Early Life Origins of Severe Personality Disorders: The Helsinki Birth Cohort Study

Marius Lahti

Institute of Behavioural Sciences,
University of Helsinki, Finland

Academic Dissertation to be publicly discussed,
by due permission of the Faculty of Behavioural Sciences,
at the University of Helsinki, Main Building, Lecture Hall 5, Fabianinkatu 33,
on the 24th of November, at 12 o` clock

University of Helsinki
Institute of Behavioural Sciences
Studies in Psychology, 84, 2012

Supervisors:

Professor Katri-Räikkönen Talvitie
Institute of Behavioural Sciences, University of Helsinki, Finland

Professor Johan G. Eriksson
Institute of Clinical Medicine, University of Helsinki, Finland

Reviewers:

Professor Juha Veijola
Department of Psychiatry, Institute of Clinical Medicine, University of Oulu, Finland

Dr. Angelina Sutin
Laboratory of Behavioral Neuroscience, National Institute of Aging National Institutes of Health, Florida, United States of America

Opponent:
Professor Erkki Isometsä
Department of Psychiatry, University of Helsinki, Finland

ISSN-L 1798-842X
ISSN 1798-842X
ISBN 978-952-10-8417-1 (pbk.)
ISBN 978-952-10-8418-8 (PDF)
http://www.ethesis.helsinki.fi
Helsinki University Print
Helsinki 2012

CONTENTS

ABSTRACT

Previous studies suggest that a suboptimal early life environment may predict an increased risk of adult personality disorders. However, most of this evidence is based on studies with retrospective accounts of early adversity. This retrospective design may induce a bias and hinder interpretation of the direction of causality.

This thesis examines, in a longitudinal study setting, the developmental origins of personality disorders severe enough to justify hospitalisation. The focus is on pre- and postnatal growth and on parental separation in childhood due to temporary evacuations from Finland during World War II in the etiology of both any and dramatic personality disorders requiring hospitalisation.

The study cohort is the Helsinki Birth Cohort Study, which comprises 13,345 individuals born 1934-1944. Data on early life growth, on childhood evacuations, and on the diagnoses of personality disorders were drawn from birth- and child welfare records and national registers. These objective record- and register-based data enabled the longitudinal design of the studies. In the current study cohort, there were 1,781 individuals who had been separated from their parents in childhood. There were 202 subjects who had been hospitalised for personality disorders, and 77 individuals with dramatic personality disorders.

The results showed that a small head circumference and a small head-to-length ratio at birth predicted an increased risk of any severe personality disorder among men and a small placental surface area at birth predicted dramatic personality disorders among women. Slower gain in BMI between birth and six months of age, faster gains in weight and in BMI between six months and one year, and slower gains in weight and in BMI between seven and 11 years of age also predicted personality disorders among men. Slower height growth between two and seven years of age predicted an increased risk of personality disorders among women. The associations between infancy and childhood growth and severe personality disorders among men were especially characteristic of dramatic personality disorders, and were independent of comorbid mood disorders.

Temporary separation from parents, particularly in the first five years of life, predicted an increased risk of severe personality disorders, and among men, of dramatic personality disorders. The effects of early parental separation were specific to

personality disorders, since they emerged in comparisons to both healthy control participants and to individuals with other mental disorders.

These longitudinal study findings strongly support an etiological role for early life, both pre- and postnatal, environmental adversity in the development of severe personality disorders, especially dramatic personality disorders. Vulnerability to severe personality disorders is developmentally programmed in early life.

TIIVISTELMÄ

Aikaisemmat tutkimukset osoittavat, että vaikea varhainen kehitysympäristö voi ennustaa kohonnutta riskiä aikuisiän persoonallisuushäiriöihin. Kuitenkin suurin osa aiemmista tutkimuksista on perustunut retrospektiivisiin raportteihin varhaiskehityksen vaikeuksista. Tämä retrospektiivinen tutkimusote saattaa aiheuttaa tuloksiin vääristymää ja ehkäisee kausaalisuhteiden tulkintaa.

Tässä väitöskirjassa tutkitaan sairaalahoitoa vaatineiden vakavien persoonallisuushäiriöiden kehityksellistä etiologiaa pitkittäistutkimuksessa. Erityisesti keskitytään tutkimaan syntymää edeltävän ja syntymänjälkeisen fyysisen kasvun sekä lapsuusiässä koetun vanhemmista eroon joutumisen mahdollista ennustavaa vaikutusta vakavien, sairaalahoitoa vaatineiden persoonallisuushäiriöiden ja erityisesti dramaattisen klusterin persoonallisuushäiriöiden kehittymiseen. Erokokemukset vanhemmista olivat väliaikaisia, ja johtuivat toisen maailmansodan aikaisista lasten evakuoinneista ulkomaille ilman vanhempiaan.

Tutkimuskohorttina toimii Helsingin Syntymäkohortti, johon kuuluu 13,345 vuosina 1934–1944 syntynyttä suomalaista. Tiedot varhaisesta kasvusta, lapsuusiän erokokemuksista, sekä persoonallisuushäiriödiagnooseista saatiin eri terveydenhuollon korteista ja kansallisista rekistereistä. Nämä objektiiviset rekisteritiedot mahdollistivat pitkittäistutkimusotteen. Kohortin jäsenistä 1,781 oli evakuoitu ilman vanhempiaan lapsuudessa, ja 202 oli joutunut sairaalahoitoon persoonallisuushäiriön takia. Näistä 77:llä oli dramaattisen klusterin persoonallisuushäiriö.

Tulokset osoittivat, että pienempi päänympärys ja pienempi päänympärys suhteessa pituuteen syntymähetkellä ennustivat miehillä kohonnutta vakavien persoonallisuushäiriöiden riskiä, ja pienempi istukan pinta-ala syntymähetkellä naisilla kohonnutta riskiä dramaattisen klusterin persoonallisuushäiriöihin. Hitaampi kasvu painoindeksissä syntymän ja kuuden kuukauden välillä, nopeampi kasvu painossa ja painoindeksissä kuuden ja 12 kuukauden välillä sekä hitaampi kasvu näissä molemmissa seitsemän ja 11 vuoden ikien välillä ennustivat miehillä myös kohonnutta vakavien persoonallisuushäiriöiden riskiä. Naisilla hitaampi kasvu pituudessa kahden ja seitsemän vuoden ikien välillä ennusti vakavien persoonallisuushäiriöiden riskiä. Miehillä löydetyt leikki- ja lapsuusiän kasvun yhteydet kuvasivat erityisesti

dramaattisen klusterin persoonallisuushäiriöitä, ja ne olivat riippumattomia yhdessä esiintyvistä mielialahäiriöistä.

Eroon joutuminen vanhemmista, erityisesti ensimmäisen viiden elinvuoden aikana, ennusti kohonnutta vakavien persoonallisuushäiriöiden riskiä, ja miehillä erityisesti dramaattisen klusterin persoonallisuushäiriöitä. Nämä varhaisten erokokemusten vaikutukset olivat spesifisiä persoonallisuushäiriöille, sillä ne tulivat esiin sekä vertailtaessa persoonallisuushäiriöisiä terveisiin että myös heihin, keillä oli muita vakavia mielenterveyden häiriöitä.

Tämän pitkittäistutkimuksen tulokset tukevat vahvasti sekä syntymää edeltävän että syntymän jälkeisen varhaiskehityksen vaikeuksien ennustavaa vaikutusta vakavien persoonallisuushäiriöiden ja erityisesti dramaattisen klusterin persoonallisuushäiriöiden kehittymiseen. Alttius vakaviin persoonallisuushäiriöihin muodostuu varhaisessa kehityksessä.

ACKNOWLEDGEMENTS

This study was conducted at the Institute of Behavioural Sciences, University of Helsinki, and in close collaboration with National Institute of Health and Welfare. I am very grateful to both these Institutions for making this study possible.

I like to express my deepest, sincere gratitude to my supervisors, Professors Katri Räikkönen and Johan Eriksson, for their insightful, thorough, helpful and supportive guidance throughout the last five years. My supervisors with their excellent scientific knowledge and great eagerness to study new research questions helped to form an exhilarating, interesting, and at the same very time friendly and warm scientific environment throughout these years. Thank you very much for everything!

I also wish to express special thanks to my reviewers Doctor Angelina Sutin and Professor Juha Veijola for their insightful and valuable advises that helped to develop and improve this work.

I want to express special, great gratitude to my great Finnish collaborators Professor Kristian Wahleck and Docents Anu-Katriina Pesonen, Kati Heinonen, Eero Kajantie, and Tom Forsén for their supportive and insightful research collaboration, and for the thorough and helpful comments and revisions on the manuscripts of the studies. Together with my supervisors, they have helped to form an interesting, thought-provoking, intellectual scientific atmosphere that has evoked enthusiasm for approaching different scientific endeavours. I like to thank them all also for their wonderful emotional support that is well needed in the early stages of a research career.

I want to express my thankfulness for our wonderful international collaborators, Dr. Clive Osmond and Professor David Barker for their collaboration, insightful comments and scientific discussions. Their support and great experience and knowledge in this research field have taught me a lot and I want to express my gratitude for the interesting discussions we have had throughout the years. Special thanks go to Dr. Osmond for his great, educative, thorough and helpful collaboration on the methodological work and on the manuscripts of this thesis, and for Professor Barker for his insightful assistance and comments on the manuscripts. A friendly, warm-hearted atmosphere is always present in the discussions with these scientists, and it has been a pleasure to get to know them.

Special thanks go also to Professor Mari Tervaniemi for thorough and insightful proofreading of this thesis and for her work as the co-ordinator for the doctoral studies.

I express my sincere gratitude for the Helsinki University Research Funds and for the National Doctoral Programme of Psychology, from whom I received my personal funding for this work. I want to also thank the funders of this research project: Emil Aaltonen Foundation, the Academy of Finland, the Ministry of Education, the British Heart Foundation, the Finnish Foundation for Cardiovascular Research, the Finnish Diabetes Research Foundation, the Finnish Medical Society, Finska Läkaresällskapet, the European Science Foundation (EuroSTRESS), Samfundet Folkhälsan, and the Päivikki and Sakari Sohlberg Foundation, Juho Vainio Foundation, Yrjö Jahnsson Foundation, Signe and Ane Gyllenberg Foundation, Sigrid Juselius Foundation, Jalmari and Rauha Ahokas Foundation, and Finnish Foundation for Pediatric Research.

I am extremely grateful to my research colleagues at the Institute of Behavioural Sciences and National Institute of Health and Welfare for their friendship, company, and scientific collaboration, and for the great shared times in Finland and abroad throughout these last years. In addition to my supervisors and collaborators, special, warm thanks go to Docents Jari Lahti, Petteri Hovi, Sakari Lemola, and Sture Andersson; to Drs. Kimmo Feldt, Nina Komsi, Sonja Strang-Karlsson, Minna Salonen and Maria Paile-Hyvärinen; to my fellow PhD students Soile Tuovinen, Riikka Pyhälä, Antti-Jussi Pyykkönen, Silja Martikainen, Katri Savolainen, Maiju Mikkonen, Samuel Sandboge and Anna-Maija Tiainen; and to Jarkko Volanen and others for all your friendship, support, and help. This has been a wonderful journey together, and I am deeply grateful for getting to know you. Hope the great times together continue! Special appreciations go also to my friends and colleagues from other research groups at the University of Helsinki; Jari Lipsanen, Tom Rosenström, Christian Hakulinen, Kim Josefsson, Tapani Riekki and others who have given me valuable advice, assistance, and support, and with whom I have shared many interesting scientific discussions.

I want to thank my parents and my sister for their love and all the support throughout my life. Heartfelt thanks to you. Very warm thanks also go to other members of my family and for my friends for all your love, support, and company, for the scientific and non-scientific conversations and for all the wonderful shared experiences throughout the years. Thank you.

LIST OF ORIGINAL PUBLICATIONS

I. Lahti, M., Räikkönen, K., Wahlbeck, K., Heinonen, K., Forsén, T., Kajantie, E., Pesonen, A. K., Osmond, C., Barker, D. J., Eriksson, J. G. (2010). Prenatal origins of hospitalization for personality disorders: the Helsinki birth cohort study. *Psychiatry Research, 179,* 226-230.

II. Lahti, M., Räikkönen, K., Wahlbeck, K., Heinonen, K., Forsén, T., Kajantie, E., Pesonen, A. K., Osmond, C., Barker, D. J., Eriksson, J. G. (2011). Growth in infancy and childhood and hospitalization for personality disorders in adulthood: the Helsinki Birth Cohort Study. *Journal of Personality Disorders, 25,* 620-623.

III. Räikkönen, K., Lahti, M., Heinonen, K., Pesonen, A. K., Wahlbeck, K., Kajantie, E., Osmond, C., Barker, D. J., Eriksson, J. G. (2011). Risk of severe mental disorders in adults separated temporarily from their parents in childhood: the Helsinki birth cohort study. *Journal of Psychiatric Research, 45,* 332-338.

IV. Lahti, M., Pesonen, A. K., Räikkönen, K., Heinonen, K., Wahlbeck, K., Kajantie, E., Osmond, C., Barker, D. J., Eriksson, J. G. (2012). Temporary Separation from Parents in Early Childhood and Serious Personality Disorders in Adult Life. *Journal of Personality Disorders, 26,* 751-762.

