling of children and the amount of questions that were asked seemed to be deterrent for some of those declining participation.

Mothers as informants

The instruments were completed exclusively by the mothers (with the exception of the LSS which was assessed by a psychologist after interviewing the mothers), and no objective measures were used. Concern has been raised as to whether mothers with depressive and anxious symptomatology tend to overestimate behavioral problems in their children. Previous studies have shown that maternal depressive symptoms are associated with positive mother-child reporting discrepancies of behavioral problems (Najman et al., 2001). However, Van der Toorn et al (2010) conclude that maternal symptoms of depression do not bias the results to a serious degree (Van Der Toorn et al., 2010). Likewise, in a review by Richters (1992) no evidence for distortion was found (Richters, 1992). On the other hand, reliable reports on child behavior require the informants to know the child well. At the age of 3 (and in most cases also at the age of 12), the parents most likely have the greatest knowledge on their child. However, using parents' reports instead of self-reports for assessing life events at age 12 could possibly increase the risk of underreported intra personal events outside the parents' awareness. The same could possibly apply to internalizing problems that might not always be visible to parents or teachers. Similarly, externalizing problems might become more pronounced in the school environment where children are required to align with present norms and rules.

Ethical considerations

Ethical issues on genotyping research

Several ethical issues have been raised as new technologies increase the possibilities of linking phenotypes with genetic variations. Foster and Sharp (2006) list some topics of concern for the field of research in medical genetics (Foster and Sharp, 2006). First, there is the question of data storage, as little phenotypic information is needed in combination with genetic data to identify an individual. This information could reveal facts about future health risks and susceptibility, and might be of interest for employers, insurers and courts of law. Secondly, there are studies that indicate different genotype frequencies in various ethnical groups and populations. Researchers must handle all such results with caution, taking care not to present results in a way that genetic stereotypes lead to stigmatization of whole populations. Thirdly, Foster and Sharp point to the risk of using medical sequencing data for controversial use such as prenatal screening and decision making, and reproductive selection. Concluding, they call for the development of effective strategies to address these challenges.

Moreover, there is a risk for a deterministic starting point when discussing genotyping of children in order to identify genes associated with negative traits or outcomes. Given that there was a consensus on a major effect of *5*-HTTLPR and *BDNF* Val66Met in individuals experiencing childhood adversities, to justify genetic analyses of children there had to be effective interventions aimed at risk-genotype carriers experiencing adverse environments. Today, psychiatric research is far from there. However, within other fields of medicine, both monogenetic and polygenetic etiology of certain diseases is known (e.g. forms of cancer, Huntington's disease etc.). The question of screening thus needs to be addressed on the basis of risk, prevention and treatment options.

Knowledge of risk factors for mental health problems in children must be spread with awareness. In the present study, concurrent or recent depressive symptoms in mothers were shown to have a negative impact on child behavior, which also have been shown previously. It is important to present such results with awareness of risk for stigmatizing depressed mothers, who may feel guilt for causing problems for their children. However, it is important that these children become noticed and that adequate intervention is carried out. It would be a greater unethical act not to take child wellbeing into consideration when parents seek health care for mental health problems.

Clinical implications

The results from the present thesis emphasize the importance of maternal mental health and sociodemographic factors for child mental health at ages 3 and 12. Moreover, it adds to the null-findings of the gene-environment interaction effect of *5*-HTTLPR and *BDNF* Val66Met on behavioral problems in children at age 3, but indicates an effect of *5*-HTTLPR on internalizing symptoms at age 12. Although the findings do not alone provide evidence strong enough for novel clinical recommendations, they do provide suggestions for important issues to address in clinical practice and highlight the importance of prevention strategies.

First, screening for depressive symptoms postpartum is an important prevention strategy in order to detect maternal depression at an early stage. The majority of Swedish parents take part in the child health care system with frequent check-ups during the first months after child birth. As of today, there is a national recommendation of using the EPDS as a screening instrument 6-8 weeks postpartum in all women entering child health care in Sweden. Equally important is the provision of interventions for women experiencing PPD, which requires adequate resources and

competencies in primary health care. Different forms of psychotherapy are used both as preventive tools for mothers at risk for developing PPD and as interventions when PPD is manifest. Usually, the mother-child dyad is in focus (Werner et al., 2015). Additionally, pharmacological treatment with Selective Serotonin Reuptake Inhibitors (SSRI) can be administered both during pregnancy and to breastfeeding mothers. Detection of older children whose mothers suffer from depression or depressive symptoms might be more difficult. It is important that professionals working in adult psychiatry, primary care and social services who meet with women suffering from depression do consider the wellbeing of the children and provide adequate support if needed. A focus on the family system rather than just the individuals is important, for example through family therapy programs such as attachment based family therapy directed at adolescents suffering from depression (Diamond et al., 2002). However, the family needs to be in focus also when cooperation between different health care establishments and social services is required.

Secondly, it is important to consider the impact of sociodemographic risk factors such as unemployment and psychosocial strain in clinical practice. Many of these factors are part of inflexible structures and tend to be continuous and co-existing. With socioeconomic inequalities increasing in Sweden, awareness is required about the potential detrimental effects for child mental health and wellbeing of these factors.

Future research

-Given the null-findings of the gene-environment effects of *5*-HTTLPR and *BDNF* Val66Met, replication studies specifically in children would be useful to better investigate the presence of an effect during childhood.
-Considering the discrepancies of gene-environment results on candidate genes for psychiatric disorders, the plasticity of the brain and diverging outcomes in response to adversities, the interest for reciprocal effects of genes and environment is currently increasing. Research of DNA methylation - ideally before exposure to environmental factors, after exposure and after treatment - could further shed light onto genetic mechanisms underlying psychiatric disorders.
-The SESBiC study offers an opportunity to follow individuals from in-utero to preadolescence. Further follow-ups of the cohort in early adulthood could add information on the developmental trajectories for children experiencing early adversity and those with behavioral problems at age 3. Thus, more specific evaluation of long term effects of factors of risk and resilience could be carried out.
-Research on resilience would benefit from a continued inclusion of biological as well as psychosocial variables in research. Here, the developmental perspective is crucial,

which opens up for the investigation of different mediating factors, – not only constitutional factors, but also additional factors of the micro and exosystems of Bronfenbrenner's human ecology model.

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