ABBREVIATIONS

11βHSD-2	11-beta hydroxysteroid dehydrogenase type 2
ADHD	Attention Deficit Hyperactive Disorder
APA	American Psychiatric Association
ASEBA	Achenbach System of Empirically Based Assessment
BMI	Body Mass Index
CHD	Coronary Heart Disease
CI	Confidence Interval
CDR	Causes of Death-Register
DOHaD	Developmental Origins of Health and Disease
DSM	Diagnostic and Statistical Manual for Mental Disorder
ELBW	Extremely Low Birth Weight
HBCS	Helsinki Birth Cohort Study
HDR	Hospital Discharge Register
HPA-axis	Hypothalamic-Pituitary-Adrenal axis
HR	Hazard Ratio
ICD	International Statistical Classification of Diseases and Related Health Problems
LBW	Low Birth Weight
MAO-A	Monoamine Oxidase A
MD	Mean Difference
NFBC	Northern Finland Birth Cohort Study
OASR	Older-Adult Self-Report
OR	Odds Ratio
SD	Standard Deviation
SGA	Small for Gestational Age
SNP	Single Nucleotide Polymorphism
TPH	Tryptophan Hydroxylase
VLBW	Very Low Birth Weight
WHO	World Health Organization

1. INTRODUCTION

Personality disorders are severe, long-lasting mental disorders [American Psychiatric Association (APA), 2000; World Health Organization (WHO), 1992] with a prevalence of 6-10 % in the general population (Huang et al., 2009; Sansone & Sansone, 2011). Personality disorders prospectively predict all-cause mortality (Grigoletti et al., 2009; Hannerz, Borgå, & Borritz, 2001) and are associated with an increased risk of suicide (Pompili, Girardi, Ruberto, & Tatarelli, 2005; Tidemalm, Elofsson, Stefansson, Waern, & Runeson, 2005; Tidemalm, Waern, Stefansson, Elofsson, & Runeson, 2008) and of cardiovascular disease (Lee et al., 2010; Moran et al., 2007). Such associations with poorer health outcomes may be especially strong for the disorders of the dramatic cluster (El-Gabalawy, Katz, & Sareen, 2010; Lee et al., 2010; Tidemalm et al., 2005).

Personality disorders also predict disability in various life domains; interpersonal, professional, emotional and global functioning are all impaired (Grant et al., 2004; Hill et al., 2011; Huang et al., 2009; Wilson & Durbin, 2012; Yang, Coid, & Tyrer, 2010; M. Zimmerman et al., 2012), and rates of criminality are increased (Coid, Yang, Tyrer, Roberts, & Ullrich, 2006; Elonheimo et al., 2007) among patients with personality disorders. These disorders also lead to higher levels of unemployment rates and to more problems with coworkers (Ettner, Maclean, & French, 2011). Comorbidity with personality disorders worsens the prognosis of other mental disorders such as depression (for a review, see Newton-Howes, Tyrer, & Johnson, 2006) and substance use disorders (Hasin et al., 2011).

In addition to the human and interpersonal suffering, personality disorders place a high burden on society; the yearly cost for European societies for personality disorders being estimated at 27.3 billion Euros (Olesen et al., 2012). Identifying their developmental precursors is thus of great public health importance.

Retrospective studies (Agrawal, Gunderson, Holmes, Lyons-Ruth, 2004; Bakermans-Kranenburg & van IJzendoorn, 2009; Crawford et al., 2006; Westen, Nakash, Thomas, & Bradley, 2006) have repeatedly shown that personality disorders may have their developmental origins in early life. These studies suggest that, in addition to hereditary predispositions (e.g. Kendler et al., 2006; Reichborn-Kjennerud et al., 2007; Torgersen et al., 2008), the risk of personality disorders is associated with

increased levels of early life environmental adversity. There are, however, methodological limitations inherent to such cross-sectional studies using retrospective accounts of early life factors (Hardt & Rutter, 2004).

Longitudinal, prospective studies are therefore needed to examine whether early life developmental factors are indeed implicated in the etiology of personality disorders. Such evidence has already started to emerge, suggesting that early life environmental, developmental factors, both pre- and postnatal, may longitudinally predict the risk of later personality dysfunction (Carlson, Egeland, & Sroufe, 2009; Johnson, Cohen, Brown, Smailes, & Bernstein, 1999; Johnson, Cohen, Chen, Kasen, & Brook, 2006; Johnson et al., 2001; Johnson, Liu, & Cohen, 2011; Johnson, Smailes, Cohen, Brown, & Bernstein, 2000; Kantojärvi, Joukamaa et al., 2008; Monfils Gustafsson, Josefsson, Ekholm Selling, & Sydsjö 2009; Widom, Czaja, & Paris, 2009). However, the evidence is inconclusive and further studies are needed to confirm or refute these associations.

Using a longitudinal study design, the current thesis examines the developmental origins of personality disorders severe enough to require hospitalisation in the Helsinki Birth Cohort Study (HBCS) 1934-1944. This is a large, representative study cohort of over 13,000 individuals with objective- health record- and register-based data on various early life exposures and with physician-based diagnostic data from national registers on all hospitalisations in Finland between 1969 and 2004.

In this thesis, a particular emphasis is placed on early life environmental factors in predicting severe personality disorders. Body size at birth, length of gestation, and growth between birth and 11 years of age are used as general, crude proxies of early life environmental adversities and their predictive role for personality disorders severe enough to justify hospitalisation is assessed. In addition, the effects of temporary parental separation in childhood due to child evacuations from Finland during World War II on any severe mental disorder and especially on personality disorders are examined in a longitudinal study setting. Also particular effects of all these developmental factors on the development of dramatic cluster personality disorders are assessed. This thesis also assesses the self-reported stressfulness of the separation exposure and whether particular aspects of the childhood environment associated with the length and the duration of the separation and/or modified the long-term consequences of the separation on adult antisocial personality traits.

1.1 Personality Disorders

1.1.1 Definitions and Diagnostic Criteria

According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text-Revision (DSM-IV-TR), personality disorders are "*severe mental disorders characterized by invasive pattern of thought, inner experience and behavior that deviates markedly from the expectations of one`s culture"* (APA, 2000, pp. 629). DSM-IV-TR further states that this pattern of experience and behaviour is stable and long-lasting, inflexible and pervasive across a wide range of personal and social situations, and leads to clinically significant distress or impairment in social, occupational, or other important areas of functioning (APA, 2000).

For a person to be diagnosed with personality disorder, she/he must show deficits in at least two of the following four areas: cognition, emotion regulation, interpersonal functioning, and impulse regulation (APA, 2000). The symptoms often manifest in the interpersonal domain and characterize qualitatively how these individuals relate to themselves and others: self- and other-perceptions differ from the typical ways in one`s cultures. These disorders usually have their onset at the latest in adolescence or early adulthood, and the associated experience and behaviour patterns are rather stable and not the "manifestation or consequence of another mental disorder" (APA, 2000, pp. 630), for example, personality changes as a consequence of acute schizophrenia. They are neither directly attributable to the physiological effects of substance use or a general medical condition (APA, 2000).

The DSM diagnostic system is used in clinical practice in the United States of America and in research practice worldwide. However, in most European countries and in Finland, the diagnoses of mental and behavioral disorders are in clinical practice made according to the International Statistical Classification of Diseases and Related Health Problems –classification, of which the tenth revision (ICD-10) is currently in use (WHO, 1992). It is of note, however, that between 1987 and 1995, although ICD-9 was generally in use in Finland, the diagnoses of mental disorders were done according to

the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R).

The general diagnostic criteria for personality disorders in ICD-10 and DSM-IV correspond closely. According to ICD-10, disorders of adult personality and behavior:

> represent extreme or significant deviations from the way in which the average individual in a given culture perceives, thinks, feels and, particularly, relates to others. Such behaviour patterns tend to be stable and to encompass multiple domains of behaviour and psychological functioning. They are frequently, but not always, associated with various degrees of subjective distress and problems of social performance. (WHO, 1992; pp. 200)

The specific personality disorders and their core symptoms according to DSM-IV are listed in Table 1. When named differently, the corresponding diagnoses in ICD-10 are listed in parenthesis. A major difference between ICD-10 and DSM-IV concerns the status of schizotypal personality disorder; while enlisted as a personality disorder in DSM-IV, it belongs to the schizophrenia cluster disorders in ICD-10. Otherwise the classifications for personality disorders in these two diagnostic systems largely resemble each other, although ICD-10 enlists narcissistic personality disorder not with its own title but under the heading “other specific personality disorders”. ICD-10 also requires more diagnostic criteria to be fulfilled for a personality disorder diagnosis than DSM-IV (APA, 2000; WHO, 1992).

Table 1. Personality disorder diagnoses according to the DSM-IV and their core symptoms

Cluster A: Eccentric Personality Disorders

Paranoid Personality Disorder

-irrational suspicions of others` motives

-a general mistrust of others, guarded isolated behavior as a consequence

-a persistent tendency to self-reference

Schizoid Personality Disorder

-no interest in social relationships

-a solitary lifestyle, lack of meaningful communication with others

-cold and indifferent behavior towards others

Schizotypal Personality Disorder *

-odd and unconventional behaviour

-cognitive and perceptual distortions

-eccentric beliefs and magical thinking

-social isolation as a consequence of strong uneasiness and anxiety in close interpersonal relationships

-paranoid ideation

-inapt or constricted affect

Cluster B: Dramatic Personality Disorders

Antisocial Personality Disorder (ICD-10: Dissocial Personality Disorder)

-consistent disregard and violation of the rights and feelings of others, callousness

-irresponsibility and disrespect of social norms

-criminality and deception

-impulsivity, failure to plan ahead

-irritability and aggressiveness

-lack of remorse

-disregard of the safety of self and others

Borderline Personality Disorder (ICD-10: Emotionally Unstable Personality Disorder)

-impulsivity

-affective dysregulation

-a strong variability and depth of moods

-unstable interpersonal relationships and self-image

-affective distress, chronic feelings of emptiness

-suicidal thoughts and behaviour

Table 1 (continued). Personality disorder diagnoses according to the DSM-IV and their core symptoms.

Cluster B: Dramatic Personality Disorders (continued)

Narcissistic Personality Disorder (ICD-10: Other Specific Personality Disorders)

-a stable, pervasive pattern of grandiosity and need for admiration

-grandiose feelings of self-importance, entitlement and being special

-lack of empathy for others, interpersonal exploitation and enviousness

Histrionic Personality Disorder

-excessive attention-seeking and extreme amounts of superficial emotionality

-restricted capacity for feeling love

-a strong need for approval and admiration

-seductive behavior

-extreme sensitivity to criticism

-impulsivity, low tolerance of frustration

-continuous seeking of approval

Cluster C: Fearful Personality Disorders

Avoidant Personality Disorder [ICD-10: Anxious (Avoidant) Personality Disorder]

-extreme fear of and sensitivity to rejection

-feelings of inadequacy and inferiority to others

-extremely low self-esteem, high self-criticism

-excess shyness and social anxiety although feels a strong need for interpersonal closeness

-self-imposed social isolation and loneliness

Dependent Personality Disorder

-extreme fear of being left alone

-pervasive dependence on other people for most life decisions

-strong feelings of self-inadequacy

-clinging and adoring interpersonal relationships, extreme loyalty to partners even when they are abusive

-feeling helpless alone

Obsessive-Compulsive Personality Disorder (ICD-10: Anancastic Personality Disorder)

-preoccupation with perfectionism, orderliness and mental and interpersonal control

-paying extreme attention to details

-polarized views of and high demands on self and others

-stubbornness

-extreme conscientiousness and need for productivity at the expense of interpersonal relationships

Personality Disorder Not Otherwise Specified (ICD-10: Other Specific, Unspecific, and Mixed Personality Disorders)

-does not meet the criteria of any specific personality disorder but has personality features that together cause clinically significant impairments of functioning in one or more important areas of functioning

* Note 1. Schizotypal Personality disorder is not included as a personality disorder in ICD-10

1.1.2 Personality Disorder Clusters

Personality Disorders are, according to DSM-IV-TR (APA, 2000), classifiable into three disorder clusters: eccentric (Cluster A), dramatic (Cluster B), and fearful (Cluster C) personality disorders (Table 1). Cluster A: eccentric personality disorders include schizoid, schizotypal, and paranoid personality disorders. These disorders are characterized by odd or eccentric thought, appearance and behaviour. Cluster B: dramatic personality disorders include antisocial, borderline, histrionic, and narcissistic personality disorders. These are disorders characterized by dramatic, emotional, or erratic behaviour. High impulsivity further characterizes both of the more common cluster B personality disorders, antisocial and borderline, and also histrionic personality disorder. Cluster C: fearful personality disorders include avoidant, dependent, and obsessive compulsive personality disorders. Individuals with these disorders are very anxious and fearful, and have highly critical views of themselves (APA, 2000).

The idea behind these disorder clusters is that the disorders within a specific cluster ought to resemble each other in symptoms and etiology more than disorders belonging to the other clusters (APA, 2000). Findings from a large twin study suggest that for the genetic origins of personality disorders, the three-cluster solution does not function adequately (Kendler et al., 2008). On the other hand, a three-factor structure corresponding well to the Clusters A, B, and C emerged for environmental risk factors, thus supporting the view that the DSM-IV cluster-based approach is valid when examining the role played by environmental factors in the developmental origins of personality disorders (Kendler et al., 2008), which is the focus of this thesis.

1.2 The Epidemiology of Personality Disorders - Prevalence and Sociodemographic Correlates

The prevalence estimates of personality disorders vary considerably across studies. A Norwegian study suggested a prevalence rate as high as 13.4 % for any DSM-III-R personality disorder (Torgersen, Kringlen, & Kramer, 2001), while a recent WHO study conducted across the globe gave an average prevalence of 6.1 % for DSM-IV personality disorders (Huang et al., 2009). On the other hand, a systematic review of

studies in the United States suggested an average prevalence of approximately 10 % (Sansone & Sansone, 2011), and another recent review suggested that the median prevalence of DSM-IV personality disorders worldwide in the studies conducted in the last decade was 9.7 % (Samuels, 2011). For ICD-10 personality disorders, an American study yielded a weighted prevalence of 5.1 % (Samuels et al., 2002) and an Australian one 6.5 % (Jackson & Burgess, 2000). In general, studies using ICD criteria yield prevalence estimates approximately half of those found with DSM-criteria due to the higher amount of required endorsed criteria for a diagnosis (Samuels, 2011).

The prevalence of hospitalisation for personality disorders has rarely been studied, but estimates of prevalence rates until young adulthood are available from three studies in the Nordic countries (Ekblad, Gissler, Lehtonen, & Korkeila, 2010; Kantojärvi et al., 2004: Monfils Gustafsson et al., 2009). Population-based studies showed a prevalence of 0.3 % of hospitalisations for personality disorders before 18 to 20 years of age in Finland (Ekblad et al., 2010), and a prevalence of 0.2% of hospitalisations for personality disorders in adolescence in Sweden (Monfils Gustafsson et al., 2009). A Finnish study in a sample of patients hospitalised for psychiatric reasons between 16 and 31 years of age showed a prevalence of 14.6 % for any personality disorder among these patients (Kantojärvi et al., 2004), but whether their hospital discharge diagnosis was personality disorder was not assessed in that study. In contrast, no studies have examined the prevalence of hospitalisation for personality disorders after age 31 years.

The association of personality disorders with different sociodemographic factors has been studied often in conjunction with their prevalence (Coid et al., 2006; Grant et al., 2004; Huang et al., 2009; Kantojärvi et al., 2004; Kessler et al., 1994; Samuels, 2002; Torgersen et al., 2001). The findings from these studies are inconsistent but when differences have been observed, the prevalence of any personality disorder has been shown to be higher among men (Coid et al., 2006; Huang et al., 2009; Jackson & Burgess, 2000), and among separated/divorced (Coid et al., 2006; Grant et al., 2004; Samuels, 2002) and/or unmarried (Grant et al., 2004; Torgersen et al., 2001) individuals, and among the less educated (Huang et al., 2009; Torgersen et al., 2001). Findings on the sociodemographic correlates of personality disorder clusters and of specific personality disorders show even more inconsistency. However, the most consistently replicated findings suggest that the prevalence of dramatic personality disorders

decreases with increasing age (Coid et al., 2006; Samuels, 2002), and antisocial personality disorder is more common among men than among women (Grant et al., 2004; Kantojärvi et al., 2004; Kasen et al., 1999; Kessler et al., 1994).

1.3 Childhood Psychopathology and Personality Disorders in Adulthood

What are the developmental precursors of personality disorders? Firstly, many studies show that there is marked continuity in psychopathology from child- to adulthood (Bornovalova, Hicks, Iacono, & McGue, 2009; Copeland, Shanahan, Costello, & Angold; 2009; Crawford, Cohen, & Brook, 2001; Kasen et al., 2001; Reef, van Meurs, Verhulst, & van der Ende, 2010; Sourander et al., 2007), with childhood psychopathology predicting an increased risk of adult mental disorders in both homo- and heterotypic ways.

Also personality disorders in adulthood are predicted by childhood psychopathology. A recent meta-analysis suggested considerable stability for personality disorders from child- to adulthood (Ferguson, 2010). Furthermore, a study by Kasen and colleagues (1999) showed that different types of personality disorders in adolescence are strong predictors of these same disorders in adulthood. Correspondingly, studies on cluster B personality disorder symptoms have shown that childhood and adolescent dramatic cluster personality disorder symptoms robustly predict adult dramatic cluster symptoms (Bornovalova et al., 2009; Crawford et al., 2001). In addition, while antisocial personality disorder cannot, according to the diagnostic criteria, be diagnosed before the age of 18 years (APA, 2000), longitudinal evidence consistently shows that childhood conduct disorder from early ages onwards predicts antisocial personality disorder in adulthood (Copeland et al., 2009; Lahey, Loeber, Burke, & Applegate, 2005; Sourander et al., 2007). Also other types of childhood psychopathology, for example depression (Kasen et al., 1999; 2001; Sourander et al., 2007), anxiety disorders (Kasen et al., 1999), and attention-deficit hyperactive disorder [ADHD (Biederman et al., 2010; Miller et al., 2008)] have been shown to predict the risk of personality disorders in adulthood.

Hence, studies consistently show that early life psychopathology predicts an increased risk of personality disorders in adulthood. Early life personality pathology,

and to an extent, also other types of childhood psychopathology can be used as vulnerability markers for adult personality dysfunction. These findings highlight the feasibility and importance of studying early life developmental factors in the etiology of personality disorders, since they show that vulnerability for these disorders is evident already in early life (Winsper, Zanarini, & Wolke, 2012).

1.4 Hereditary Factors in the Etiology of Personality Disorders

Studies on the hereditary origins of personality disorders have mostly followed the approaches of family (Belsky et al., 2012; Cheng, Huang, Liu, & Liu, 2010; Dean et al., 2010; Ekblad et al., 2010; Lahey et al., 2005), twin (Belsky et al., 2012; Distel et al., 2008, 2009, 2011; Kendler, Prescott, Myers, Neale, 2003; Torgersen et al., 2000, 2008), and candidate gene (Basoglu et al., 2011; Caspi et al., 2002; Douglas et al., 2011; Fergusson, Boden, Horwood, Miller, & Kennedy, 2011; Garcia, Aluja, Fibla, Cuevas, & García, 2010; Li et al., 2012; Ni et al., 2006, 2007; Ni, Chan, Chan, McMain, & Kennedy, 2009; Perez-Rodriguez et al., 2010; Taylor & Kim-Cohen, 2007; Tadić et al., 2009, 2010; Zaboli et al., 2006) studies. Associations between largely heritable temperament traits and personality disorders have also been assessed (Basoglu et al., 2011; Belsky et al., 2012; Caspi, Moffitt, Newman, & Silva, 1996; Glenn, Raine, Venables, & Mednick, 2007; Joyce et al., 2003; Kantojärvi, Miettunen et al., 2008; Kimbrel, Mitchell, Hundt, Robertson, & Nelson-Gray, 2012; Mulder, Joyce, & Cloninger, 1994; Svrakic et al., 2002). Taken together, these studies on the genetic origins of personality disorders, reviewed in detail below, show that there is a marked genetic component to the development of personality disorders.

1.4.1. Psychopathology in the Family

Previous studies have consistently shown that parental psychopathology predicts psychopathology in the offspring (Belsky et al., 2012; Cheng et al., 2010; Dean et al., 2010; Ekblad et al., 2010; Gunderson et al., 2011; Lahey et al., 2005). For personality disorders, a register-based study among over 80,000 participants showed that the risks for mental disorders of all categories and particularly for personality disorders were

elevated in the offspring of parents with mental disorders (Dean et al., 2010). Risks for personality disorders were particularly increased when both parents had been treated for mental disorders. However, this risk was increased across parental diagnostic categories and the type of parental diagnosis did not have a major impact. Also a methodologically solid family study (Gunderson et al., 2011) suggested familial liability of borderline personality disorder with an approximately threefold risk among the relatives of probands. In a recent study (Belsky et al., 2012), family history of hospitalisation for any mental disorder predicted increased borderline personality disorder symptoms that were assessed at 12 years of age. A small clinical study (Johnson et al., 1995) suggested that the first degree-relatives of cluster C personality disorder patients had higher rates of any personality disorder than control subjects, who were psychiatric patients but did not have personality disorders. Particularly avoidant and borderline personality disorder patients had more corresponding personality pathology than those without personality disorders, but family members of patients with other personality disorders did not differ from the control subjects in the rates of corresponding personality disorders (Johnson et al., 1995). On the other hand, in the Northern Finland Birth Cohort Study (NFBC) 1966, a cohort study of over 12,000 individuals born in Northern Finland in 1966, parental hospitalisations for mental disorders were not predictive of personality disorders in the offspring (Kantojärvi, Joukamaa et al., 2008), and Lahey and colleagues (2005) showed that rates of maternal but not paternal antisocial personality disorder predicted an increased risk of antisocial personality disorder in the offspring.

While the majority of studies thus suggest familial aggregation of personality disorders, there is some inconsistency in the findings. These studies also show that not all individuals with affected parents will develop a personality disorder, and that parental psychopathology seems to pose a general risk for various types of psychopathology in the offspring rather than forming a specific risk for concordant disorders (Dean et al., 2010; Johnson et al., 1995; Trull 2001a, 2001b).

1.4.2 Twin Studies

Twin studies on personality disorders have yielded varying heredity estimates. A small study suggested heredity rates of .60 for any personality disorder, and .37, .60, and .62

for cluster A, B, and C personality disorders, respectively (Torgersen et al., 2000). On the other hand, a series of larger twin studies assessed the heritability of dimensionally assessed personality disorder traits (Kendler et al., 2006; Reichborn-Kjennerud et al., 2007; Torgersen et al., 2008), and yielded somewhat lower estimates, with heritability estimates of personality disorders traits varying between .21 and .41. Cluster B and avoidant personality disorder traits showed the highest heredity, while cluster A personality disorders were also here the least heritable. Other twin studies have assessed genetic effects particularly on the two most extensively studied personality disorders, borderline and antisocial personality disorder, and on their symptoms. Overall, heredity estimates have, in the more representative studies on these disorders, varied between .35. and .66 (Belsky et al., 2012; Distel et al., 2008; 2009; 2011; Kendler et al., 2011; Torgersen et al., 2008) for borderline and .35 and .50 (Kendler et al., 2003; 2011; Torgersen et al., 2008) for antisocial personality disorder.

1.4.3 Candidate Gene Studies

To the author`s knowledge, no genome-wide association studies have been conducted on personality disorders. However, many candidate gene studies have assessed the molecular genetic basis of antisocial (Basoglu et al., 2011; Douglas et al., 2011; Garcia et al., 2010; Li et al., 2012; Lyons-Ruth et al., 2007) and borderline (Hankin et al., 2011; Ni et al., 2006, 2007, 2009; Pascual et al., 2008; Perez-Rodriguez et al., 2010; Tadić et al., 2009; 2010; Wilson et al; 2009; Zaboli et al., 2006) personality disorders.

Studies on borderline personality disorder have associated genes regulating serotonin, noradrenalin, and dopamine neurotransmission to the risk of borderline personality disorder. In particular, certain single nucleotide polymorphisms (SNPs) and/or haplotypes of the serotonin transporter (5HTT) gene (Hankin et al., 2011; Lyons-Ruth et al., 2007; Ni et al., 2006, 2008; Tadić et al., 2009), tryptophan hydroxylase 1 (TPH-1: Wilson et al., 2009; Zaboli et al., 2006) and tryptophan hydroxylase 2 (TPH-2: Ni et al., 2008; Perez-Rodriguez et al., 2010) genes, monoamine oxidase A (MAO-A) gene variant (Ni et al., 2007) and catechol-O-methyl-transferase (COMT) genes (Tadić et al., 2009) have each been shown to predict an increased risk of borderline personality disorder. Interaction effects between these genes have also been observed (Ni et al.,

2009; Tadić et al., 2009). However, the majority of these effects have not been consistently replicated (e.g. Tadić et al., 2010), and more studies are needed to confirm whether these genes and/or interactions between them play a relevant role in the development of borderline personality disorder.

In a recent study, a SNP of the COL25A1 gene, previously associated with Alzheimer`s disease, was associated with an increased risk of antisocial personality disorder (Li et al., 2012). Another study found that polymorphisms of the SNAP 25 gene predicted antisocial personality disorder (Basoglu et al., 2011), and retrospectively assessed temperamental traits acted as moderators of this association. Also serotonin transporter genes have been in the focus of many studies on antisociality. One study suggested gene-gene interactions: individuals with two particular polymorphisms (5-HTTLPR and 5-HTTVNTR) of the serotonin transporter (5HT/SLC6A4) gene had a particularly heightened risk of antisocial personality disorder (Garcia et al., 2010). At least two other studies have assessed the main effects of the 5-HTTLPR genotype (Douglas et al., 2011; Lyons-Ruth et al., 2007) on antisocial personality disorder with conflicting results. One study found a predisposing effect of s/s genotype on both antisocial and borderline personality disorder traits (Lyons-Ruth et al., 2007). The other study showed no main effect of genotype on antisocial personality disorder. However, in that study, the 5-HTTLPR genotype showed an interaction effect with early life adversity in a subsample of African American women (Douglas et al., 2011). Also the MAO-A gene has been assessed as an etiological contributor to antisocial personality disorder but as discussed in detail later, it seems to interact with early life adversity in predicting antisocial outcomes rather than exert independent effects (Caspi et al., 2002; Fergusson et al., 2011; Kim-Cohen et al., 2006; Taylor & Kim-Cohen, 2007).

1.4.4 Temperament

Temperamental traits are considered the biological basis of adult personality (Caspi, Roberts, & Schiner, 2005). These highly heritable features present already in infancy, refer to the individual`s automatic, characteristic way of reacting to specific environmental stimuli such as novelty, danger, and reward (Basaglu et al., 2011). Their associations to personality disorders have been the focus of much research interest, and

temperamental traits indeed associate with the risk of personality dysfunction (Basaglu et al., 2011; Belsky et al., 2012; Carlson et al., 2009; Caspi et al., 1996; Fossati et al., 2001; Glenn et al., 2007; Joyce et al., 2003; Kantojärvi, Miettunen et al., 2008; Kimbrel et al., 2012; Mulder et al., 1994; Svrakic et al., 2002). However, the majority of this evidence stems from retrospective studies.

In a longitudinal study, Carlson and colleagues (2009) showed that temperamental traits of infant activity at six months and of emotionality at 30 months of age predicted borderline personality disorder symptomatology at 26 years of age. Correspondingly, higher scores on temperamental trait lack of control including features of emotional lability, negativism, restlessness, and short attention span, assessed at five years of age, prospectively predicted higher borderline personality symptoms at 12 years of age (Belsky et al., 2012). In the Dunedin cohort, observed behavioural differences in children at the age of three years, used as indicators of temperamental traits, prospectively predicted the risk of different types of mental disorders (Caspi et al., 1996), these including antisocial personality disorder, at 21 years of age. The risks of antisocial personality disorder and of violent crimes were notably increased among subjects with an undercontrolled behaviour style at three years of age. This behaviour style was described by irritable, impulsive, restless, and impersistent behaviour. In another large prospective study, temperamental traits of low fearfulness and low inhibition at three years of age predicted increased psychopathic personality traits in adulthood (Glenn et al., 2007). Although not a specific personality disorder in ICD-10 or DSM-IV, psychopathic features are very common among patients with antisocial personality disorder (Decuyper, De Fruyt, & Buschman, 2008; Miller & Lynam, 2011).

There thus seems to be particular temperament traits that predict personality disorders, and these effects are evident both in longitudinal and retrospective studies. Nevertheless, more longitudinal studies, especially on other personality disorders than borderline and antisocial, are needed to confirm whether, and if so, which temperament traits actually predict the development of personality disorders.

1.5 Early Life Environmental Adversity in the Developmental Origins of Personality Disorders

Although hereditary predispositions, whether assessed from the transmission of psychopathology across generations, from the heredity estimates of twin studies, from the predictive role played by candidate genes, or from the effects of markedly hereditary temperament traits, thus consistently contribute to the risk of personality disorders, in none of the studies is their explanatory power even close to complete. Hence, other, environmental factors also exert effects on the development of personality disorders. To explain the environmental, developmental origins of chronic adult diseases, David Barker (1995; 2004; Barker & Osmond 1986) developed the Developmental Origins of Health and Disease (DOHaD) –hypothesis, which suggests that early life environmental adversities may predispose to chronic diseases in adulthood.

1.5.1 The Developmental Origins of Health and Disease –framework

We suggest that the geographical distribution of ischaemic heart disease in England and Wales reflects variations in nutrition in early life, which are expressed pathologically in exposure to later dietary influences (Barker & Osmond, 1986).

A major public health concern in the latter part of the last century, especially from 1960s onwards was the steep increase in deaths for coronary heart disease (CHD) in Western societies at times when these societies were becoming more affluent. Lifestyle factors could offer a partial explanation. Namely, in more affluent societies the diet was becoming unhealthier and exercise levels were decreasing. However, these changes could not explain why this disease was becoming more frequent in lower socioeconomic groups, while the increase in CHD death rates was associated with increased affluence at the societal level (Barker & Osmond, 1986). In the 1970s and 1980s, geographical association studies in Norway (Forsdahl, 1977, 1978), in Great Britain (Barker & Osmond, 1986), and in the Netherlands (Ravelli, Stein, & Susser, (1976) suggested that impoverished living conditions in early life may predict the risk of CHD and its risk factors in adulthood. In these studies, heightened infant mortality in

a geographical area predicted increased adult mortality, particularly from cardiovascular causes, in the same areas four to seven decades later (Barker & Osmond, 1986; Forsdahl, 1977). Geographical associations between malnutrition exposures prenatally and/or in early postnatal life and adult obesity rates were also observed (Ravelli et al., 1976).

To explain these findings, David Barker put forward a hypothesis suggesting that environmental adversity (e.g. inadequate nutrition) in prenatal and early postnatal life may predict the risk of CHD and chronic disease more generally in adulthood (Barker & Osmond, 1986). This hypothesis was later in a revised form named the fetal origins hypothesis, which stated that environmental adversities during prenatal life may through enduring changes on developing organs place an individual at increased risk for chronic diseases subsequently: that is, vulnerability to chronic disease is programmed prenatally (Barker, 1995).

Yet later it was developed further to the DOHaD –hypothesis, which, in addition to prenatal adversities, includes also adversities occurring in early postnatal life, in infancy and in childhood (Barker, 2004). It states that a suboptimal environment in early life may permanently alter the structure and functioning of developing organs, tissue, cells, and body's biological feedback systems and by this mechanism leave an individual vulnerable to chronic disease. While such programming effects in response to an adverse environment may improve survival in the short term, they set forth an increased risk for chronic diseases later in life (Barker, 2004; Gluckman, Hanson, & Low, 2011).

Supporting this hypothesis, the associations between small body size at birth and/or preterm birth, crude proxies of prenatal environmental adversity, and CHD (Andersen et al., 2010; Barker et al., 2005; Eriksson et al., 1999; Fan et al., 2010; Huxley et al., 2005; Lawlor, Ronalds, Clark, Smith, & Leon, 2005), type II diabetes (Barker, Osmond, Kajantie, & Eriksson, 2009; Forsén et al., 2000; Kajantie, Osmond, Barker, & Eriksson, 2010; Mishra et al., 2008; Norris et al., 2012; Pilgaard et al., 2010; Whincup et al., 2008) and their biological risk factors (Barker et al., 1989; de Jong, Monuteaux, van Elburg, Gillman, & Belfort, 2012; Eriksson, Forsén, Kajantie, Osmond, & Barker, 2007; Hovi et al., 2010; Kajantie, Barker, Osmond, Forsén, & Eriksson, 2008; Norman, 2008; Norris et al., 2012; Pilgaard et al., 2010; Sandboge et al., 2012) are now well established. These effects are consistently evident in different cultures and independent of sociodemographic covariates and the time period when the subjects were born.

Consistent, corresponding associations emerge also for mortality. A recent meta-analysis (Risnes et al., 2011) showed that lower birth weight predicted higher all-cause and cardiovascular mortality, with effects leveling off at higher birth weight, at above four kilograms. These effects were similar among men and women. In contrast, among men only, higher birth weight predicted higher cancer mortality. On the other hand, preterm babies are also at increased risk of all-cause mortality, with effects extending onto adulthood (Crump, Sundquist, Sundquist, & Winkleby, 2011).

Several studies have showed that also slower growth in infancy and faster gain in BMI later in childhood predict the development of CHD (Barker et al., 2005, Eriksson et al., 1999) and type II diabetes (Eriksson, Osmond, Kajantie, Forsén, & Barker, 2006; Forsén et al., 2000). Also shorter attained height in childhood may predict CHD risk (Silventoinen, Baker, & Sorensen, 2012). Biological risk factors for CHD and diabetes are also associated with suboptimal growth in infancy and/or childhood (Eriksson et al., 2006, 2007: Jones et al., 2012; Kajantie et al., 2008; Sabo, Lu, Daniels, & Sun, 2012), and for the development of stroke, slower growth in infancy may be predictive (Osmond, Kajantie, Forsén, Eriksson, & Barker, 2007).

1.5.2 The Developmental Origins of Personality Disorders

In addition to the emphasis placed on the DOHaD framework on the early life developmental origins of chronic somatic illnesses, increasing amounts of research activity has examined the role of early life developmental factors in the etiology of adult mental disorders. The hypothesis that early life environmental adversity sets forth an increased risk for mental disorders in adulthood is shared by various theories in developmental and clinical psychology, both current and historical ones (Bateman & Fonagy, 2010; Belsky & Pluess, 2009; Bowlby, Miller, Winnicott, 1939; Bowlby, 1969, 1988; Freud, 1910; Harris & Seckl, 2011; Lupien, McEwen, Gunnar & Heim, 2009).

Research wise, the most optimal setting for examining the possible causal effects of early life adversity on adult mental health would be offered by experimental studies where subjects are randomly assigned to either the exposure or non-exposure group, keeping other confounding factors constant and following these subjects until adulthood. Animal studies with such an experimental design indeed convincingly show the long-

term effects of early life adversity on adult behaviour (Harris & Seckl, 2011; Wang et al., 2012; Weaver, Meaney, & Szef, 2006). However, in humans, conducting randomized experimental studies to assess the developmental consequences of particular early life adversities is impossible for ethical reasons.

Studies with retrospective self-report data of early life developmental adversities are possible and relatively easy to conduct and have been the most common research design. However, retrospective accounts of early adversity are open to serious validity problems. In general, people tend to underreport exposure to early life adversities (Hardt & Rutter, 2004; Scott, Smith, & Ellis, 2010). This kind of underreporting leads to false negatives, traumatic exposures left unreported. Since such underreporting is particularly characteristic of well-functioning individuals (Hardt & Rutter, 2004) studies based on retrospective accounts may overestimate the associations between early life adversity and later psychopathology.

Causality of early adversity effects on psychopathology can actually only be inferred from experimental studies. However, taking into consideration that such studies are ethically impossible, longitudinal studies with objective data on early life developmental factors can yield important information on the temporal relation of such associations and of their independence of possible recall bias.

Nevertheless, numerous studies with retrospective self-report measures of early life developmental factors have suggested that the risk of personality disorders in adulthood is associated with early life adversities. Such studies have shown that preterm birth and obstetric complications (Helgeland & Torgersen, 2004), and more extensively, early life interpersonal adversity [(e.g. insecure attachment, poor parenting, childhood maltreatment, and parental separation) (Agrawal et al., 2004; Bakermans-Kranenburg & van IJzendoorn, 2009; Bandelow et al., 2005; Battle et al., 2004; Byrne, Velamoor, Cernovsky, Cortese, & Losztyn, 1990; Crawford et al., 2006; Fossati et al., 2001; Gibbon, Ferriter, & Duggan, 2009; Huang et al., 2012; Igarashi et al., 2010; Joyce et al., 2003; Kimbrel et al., 2012; Mulder et al., 1994; Pert, Ferrier, & Saul, 2004; Saleptsi et al., 2004; Trull, 2001a, 2001b; Weaver & Clum, 1993; Westen et al., 2006; Wilson et al., 2012)] may be associated with an increased risk of personality disorders. While early life environmental factors also associate with the risk of other mental disorders (Abel et al., 2010; Bakermans-Kranenburg & van IJzendoorn, 2009; Battle et al., 2004; Cutajar

et al., 2010; Danese et al., 2009; Green et al., 2010; Igarashi et al., 2010; Joyce et al., 2003; Kessler et al., 2010; Saleptsi et al., 2004; Scott et al., 2010; Shenk, Noll, Putnam, & Trickett, 2010; Varese et al., 2012), specifically elevated rates of early interpersonal adversities also compared to individuals with other forms of psychopathology have been found among individuals with personality disorders (Bakermans-Kranenburg & van IJzendoorn, 2009; Battle et al., 2004; Byrne et al., 1990; Gibbon et al., 2009; Joyce et al., 2003; Saleptsi et al., 2004). However, these retrospective studies cannot imply anything about the direction of causation due to their methodological settings.

On the other hand, physical growth combines the effects of multiple environmental adversities and of genetic predispositions (Henrichs et al., 2010; Jones et al., 2010; Silventoinen et al., 2007, 2008, 2011) but its availability in national records and registers enables objective, longitudinal studies not dependent on the subjects' memories. Growth can be reliably used as a crude proxy of the developmental circumstances for each individual. Furthermore, studies based on register data identifying documented cases of specific early life adversities (e.g. maltreatment, parental separation, and maternal illnesses during pregnancy) (e.g. Johnson et al., 1999; Jonson-Reid et al., 2010; Tuovinen et al., 2012; Veijola et al., 2008; Widom et al., 2009) enable longitudinal studies not dependent on retrospective reports on the role played by particular developmental adversities. In addition, historical events have sometimes unfortunately offered naturalistic possibilities for examining the long-term consequences of specific adversities, as in the case of Dutch Hunger Winter studies examining the effects of prenatal malnutrition (Roseboom, Painter, van Abeelen, Veenendaal, & de Rooij, 2011) or in the Holocaust survivor studies assessing the health of the Holocaust surviving Jews in adulthood after this extreme early malnutrition and severe early life stress (Yehuda, Bierer, Andrew, Schmeidler, & Seckl, 2009).

The scanty available longitudinal studies on particular prenatal adversities in the etiology of personality disorders have shown that prenatal malnutrition may predict the risks of antisocial (Neugebauer, Hoek, & Susser, 1999) and schizotypal (Hoek et al., 1996) personality disorders among men. Maternal smoking during pregnancy has been shown to predict an increased risk of hospitalisation for personality disorder (Ekblad et al., 2010), and of criminal offending (Brennan, Grekin, & Mednick, 1999; Brennan, Grekin, & Mortensen, Mednick, 2002; D'Onofrio et al., 2010; Räsänen et al., 1999).

Offending is a characteristic symptom of antisocial personality disorder (APA, 2000), and the prevalence of personality disorders (Putkonen et al., 2010), especially antisocial (Black, Gunter, Loveless, Allen, & Sieleni, 2010) is very high among violent offenders. Maternal psychosocial stress during pregnancy prospectively predicts increased symptoms of borderline (Winsper et al., 2012), and antisocial (Rice et al., 2010) personality disorders and higher rates of criminal offending (Huttunen & Niskanen, 1978; Mäki, Veijola, Räsänen et al., 2003). Symptoms of schizotypal personality disorder are increased among offspring of mothers who were pregnant during an influenza epidemic (Machón et al., 2002; Venables, 1996), but whether a particular mother indeed had suffered from influenza was not assessed in these studies.

Longitudinal evidence also supports an etiological role for early life interpersonal adversity in the forms of insecure attachment (Carlson et al., 2009), poor parenting (Belsky et al., 2012; Johnson et al., 2006, 2011), and childhood maltreatment [emotional, physical, and sexual abuse and emotional and physical neglect (Belsky et al., 2012; Carlson et al., 2009; Cutajar et al., 2010; Johnson et al., 1999; 2000; 2001; Jonson-Reid et al., 2010; Luntz & Widom, 1994; Shenk et al., 2010; Widom et al., 2009)] in the development of personality disorders and related symptoms. Dramatic cluster personality disorders seem to be particularly strongly predicted by early relational adversity (Cutajar et al., 2010; Johnson et al., 1999, 2006). Genetically informed studies (Belsky et al., 2012; Johnson et al., 2006; 2011; Jonson-Reid et al., 2010) have suggested that the effects of these early interpersonal adversities on personality disorders are environmentally mediated, rather than effects confounded by gene-environment correlations. However, many longitudinal studies have assessed personality disorder symptoms only in childhood or adolescence, and studies on personality dysfunction justifying a personality disorder diagnosis in adulthood are scarce (Johnson et al., 1999; 2000; 2001, 2006; Widom et al., 2009).

The current study cohort, HBCS, has objective, record- and register-based longitudinal data on pre- and postnatal physical growth and on a particular early life exposure, namely on temporary separation from parents. Next, we turn our attention to what is known about pre- and postnatal physical growth and about parental separation in the development of mental and particularly personality disorders in adulthood, concentrating on the findings of longitudinal studies.

1.5.3 Preterm Birth, Early Life Growth and Mental Disorders

Recently, the DOHaD framework has also attracted more attention in studies focusing on the etiology of mental disorders. Schizophrenia has been the most studied mental disorder within the DOHaD framework (Abel et al., 2010; Cannon, Jones, & Murray, 2002; Gunnell et al., 2005; Gunnell, Rasmussen, Fouskakis, Tynelius, & Harrison, 2003; Haukka, Suvisaari, Häkkinen, & Lönnqvist, 2008; Moilanen et al., 2010; Niemi, Suvisaari, Haukka, & Lönnqvist, 2005; Nilsson et al., 2005; Perrin, Chen, Sandberg, Malaspina, & Brown, 2007; Wahlbeck, Forsén, Osmond, Barker, & Eriksson, 2001; Wegelius et al., 2011; Welham et al., 2009). In their meta-analytic study in 2002, Cannon and colleagues showed that low birth weight [LBW; < 2500 grams (g)] predicted a higher risk of schizophrenia, while small head circumference showed a marginally significant association. More recent evidence also suggests that suboptimal prenatal growth is predictive of adult schizophrenia (Abel et al., 2010; Gunnell et al., 2003, 2005; Niemi et al., 2005; Nilsson et al., 2005), and that such associations may also be evident among twins (Nilsson et al., 2005). This suggests an independent predictive role for fetal growth restriction in schizophrenia development. In addition to lower birth weight (Abel et al., 2010; Moilanen et al., 2010; Nilsson et al., 2005; Wahlbeck et al., 2001), many other indices of suboptimal prenatal growth have been associated with increased schizophrenia risk, with prematurity (Abel et al., 2010), small head circumference (Nilsson et al., 2005), lower placental weight (Wahlbeck et al., 2001) and shorter length at birth (Gunnell et al., 2005; Moilanen et al., 2010; Wahlbeck et al., 2001) each showing significant effects. Some evidence suggests that the effects of birth size on schizophrenia may be nonlinear (Gunnell et al., 2003; Moilanen et al., 2010); the highest risks being observed among the smallest babies, but increased risks compared to those with birth weight between three and four kilograms being found also among babies weighing over four (Gunnell et al., 2003) or 4.5 (Moilanen et al., 2010) kilograms. This nonlinearity might explain some of the inconsistencies in the findings, as not all studies report significant effects of birth size (Haukka et al., 2008; Perrin et al., 2007), and some report associations in the opposite direction (Wegelius et al., 2011; Welham et al., 2009), with the biggest babies showing the highest risks. However,

nonlinear effects have not been studied extensively and do not emerge in all studies (e.g. Abel et al., 2010; Wahlbeck et al., 2001).

Prematurity and/or suboptimal prenatal growth may also play a role in the etiology of other mental disorders. The largest study in the field to date was conducted combining datasets from Sweden and Denmark (Abel et al., 2010). Among over 3,000,000 participants, lower birth weight predicted an increased risk of mental disorders requiring hospitalisation, independently of diagnostic outcome. The risk was increased for all the diagnostic groups studied; substance use disorders, neurotic and stress-related disorders, mood disorders, and schizophrenia. The increased risk was independent of parental psychopathology, sex, year of birth, and social class; and evident across the whole birth weight spectrum. Also both being born preterm and being born small for gestational age (SGA) exerted independent, significant effects on all the diagnostic categories studied.

While Abel and colleagues (2010) assessed mood disorders as one general category, several other studies have suggested that slower prenatal growth and/or preterm birth may particularly predict an increased risk of depression (Alati et al., 2007; Costello, Worthman, Erkanli, & Angold, 2007; Danese et al., 2009; Gale & Martyn, 2004; Räikkönen et al., 2007; Räikkönen, Pesonen, Heinonen, Kajantie, et al. 2008; Thompson, Syddall, Rodin, Osmond, & Barker, 2001), although the findings are inconsistent (Herva et al., 2008; Vasiliadis, Gilman, & Buka, 2008).

Assessed across its whole range of variation, smaller body size at birth has in several studies been associated with the risk of anxiety disorders such as post-traumatic stress disorder (Betts, Williams, Najman, & Alati, 2011) and generalized anxiety disorder (Vasiliadis, Buka, Martin, & Gilman, 2010). Smaller body size at birth and prematurity have also been associated with an increased risk of suicide, but the findings are inconsistent (Cnattingius, Svensson, Granath, & Iliadou, 2011; Danziger, Silwerwood, & Koupil, 2011; Lindström, Lindblad, & Hjern, 2009; Mathiasen, Hansen, Forman, Kessing, & Greisen, 2011; Mittendorfer-Rutz, Wasserman, & Rasmussen; 2008; Young, Riordan, & Stark 2011).

Many studies have also assessed the risk of psychopathology particularly among individuals born at the lowest extremities of birth size, among individuals with LBW (Burnett et al., 2011; Elgen, Holsten, & Odberg, 2012; Nomura, Brooks-Gunn, Davey, Ham, & Fifer, 2007), very low birth weight (VLBW; < 1500 g) (Hack et al., 2004; Lund,

Vik, Skranes, Brubakk, & Indredavik, 2011; Räikkönen, Pesonen, Heinonen, Kajantie, et al. 2008; Westrupp, Northam, Doyle, Callanan, & Anderson, 2011) or extremely low birth weight (ELBW; < 1000 g; Boyle et al., 2011). These studies have highlighted the heightened risk of psychopathology in general and particularly of internalizing symptoms among individuals born ELBW (Boyle et al., 2011), VLBW (Hack et al., 2004; Lund et al., 2011; Westrupp et al., 2011), and LBW (Burnett et al., 2011; Elgen et al., 2012; Nomura et al., 2007). Among men, associations of LBW to alcohol use disorders in adulthood have also been reported (Knop et al., 2003).

Preterm birth may exert its own effects on the risk of mental disorders, independently of birth size, as suggested by the study of Abel and colleagues (2010). Two studies with partially overlapping samples with that study also showed that the risk of any mental disorder requiring hospitalisation in adolescence and young adulthood is increased among individuals born preterm (Lindström et al., 2009; Mathiasen et al., 2011). A recent meta-analysis found that the risk of receiving any psychiatric diagnosis between ages 10-25 years was 3.7-fold and particularly of anxiety or depressive disorders 2.8 -fold among individuals born preterm or with LBW (Burnett et al., 2011) compared to term-born controls. However, although prematurity exerts independent effects, particularly increased risks of psychopathology have often been found also among subjects born SGA (Abel et al., 2010; Boyle et al., 2011; Lund et al., 2011; Räikkönen, Pesonen, Heinonen, Kajantie, et al. 2008), suggesting particular effects of fetal growth restriction.

Suboptimal prenatal growth and/or prematurity also emerge as risk factors for disorders of psychological development. In particular, several studies have shown that the risks of ADHD (Galera et al., 2011; Groen-Blokhuis, Middeldorp, van Beijsterveldt, & Boomsma, 2011; Gustafsson & Källén, 2011; Heinonen et al., 2011; Hultman et al., 2007; J. Lahti et al., 2006; Strang-Karlsson et al., 2008) and of autism spectrum disorders (Guinchat et al., 2011; Losh et al., 2012) are predicted by slower prenatal growth and/or prematurity. Furthermore, twin studies (Groen-Blokhuis et al., 2011; Hultman et al., 2007; Losh et al., 2012) suggest that, for both of these disorders, the predisposing effects of lower birth weight are independent of genetic effects, since independent, significant associations are found also among monozygotic twins. Hence,

the findings support an independent predictive role for prenatal environmental factors in the development of autism and ADHD.

Infancy and childhood growth has repeatedly been assessed in relation to schizophrenia, with inconsistent findings (Gunnell et al., 2005; Haukka et al., 2008; Perrin et al., 2007; Niemi et al., 2005; Sørensen, Mortensen, Reinisch, & Mednick, 2006; Wahlbeck et al., 2001). In a Finnish study, the risk of schizophrenia was highest in those individuals who were shortest at birth and thinnest at seven years of age (Wahlbeck et al., 2001). In contrast, among offspring of mothers with psychosis, being thin at birth but belonging to the highest tertile in BMI at seven years predicted an increased risk of schizophrenia (Niemi et al., 2005). Another study found that women with schizophrenia had grown slower in height between birth and 2.5 years (Perrin et al., 2007). A study among subjects who had family members with schizophrenia found no differences in the growth of those who developed or did not develop schizophrenia (Haukka et al., 2008). On the other hand, among men, two studies suggested that thinness at 18 years of age may predict schizophrenia (Gunnell et al., 2005: Sørensen et al., 2006), while one of them also showed a significant association between low body weight (Sørensen et al., 2006) and the other between short stature (Gunnell et al., 2005) at 18 years and the risk of schizophrenia. No associations between body size at 18 years and schizophrenia were found among women (Gunnell et al., 2005). Finally, a study assessing the role of growth in the development of psychotic symptoms at 12 years of age found that lower birth weight but not postnatal growth predicted increased psychotic symptoms (Thomas et al., 2009).

In contrast, studies on the associations between infancy and childhood growth and other mental disorders are much scantier. Two studies (Anderson, Cohen, Naumova, Jacques, & Must, 2007; Anderson, Cohen, Naumova, & Must, 2006) in the same cohort assessed the associations between BMI and change in it from the age of nine years onwards and the risk of anxiety and depressive disorders. Among women, obesity in adolescence predicted higher risks of both these disorders in adulthood (Anderson et al., 2007). There was a linear association between higher attained BMI in adolescence and in early adulthood and anxiety disorders, while the risk of depressive disorders was associated with higher BMI gain from adolescence onwards (Anderson et al., 2006).

Among men, depression in childhood was associated cross-sectionally with lower BMI but in later ages, no such association was found.

In an early study (Barker, Osmond, Rodin, Fall, & Winter, 1995), slower weight gain between birth and one year of age predicted an increased risk of suicide. Shorter height (Magnusson, Gunnell, Tynelius, Davey Smith, & Rasmussen, 2005; Mittendorfer-Rutz et al., 2008) and lower BMI (Batty, Whitley, Kivimäki, Tynelius, & Rasmussen, 2010; Magnusson, Rasmussen, Lawlor, Tynelius, & Gunnell, 2006; Osler, Nybo Andersen, & Nordentoft, 2008) at 18 years of age have repeatedly shown associations with later risk of suicide and suicide attempts. For ADHD and autism, growth in infancy has been shown to be predictive. Smaller head circumference from birth onwards throughout infancy and slower BMI gain between 20 and 56 months of age were both found to predict higher ADHD symptoms (Heinonen et al., 2011). Autism, on the other hand, has been associated with accelerated head (Chawarska et al., 2011; Courchesne et al., 2011) and possibly accelerated length and weight growth (Chawarska et al., 2011) in infancy.

1.5.4 Pre- and Postnatal Growth and Personality Traits

Associations of pre- and postnatal growth to dimensionally evaluated personality and temperament traits, both of which are associated with the risk of personality disorders (Samuel & Widiger, 2008; Svrakic et al., 2002), have repeatedly been shown (Allin et al., 2006; Congdon et al., 2012; J. Lahti et al., 2008; Pesonen et al., 2006, 2008, 2009; Pyhälä et al., 2009; Räikkönen, Pesonen, Heinonen, J. Lahti, et al. 2008; L. Schmidt, Miskovic, Boyle, & Saigal, 2008). Thinness at birth predicted higher temperamental trait negative affectivity at five years of age (Pesonen et al., 2006). In a study among preterm babies, lower birth weight, smaller head circumference, and shorter length at birth predicted higher negative affectivity and lower effortful control at two years of age (Pesonen et al., 2009). In the NFBC, temperamental trait persistence in adulthood was, among women, predicted by shorter birth length (Congdon et al., 2012). On the other hand, earlier studies in the HBCS have found that lower birth weight and shorter length at birth were associated with higher scores on temperamental trait harm avoidance in late adulthood (J. Lahti et al., 2008), and that high scores on personality trait hostility were predicted by small body size at birth and slower infancy growth (Räikkönen,

Pesonen, Heinonen, J. Lahti., et al. 2008). Also in the HBCS, higher trait anxiety in old age was predicted by smaller body size at birth, in infancy, and again in adulthood (J. Lahti et al., 2010). Of postnatal growth, faster growth between seven and 11 years and slower growth between 11 years and adulthood were especially predictive.

In the Helsinki Study of VLBW Young Adults, young adults born with VLBW scored higher on the Five Factor Model personality traits of conscientiousness and agreeableness and lower on openness to experience than term-born controls (Pesonen et al., 2008). VLBW young adult women born SGA also scored higher than term-born women on behavioral inhibition (Pyhälä et al., 2009). On the other hand, in a Canadian study, young adults born with ELBW scored higher on shyness, behavioural inhibition, and socialization and lower on sociability than term-born controls (L. Schmidt et al., 2008), and in a study among 18 year-olds, very preterm birth predicted higher neuroticism and lower extraversion (Allin et al., 2006).

Hence, accumulating evidence suggests that in addition to somatic health, both suboptimal prenatal growth and shorter length of gestation may predict the risk of mental disorders and individual differences in temperament and personality traits, and that these effects may extend across the lifespan. Suboptimal prenatal growth and shorter length of gestation seem to be general vulnerability factors for psychopathology rather than specific risk factors only to certain disorders. In addition, twin studies and studies with controls for parental psychopathology suggest that the effects of body size at birth on mental disorders may be independent of genetic liabilities (Hultman et al., 2007; Losh et al., 2012; Nilsson et al., 2005). Such environmental causation has, however, been studied rarely, and needs confirmation in further studies. Furthermore, although poor childhood socioeconomic position is associated with pre- and postnatal growth and with the risk of mental disorders (e.g. Danese et al., 2009; Grantham-McGregor et al., 2007), many studies have found that the effects of pre-and postnatal growth on psychopathology and on personality traits are also independent of childhood socioeconomic adversity (Abel et al., 2010; Boyle et al., 2011; Lindström et al., 2009; Perrin et al., 2007; Räikkönen, Pesonen, Heinonen, J. Lahti, et al. 2008).

A limitation of the available studies is that the majority of them have assessed only the effects of prematurity or the most widely available measure of body size at birth, birth weight. Much fewer studies have assessed the associations of length, head

circumference, or ponderal index at birth, or the importance of the placenta on mental health and disorders. Furthermore, some studies suggest that the effects of birth size and/or prematurity on mental disorders may be sex-specific (e.g. Monfils Gustafsson et al., 2009; Thompson et al., 2001), or that the associations of birth size with mental disorders (Gunnell et al., 2003; Moilanen et al., 2010) and temperament traits (J. Lahti et al., 2008) may be nonlinear. However, the findings on the modifying role of sex are inconclusive, and the possible nonlinearity of these associations has not been assessed thoroughly. Also the effects of infancy and childhood growth on psychopathology, especially on other mental disorders than schizophrenia, have been studied too rarely to draw any firm conclusions.

1.5.5 Preterm Birth, Early Life Growth and Personality Disorders

To date, only few studies (Boyle et al., 2011; Carlson et al., 2009; Elgen et al., 2012; Fazel et al., 2012; Helgeland & Torgersen, 2004; Ikäheimo et al., 2007; Khalife et al., 2012; J. Lahti et al., 2009; Monfils Gustafsson et al., 2009) have assessed the possible associations between gestation length and/or pre- and postnatal growth with personality disorders and their symptoms. In a Swedish study, compared to controls with no hospitalisation for mental disorders, offenders with personality disorders had more often been born preterm, and with LBW and a small head circumference (< 33 cm) at birth (Fazel et al., 2012). This study comprised 150 subjects with personality disorder and 1,498 healthy controls. Also being born SGA predicted an increased risk of personality disorders. The findings showed that preterm birth predicted the risk of severe personality disorders also in comparison to approximately 100 offenders with no mental disorder matched for sex, socioeconomic position in childhood, and for ethnicity. Prematurity had the strongest independent effects of perinatal measures on personality disorders (Fazel et al., 2012). On the other hand, in a large epidemiological study, boys born preterm and SGA were at an increased risk of hospitalisation for personality disorders in young adulthood (Monfils Gustafsson et al., 2009), but neither factor alone predicted hospitalisation for personality disorders, and there were no significant effects among women. In another longitudinal study, ELBW young adults had significantly higher levels of avoidant but not antisocial personality disorder problems in young

adulthood in comparison to normal birth weight controls (Boyle et al., 2011). A recent study found an over twofold but non-significantly increased risk of antisocial personality disorder in young adulthood among individuals born with LBW, which was defined here as birth weight below two kilograms (Elgen et al., 2012). However, the sample size of that study was very small, and no conclusions from the non-significant association to antisocial personality disorder can be made, especially since LBW individuals did have a significantly increased risk of any mental disorder (Elgen et al., 2012). On the other hand, two studies with generalized measures of peri- and prenatal adversities, these including prematurity, did not find associations between these adversities and borderline personality disorder (Carlson et al., 2009; Helgeland & Torgersen, 2004). However, also these studies had small samples.

Among over 3,000 boys, a larger weight and surface area of the placenta at birth predicted higher risks of antisocial problems and overall psychiatric disturbance at eight years of age, and of ADHD symptoms at eight and at 16 years of age (Khalife et al., 2012). However, many of these effects, including those found on antisociality, became significant only after adjustment for birth size and gestational length, suggesting compensatory placental growth to be particularly relevant rather than linearly increased placental size. In contrast, no associations between placental size and mental health outcomes were found among the over 3,000 women of this sample.

Two longitudinal studies among approximately 5,000 subjects assessed prenatal and infancy growth in relation to personality disorder symptoms in young adulthood (Ikäheimo et al., 2007; J. Lahti et al., 2009). The earlier study, conducted among men only, showed that smaller head circumference and larger BMI at one year of age predicted higher levels of violent offending, identified from official criminal records, in adulthood (Ikäheimo et al., 2007). On the other hand, higher scores on positive schizotypal traits (distorted perceptions of one`s body or other objects) were predicted by lower placental weight at birth, lower birth weight and smaller head circumference at one year of age (J. Lahti et al., 2009) among women. Also among women, longer length of gestation adjusted for body size at birth predicted elevated levels of negative schizotypal symptoms (physical anhedonia).

Hence, while the few available studies suggest that suboptimal prenatal and/or infancy growth may predict the risk of personality disorders and their symptoms,

possibly in a sex-specific manner, the evidence is scarce and inconclusive. Furthermore, no studies have assessed the associations between body size at birth or length of gestation across their whole ranges of variation with diagnosed personality disorders. There is hence a clear need for further study.

There are no previous studies on physical growth between specific ages in infancy or in childhood and personality disorders. However, a cross-sectional small-scale study found that adolescent boys with schizoid personality had significantly lower attained BMI than a German population-based reference sample (Hebebrand et al., 1997).

1.5.6 Parental Separation and Personality Disorders

> It is quite possible for a child of any age to feel sad or upset at having to leave home, but the point that we wish to make is that such an experience in the case of a little child can mean far more than the actual experience of sadness. It can in fact amount to an emotional "black-out," and can easily lead to a severe disturbance of the development of the personality which may persist throughout life.
>
> … If these opinions are correct it follows that evacuation of small children without their mothers can lead to very serious and widespread psychological disorder. For instance, it can lead to a big increase in juvenile delinquency in the next decade (Bowlby et al., 1939, pp. 1202-1203).

An early life stressor with long-lasting effects on offspring development is separation from parents in early childhood. Early life stress is conceptualized as different types of adverse experiences in early development, including childhood maltreatment (sexual, verbal, emotional, and physical abuse and parental neglect), socioeconomic adversity in childhood, poor parenting, insecure attachment, and parental separation. Already in 1939, Bowlby postulated the aforementioned hypothesis as how parental separation, in the aforementioned case due to child evacuations from United Kingdom during World War II, may affect personality development until adulthood.

However, longitudinal evidence on such effects of parental separation on personality disorders is scanty. Studies conducted in the NFBC have shown that children who had a single parent at birth, at age 14 or whose parents had divorced were at an increased risk of personality disorders requiring hospitalisation in adulthood (Mäkikyrö, Sauvola et al., 1998). A follow-up study (Kantojärvi, Joukamaa et al., 2008) in the same cohort showed that the effects of single parent family status at birth were particularly characteristic of dramatic personality disorders, and evident also on personality disorders not in need of hospitalisation. Furthermore, another prospective study found that early maternal separation, particularly before five years of age, predicted elevated borderline personality disorder symptoms and a lesser decline in them from adolescence to young adulthood (Crawford, Cohen, Chen, Anglin, & Ehrensaft, 2009). These effects were independent of several confounders, such as temperament and early maltreatment history.

Antisocial personality disorder related traits (e.g., antisocial personality symptoms, psychopathy, and criminal offending) have repeatedly been shown to be prospectively predicted by early parental separation. A prospective study showed that parental separation predicted an increased risk of psychopathic disorder and other antisocial traits (Cederblad, Dahlin, & Hagnell, 1988). A recent study showed that parental separation, particularly in the first three years of life, prospectively predicted psychopathic personality in adulthood (Gao, Raine, Chan, Venables, & Mednick 2010). However, this study included only six separated subjects, thus limiting the generalizability of the findings. Among men, violent and non-violent offending have been shown to be prospectively predicted by temporary parental separation at birth (Mäki, Hakko et al., 2003) and by parental death or divorce in childhood (Sauvola et al., 2002). A single parent family type at birth or throughout childhood predicted particularly violent offending. Among women, temporary parental separation at birth predicted an increased risk of non-violent offences (Mäki, Hakko et al., 2003), while violent crimes were too rare to be studied. Also other prospective studies have shown that, separation from parents, especially when due to parental imprisonment, is associated with increased antisocial symptoms in child- and adulthood (Murray & Farrington, 2005; for a meta-analytic review, see Murray, Farrington, & Sekol, 2012), and behavioural genetic evidence from adoption studies suggests that parental

separation sets forth rather environmentally than genetically mediated effects on antisociality (Burt, Barnes, McGue, & Iacono, 2008).

A Swedish study assessing the mental well-being of intercountry adoptees found that children adopted from abroad showed higher rates of any and severe criminal offences, other indices of social maladjustment, mental disorders, and suicide attempts and completed suicide than their Swedish-born counterparts (Hjern, Linneblad, & Vinnerljung, 2002). In contrast, although a Dutch study also showed higher rates of any mental disorder, and more specifically substance use, anxiety, and, among men, mood disorders among intercountry adoptees than among the Dutch-born non-adopted children, the adopted children did not differ from those without adoption exposure in their risks of antisocial personality disorder (Tieman, van der Ende, & Verhulst, 2005) in young adulthood. However, in these adoption studies the adopted individuals may have come from very different early life circumstances than the non-adopted controls, and it is difficult to separate the particularly important exposures here; whether they all occurred before adoption or whether the parental separation caused by the adoption had its own impact on well-being.

Parental separation in childhood thus seems to predict the risk of personality disorders, especially disorders of the dramatic cluster, although there is a need for further longitudinal studies, especially among individuals with personality disorders justifying a diagnosis. More detailed study questions concern whether the effect of parental separation is specific to personality disorders in comparison to other mental disorders and does age at separation or duration of separation exposure modify these associations. That is, are early or later separations more influential on offspring personality development, and are longer or shorter separations more harmful?

Indeed, prospective studies suggest that borderline personality disorder symptoms may be particularly increased among children with early childhood parental separation, particularly before five years of age (Crawford et al., 2009), and that psychopathic personality is predicted particularly by parental separation in the first three years of life (Gao et al., 2010). Furthermore, the NFBC study suggested much stronger associations of single parent family status at birth than at 14 years of age with any personality disorder and with dramatic personality disorders (Kantojärvi, Joukamaa et al., 2008).

However, a meta-analytic study of parental incarceration effects on antisociality found no modifying effects of age at separation due to imprisonment (Murray et al., 2012).

There is also some evidence suggesting that duration of separation may modify its long-term effects (Anglin, Cohen, & Chen, 2008; Pesonen et al., 2007). A longitudinal study showed that longer separation duration from the mother in the first two years of life predicted higher schizotypal personality disorder symptoms in adolescence and adulthood (Anglin et al., 2008), and in the HBCS, particularly parental separations of longer duration predicted higher depressive symptoms in adulthood (Pesonen et al., 2007). In contrast, no longitudinal studies have shown modifying effects of separation duration on diagnosed personality disorders.

The evidence on the possible specificity of parental separation effects on personality disorders in comparison to other mental disorders is scarce and inconsistent. In a longitudinal study (Helgeland & Torgersen, 2004), parental separation did not predict borderline personality disorder in a small sample of subjects identified at a psychiatric ward in their adolescence (Helgeland & Torgersen, 2004). However, a high number of the subjects in the control group had other, non-borderline personality disorders, thus the study assessed specificity only for borderline personality disorder. In contrast, three studies showed that the rates of retrospectively self-reported parental separation were higher among individuals with personality disorders than among individuals with schizophrenia (Byrne et al., 1990; Gibbon et al., 2009; Pert et al., 2004). However, retrospectively self-reported parental separation did not differentiate depressed patients with borderline personality disorder from depressed patients without this comorbidity (Weaver & Clum, 1993).

The evidence on the specificity of the association between parental separation and personality disorders is hence contradictory, suggesting specificity in comparison to schizophrenia but not to depression, and stems only from retrospective studies. Furthermore, the study samples have been small (Weaver & Clum, 1993; Byrne et al., 1990; Helgeland & Torgersen, 2004) or comprised only subjects with a criminal history (Gibbon et al., 2009; Pert et al., 2004), which limits the generalizability of the findings.

Concerning the specificity question, it is important to note that parental separation has also been prospectively shown to predict an increased risk of other, non-personality, mental disorders. For example, a series of longitudinal studies (Mäki, Hakko et al., 2003;

Mäki, Veijola, Joukamaa et al., 2003; Veijola et al., 2004, 2008) assessed the effects of temporary parental separation at birth due to maternal tuberculosis on the psychological well-being of the offspring in adulthood. In addition to showing predisposing effects on criminality as mentioned above (Mäki, Hakko et al., 2003), these studies showed that temporary parental separation at birth was associated with an increased risk of hospitalisation for substance use disorders (Veijola et al., 2008), and among men also for mood disorders (Veijola et al., 2004) but had no effect on schizophrenia risk (Mäki, Veijola, Joukamaa et al., 2003). In the NFBC, in addition to predicting personality disorders, parental divorce also predicted severe alcohol use and anxiety disorders (Mäkikyrö, Sauvola et al., 1998). Parental death in childhood predicted hospitalisation for mood disorders. In an earlier study in the HBCS, separation from both biological parents in childhood prospectively predicted increased depressive symptoms in old age (Pesonen et al., 2007). Hence, in addition to personality disorders, the risks of mood (Mäkikyrö, Sauvola et al., 1998; Pesonen et al., 2007; Veijola et al., 2004) and substance use disorders (Mäkikyrö, Sauvola et al., 1998; Veijola et al., 2008) have repeatedly been shown to be elevated among individuals with parental separation in childhood.

In addition to the aforementioned evidence of sex possibly modifying the effects of physical growth on personality disorders (Khalife et al., 2012; J. Lahti et al., 2009; Monfils Gustafsson et al., 2009), there is some evidence suggesting that also the effects of parental separation at least on antisocial personality disorder traits may be stronger among men (Murray et al., 2012; Mäki, Hakko et al., 2003; Sauvola et al., 2002). However, the evidence of the modifying the effects of sex on the associations between parental separation and antisocial or other personality disorders is inconclusive (Murray et al., 2012; Mäkikyrö, Sauvola et al., 1998).

1.5.7 Socioeconomic Adversity in Early Life and Personality Disorders

Socioeconomic position in childhood, defined usually based on indicators of parental income, occupational status, or education level, is associated with early life growth and with the levels of early life stress (Grantham-McGregor et al., 2007; Kang Sim et al., 2012; Widom et al., 2009). Studies also support an inverse association between different

indicators of socioeconomic position in childhood, especially financial hardship, and the risk of mental disorders (Danese et al., 2009; McLaughlin et al., 2011).

The evidence of effects on personality disorders is inconclusive, however. In a longitudinal study, lower socioeconomic position in childhood, as defined by an index combining parental educational level, occupational level and household income, independently predicted higher levels of self-reported borderline and schizotypal personality disorder symptoms in adolescence and adulthood (Cohen et al., 2008). Independent effects of poverty on borderline symptoms from the same cohort have also been reported (Crawford et al., 2009). Longitudinal evidence also suggests that the risk of adult antisocial personality disorder is increased among boys with lower socioeconomic position in childhood (Lahey et al., 2005). In contrast, Widom and colleagues (2009) did not find significant effects of having a parent on welfare on the risk of diagnosed borderline personality disorder, and in the NFBC, the risks of personality disorders of any cluster did not differ as a function of childhood socioeconomic position (Kantojärvi, Joukamaa et al., 2008). The findings are thus contradictory and more studies are needed to elucidate whether lower childhood socioeconomic position is indeed a risk factor for personality disorders.

Since poorer socioeconomic position in childhood may be associated with the risk of personality disorders, and is associated with suboptimal growth pre- and postnatally and with higher levels of early life adversity, it is also a possible confounder of the associations between other early life adversities and personality disorders. Of the available longitudinal studies assessing the effects of physical growth or parental separation on personality disorders or on their symptoms, most have controlled for the effects of childhood socioeconomic position (Boyle et al., 2011; Carlson et al., 2009; Crawford et al., 2009; Gao et al., 2010; Ikäheimo et al., 2007; Kantojärvi, Joukamaa et al., 2008; Khalife et al., 2012; J. Lahti et al., 2009; Monfils Gustafsson et al., 2009; Murray & Farrington, 2005; Mäkikyrö, Sauvola et al., 1998), while others have not (Fazel et al., 2012; Helgeland & Thoresen, 2004). Overall, when assessed, these studies have found that the associations between these early life adversities and personality disorders have been independent of socioeconomic adversity. Nevertheless, since longitudinal studies on the effects of parental separation and pre- and postnatal growth

on diagnosed personality disorders are still scarce, consideration of possible confounding by socioeconomic position in childhood is still needed in further studies.

There is also some evidence that socioeconomic position in childhood may modify the effects of separation from biological parents, at least when it is due to adoption, on mental disorders in adulthood (Tieman et al., 2005). Children with higher socioeconomic position in childhood were shown to differ from their non-adopted counterparts more than those from lower socioeconomic groups. Hence, in this thesis, childhood socioeconomic position is assessed both as a possible independent predictor of severe personality disorders, as a possible mediator of the effects of growth and parental separation on personality dysfunction, and as a potential modifier of the effects of temporary parental separation.

1.5.8 Perinatal Covariates: Maternal Age at Childbirth and Parity

In the recent study on perinatal circumstances and personality disorders among offenders, both teenage childbirth and multiparity in the form of being born to mothers with two or more previous children were associated with an increased risk of offspring personality disorders (Fazel et al., 2012). Both risks were elevated in comparison to healthy controls with no criminal history or severe mental disorder, while teenage birth also predicted an increased risk of personality disorders particularly among offenders. In contrast, the NFBC study showed no effect of teenage birth on any personality disorder (Kantojärvi, Joukamaa et al., 2008).

However, previous studies suggest that younger maternal age at childbirth may be especially associated with personality disorders of the dramatic cluster (Kantojärvi, Joukamaa et al., 2008) and with the symptoms related to these disorders (Farrington, 2000; Jaffee, Caspi, Moffitt, Belsky, & Silva, 2001; Kuja-Halkola et al., 2012; Mitrou et al., 2010). In contrast, grand multiparity, in particular being born to mothers with six or more previous deliveries was not associated with the risk of severe personality disorders in the NFBC, although it was associated with other severe mental disorders (Kemppainen et al., 2000).

Being born to younger (Gibbs, Wendt, Peters, & Hogue, 2012), and to primiparous mothers (Shah, 2010) predict prematurity and lower birth weight. In our study cohort,

maternal age at childbirth and parity were also associated with the probability of being evacuated (Pesonen et al., 2007; 2010), and these factors were hence controlled for in the analyses on the associations between body size at birth, gestation length, and parental separation and any and dramatic personality disorders.

1.6 Neurobiological Mechanisms for the Long-Term Effects of Early Life Environmental Adversity and Neurobiological Origins of Personality Disorders

1.6.1 The Life Cycle Model

Although no studies in this thesis directly assess the neurobiological underpinnings of personality disorders, I present here an overview of some of the potential neurobiological pathways through which early life adversity may exert its possible effects on personality dysfunction.

According to the DOHaD hypothesis, developmental adversities reflected in physical growth lead to an increased risk of chronic illnesses by programming the structure and function of target organs, cells, and tissues (Barker, 2009). Since growth and specific early life adversities such as parental separation seem to be associated with the risk of mental disorders, this suggests that the developing brain may be particularly susceptible to such programming effects.

In conjunction, the life cycle model of stress by Lupien and colleagues (2009) states that exposure to environmental adversity in early life can have long-lasting effects on brain development, particularly on the development of the brain areas implicated in the regulation of stress. Brain areas implicated in the stress system include, among others, the hypothalamus-pituitary-adrenal cortex (HPA)-axis, amygdala, hippocampus, and the prefrontal cortex. This system is interconnected with feedback loops at different stages (Charmandari, Tsigos, & Chrousos, 2005; Lupien et al., 2009).

By affecting the functioning of this system, early life adversity then exerts its effects on later psychopathology (Lupien et al., 2009). The life cycle model suggests that exposure to stress at a particular age would be associated with especially evident changes in the development of those brain regions that have their highest developmental

plasticity during those ages. During the prenatal period, programming effects on the structures that regulate the HPA axis, hippocampus, amygdala, and the prefrontal cortex all take place (Lupien et al., 2009). Thereafter, hippocampus develops most rapidly in the early postnatal years, from birth to two years, while amygdala continues developing throughout childhood and adolescence. The most important period for the development of the prefrontal cortex is adolescence. Hippocampus, amygdala, and prefrontal cortex all regulate the development and functioning of the HPA axis, and the effects of environmental adversity on the development of these brain areas are then also reflected in corresponding long-lasting changes in HPA axis function (Lupien et al., 2009).

According to the life cycle model (Lupien et al., 2009) early life stress at a certain age exerts predisposing effects especially for those mental disorders that are characterized by changes in the functioning of the brain areas that have their highest developmental plasticity at this age. Hence, if a disorder is characterized by hippocampus function or structure changes and cortisol levels that correspond to the changes caused by stressors in infancy, vulnerability for this disorder would be most affected by environmental adversity in infancy.

Supporting this model, animal studies consistently show that exposure to pre- and postnatal environmental adversities lead to long-lasting neurobiological and behavioral changes in the offspring (Banerjee, Arterbery, Fergus, & Adkins-Regan, 2012; Glover, O`Connor, & O`Donnell, 2010; McGowan et al., 2011; Vieau et al., 2007; Weaver et al., 2006). These studies show that early life adversities such as prenatal malnutrition (Vieau et al., 2007), maternal stress during pregnancy (for a review, see Glover, O`Connor, & O`Donnell, 2010), maternal separation (Feng et al., 2011; Workel et al., 2001), and poor maternal care (Banerjee et al., 2012; Liu et al., 1997) in early life all predict altered functioning of the HPA axis and the stress system in general.

Naturalistic experiments and studies with retrospective accounts have shown that also in humans, adversities in early life, both pre- and postnatally, may lead to altered functioning of the HPA axis (Entringer, Kumsta, Hellhammer, Wadhwa, & Wüst, 2009; Goldman-Mellor, Hamer, & Steptoe 2012; McCrory, De Brito, & Viding, 2011; O`Connor et al., 2005; Pesonen et al., 2010; Tyrka et al., 2008), amygdala (Dannlowski et al., 2012; McCrory et al., 2011), hippocampus (Dannlowski et al., 2012; McCrory et al., 2011; Teicher, Anderson, & Polcari, 2012), and prefrontal cortex (Dannlowski et al.,

2012: McCrory et al., 2011); the particular brain areas implicated as affected by early life adversity and regulating responses and vulnerability to stress in the life cycle model (Lupien et al., 2009). Studies have also shown that synthetic glucocorticoid treatment during pregnancy may alter the functioning of the HPA axis (Davis et al., 2010) and hippocampus (Tijsseling et al., 2012) in the offspring, suggesting developmental programming by glucocorticoids. Correspondingly, maternal cortisol levels during pregnancy predict offspring cortisol levels in infancy (O'Connor, Bergman, Sarkar, & Glover, 2012). Smaller body size at birth is also predictive of altered HPA axis function (Kajantie et al., 2003; Kajantie & Räikkönen, 2010; R. Reynolds et al., 2005). While findings show some inconsistency, the general pattern of the findings corresponds well with the life cycle model; the stress system is developmentally "programmed" by early life stressors, and adversities at different stages of development may indeed show some specificity in their neurobiological consequences.

Functional and structural neuroimaging studies and neuroendocrinological studies also support a role for changes in the functioning of these brain areas in the development of personality disorders. Such studies have repeatedly shown that the functioning of the HPA axis (Carvalho Fernando et al., 2012; D. Zimmerman & Choi-Kain**,** 2009), and the structure and/or function of amygdala (Herpertz et al., 2001; Nunes et al., 2009; Ruocco, Amirthavasagam, & Zakzanis, 2012; Soloff, Nutche, Goradia, & Diwadkar, 2008), hippocampus (Nunes et al., 2009; Ruocco et al., 2012; Soloff et al., 2008), and prefrontal cortex (Brunner et al., 2010; Carrasco et al., 2012; Herpertz et al., 2001; Wolf et al., 2012) are all altered in personality disorders. Most of the available evidence concerns borderline personality disorder. Further supporting the life cycle model (Lupien et al., 2009), some studies suggest that these neurobiological effects may appear particularly for those individuals who were exposed to early life adversities such as childhood maltreatment (Carvalho Fernando et al., 2012; Rinne et al., 2002).

1.6.2 Gene-Environment Interactions in the Etiology of Personality Disorders

Effects of early life interpersonal adversity on personality disorders may be moderated by genotype. Starting from a seminal study by Caspi and colleagues (2002), evidence

has accumulated to show that the low activity allele carriers of the MAO-A, a gene implicated in the regulation of serotonin, dopamine, and norephinephrine neurotransmitter function, are more vulnerable to the effects of childhood maltreatment, and that this vulnerability is highlighted in the prediction of antisocial personality disorder traits (Caspi et al., 2002; Fergusson et al., 2011; Kim-Cohen et al., 2006, Taylor & Kim-Cohen, 2007). This is one of the few replicated gene-environment interactions in the field of molecular psychiatry. A meta-analysis confirmed this finding, and showed that a similar interaction effect exists for antisocial symptoms both in child- and adulthood (Kim-Cohen et al., 2006). More specifically, these studies suggest that individuals with the low activity allele of MAO-A gene and with a history of childhood maltreatment have the highest risk of antisocial personality disorder and related symptoms, in comparison to those with either one or neither of these risk factors present.

On the other hand, among patients with mood disorders, the TPH 1 gene interacted with retrospectively assessed childhood maltreatment to predict borderline personality disorder (Wilson et al., 2012), and the risk increased with increasing levels of abuse. Furthermore, studies on antisocial (Jonson-Reid et al., 2010) and borderline (Belsky et al., 2012) personality disorders, which suggested main effects of childhood maltreatment on these disorders, also assessed interaction effects with familial liabilities. One of these studies found no interaction between familial liability for antisocial personality disorder and childhood maltreatment on the risk of antisocial personality disorder (Jonson-Reid et al., 2010). However, in the other study, children whose parents had been hospitalised for mental disorders were more sensitive to the effects of maltreatment; when maltreated, their risk for borderline personality disorder symptoms was much more elevated than for those with one or neither exposure (Belsky et al., 2012).

Overall, there is rather consistent evidence suggesting gene-environment interactions on the development of borderline and antisocial personality disorders. However, again, most of the available studies used retrospective self-reports of early life stressors. More prospective studies with objectively ascertained measures of early life stress are needed to elucidate whether such interactions indeed are implicated in the etiology of personality dysfunction.

1.6.3 Epigenetics

One plausible molecular genetic mechanism for the effects of early life stress on later health is via epigenetic DNA changes, as a consequence of early life adversity. Studies by Michael Meaney`s research group (Liu et al., 1997) found that differences in maternal licking behaviour among rats, a proxy of maternal care, predicted long-lasting gene expression changes, particularly in the methylation of the promoter region of the hippocampal glucocorticoid receptor gene, which is strongly implicated in the regulation of HPA axis function. This finding has been replicated in several studies (Fenoglio, Brunson, Avishai-Eliner, Chen, Baram, 2004; van Hasselt et al., 2012; Weaver et al., 2004). In animal studies, DNA methylation effects are evident for different early life stressors, both pre- and postnatal, and to several specific genes involved in the regulation of stress (Fenoglio et al., 2004; Meaney, 2001; Matrisciano et al., 2012; McGowan et al., 2011; Weaver et al., 2006; Zhang et al., 2010). These findings suggest that early life adversity programs the expression of genes that are involved in the responses of the stress system.

Also recent human studies suggest that both pre- (e.g. maternal depression, prenatal malnutrition) and postnatal (e.g. childhood maltreatment, parental separation, poor parental care) early life environmental adversities lead to epigenetic changes in gene expression (Bagot & Meaney, 2010; Beach, Brody, Todorov, Gunter, & Philibert, 2011; Franklin et al., 2010; Gluckman et al., 2011; Heijmans et al., 2008; McGowan et al., 2009; Oberlander et al., 2008; Tyrka et al., 2012), especially to methylation changes in genes implicated in the regulation of the stress system (Beach et al., 2011; McGowan et al., 2009; Oberlander et al., 2008; Tyrka et al., 2012). Birth weight and preterm birth also associate with specific patterns of DNA methylation (Menon, Conneely, & Smith 2012; Michels, Harris, & Barault, 2012). Such epigenetic changes as a consequence of early life adversity are then reflected in long-term changes in neuroendocrine function and in organ development, leading to an altered vulnerability to stress. This may be one major biological pathway through which early life environmental influences affect adult health (Bagot & Meaney, 2010; Beach et al., 2011; Gluckman et al., 2011).

During pregnancy, placental 11-beta hydroxysteroid dehydrogenase type 2 (11βHSD-2) enzyme regulates the effects of maternal cortisol on the fetus (Jensen Peña,

Monk, & Champagne, 2012; Wyrwoll, Holmes, & Seckl, 2011). On standard levels of stress, a fetal-placental barrier regulated by this hormone protects the fetus from maternal cortisol but with increasing amounts of maternal cortisol, this enzyme becomes inactivated leaving the fetus more vulnerable to maternal glucocorticoids. Studies have shown that prenatal stress may lead to altered methylation of the HSD11B2 gene encoding the 11βHSD-2 enzyme in the placenta and to epigenetic changes in the genes regulating fetal HPA axis function (Jensen Peña et al., 2012). Methylation of placental HSD11B2 gene has also been shown to predict individual differences in birth size (Marsit, Maccani, Parbury, & Lester, 2012; Wyrwoll et al., 2011), and neurobehavioural functioning at four years of age (Marsit et al., 2012). These epigenetic methylation effects of the HSD11B2 gene encoding the 11βHSD-2 enzyme function may hence be one epigenetic pathway, through which prenatal environmental factors affect offspring well-being.

Recent studies have also started to assess methylation differences among individuals with different mental disorders. Particular methylation differences have, for example, been observed in major depression (Sabunciyan et al., 2012), bipolar disorder (Dempster et al., 2011; Ghadirivasfi et al., 2011; Rosa et al., 2008), and schizophrenia (Dempster et al., 2011; Ghadirivasfi et al., 2011).

For personality disorders, a study examining the independent and the interactive effects of genotype and retrospectively self-reported childhood sexual abuse on antisocial personality disorder symptoms found significant effects of childhood sexual abuse on antisocial symptoms, and these effects were epigenetically mediated (Beach et al., 2011). These methylation changes as a consequence of the abuse in the serotonin transporter 5HTT -gene also interacted with the genes` genotype in predicting the antisocial symptoms. Another study showed that aberrant methylation of genes related to neuropsychiatric disorders occurs in borderline personality disorder (Dammann et al., 2011). Hence, epigenetic changes may also be a neurobiological mechanism underlying the effects of early life adversity on the risk of personality disorders (Bagot & Meaney, 2010; Beach et al., 2011; Depue, 2009), and such effects may be exerted possibly in interaction with genotype (Beach et al., 2011; Depue, 2009). However, studies with a prospective design assessing the epigenetic effects of early life stress on personality disorders are, to the author`s knowledge, still lacking.

2. AIMS OF THE STUDY

Previous studies mostly support an etiological role for early life environmental adversity in the etiology of personality disorders. Nevertheless, there is still an obvious need for longitudinal studies to confirm or disprove such effects. The effects of pre- and postnatal growth have scarcely been assessed in relation to personality disorders. Also parental separation in childhood has rarely been assessed with a longitudinal design as a predictor of diagnosed personality disorders.

In this thesis, the early life developmental origins of severe personality disorders leading to hospitalisation are examined in a longitudinal cohort study, the HBCS 1934-1944. This cohort comprises 13,345 individuals and has health record- and register-based data across the lifespan, enabling us to identify a) the growth of the cohort members from birth to 11 years of age, b) cohort members who were separated from both of their biological parents in childhood during World War II, c) socioeconomic position in childhood and certain particular exposures from birth-, child welfare-, and school records, and d) the diagnosis of any mental and of personality disorders from the Finnish Hospital Discharge- and Causes of Death –registers. All these health record- and register-based data are objective and not dependent on the subjects` self-reports of early life adversity or of mental disorders. Our main research questions concern the role played by early life growth and by parental separation in childhood in the developmental origins of severe personality disorders. Our follow-up for mental disorders expands for over 35 years across adulthood, a much lengthier follow-up than in previous studies on severe personality disorders that required hospitalisation.

2.1 Study Questions

2.1.1 Study I:

Does prenatal growth predict the risk of severe personality disorders among men or women?

Are there particular effects on the disorders of the dramatic cluster?

2.1.2 Study II:

Is growth in infancy and/or in childhood predictive of severe personality disorders among men or women?

2.1.3 Studies III and IV:

Does parental separation predict the risk of any severe mental disorder and personality disorders in adulthood?
Is the risk for personality disorders also increased in comparison to other severe mental disorders, that is, is the risk specific?
Are there particular effects of parental separation on dramatic cluster personality disorders?
Does age at first separation or the duration of separation modify the effects of separation?

Sex and socioeconomic position in childhood are assessed as potential moderators and mediators of the associations. We also assess maternal age at childbirth and parity as potential mediators of the associations between body size at birth and parental separation and personality disorders. Additional analyses not included in the original manuscript include analyses of the associations between infancy and childhood growth and dramatic cluster personality disorders.

2.1.4 An Additional Study Question

Finally, as an additional study question, we assess, among the separated children, with retrospective questionnaire data whether particular aspects of the separation experience and the childhood environment more generally modified the separation experience and its possible effects on adult personality dysfunction. Since we had almost no questionnaire data available from the subjects hospitalised for personality disorders, we assess the effects of these different aspects of the separation and childhood environment on self-reported antisocial personality disorder traits in late adulthood.

3. METHODS

3.1 Helsinki Birth Cohort Study

The study cohort in this thesis was the HBCS 1934-1944. This cohort comprises 13,345 individuals (6,975 men and 6,370 women) born in Helsinki, Finland in one of the two public maternity hospitals of the city between 1934 and 1944. However, due to missing data and adjustment for different confounders, the sample sizes varied across studies. The sample sizes in the different studies and the exclusion criteria used are described in Figure 1. The effects of attrition (comparisons between the included and the excluded subjects) are described in the individual manuscripts.

3.2 Growth Measurements

Data on body size at birth (birth weight, length and head circumference at birth, placental weight and placental diameters), date of birth, and the date of mothers` last menstrual period were extracted from hospital birth records. Length of gestation was calculated by subtracting the date of mother's last menstrual period from the birth date of the child. Ponderal index at birth, a measure of thinness, was calculated as weight divided by length at birth^3 (kilograms (kg)/metres (m)^3). We calculated head-to-length ratio to reflect the proportion of brain compared to trunk growth. Also two measures of placental diameter (lesser, maximal) were recorded routinely in these maternity hospitals until 1970s. Assuming an elliptical surface, we estimated the surface area of the placenta as maximal *x* lesser diameter *x* $\pi/4$ (Roseboom et al., 1999). The size of the placental area reflects the spread of the placenta across the inner wall of the uterus.

Data on weight and length/height growth in infancy and in childhood were obtained from child welfare clinic and school health records. Monthly growth data was available from birth to two years, and yearly growth data thereafter until 11 years of age. For the growth analyses, we used growth data at birth, six months, and one, two, seven, and 11 years. BMI at each age was calculated as weight divided by length/height^2 (kg/m^2).

<table>
<tr><td colspan="5">13345 HBCS Subjects</td></tr>
<tr><td colspan="2">↓</td><td>↓</td><td>↓</td><td>↓</td></tr>
<tr><td colspan="2">Studies 1-2: Pre-and Postnatal Growth and Personality Disorders</td><td colspan="2">Studies 3-4: Temporary Parental Separation and Severe Personality Disorders</td><td>Unpublished study: Childhood Experiences among the separated Children and Antisocial Personality Traits</td></tr>
<tr><td colspan="2">↓</td><td colspan="2">↓</td><td>↓</td></tr>
<tr><td colspan="2">-241 subjects moved abroad or died before the start of HDR data collection in 1969</td><td colspan="2">- 57 subjects died with no data on year of death</td><td>4,147 subjects were administered the questionnaire</td></tr>
<tr><td colspan="2">↓</td><td colspan="2">↓</td><td>↓</td></tr>
<tr><td colspan="2">-487 with missing data on socioeconomic position in childhood</td><td colspan="2">-189 subjects self-reported that they had been evacuated, but could not be found in the register</td><td>709 had died</td></tr>
<tr><td colspan="2">↓</td><td colspan="2">↓</td><td>↓</td></tr>
<tr><td colspan="2">-19 subjects with comorbid schizophrenia spectrum and personality disorder</td><td colspan="2">-348 subjects with missing data on childhood socioeconomic background</td><td>312 had declined participation</td></tr>
<tr><td>↓</td><td>↓</td><td colspan="2">↓</td><td>↓</td></tr>
<tr><td rowspan="4"></td><td rowspan="4"></td><td colspan="2">-4 subjects with missing or imprecise data on diagnosis of mental disorder</td><td>1042 did not return the questionnaire</td></tr>
<tr><td>↓</td><td>↓</td><td>↓</td></tr>
<tr><td rowspan="3"></td><td rowspan="3"></td><td>8 subjects with missing data on maternal age</td><td>1,893 subjects returned the questionnaire</td></tr>
<tr><td>↓</td><td>↓</td></tr>
<tr><td>5 subjects with missing data on parity</td><td>1,691 subjects were non-separated</td></tr>
<tr><td>235 subjects with gestation length unavailable</td><td>3,709 subjects with growth data missing</td><td></td><td>8 subjects with missing data on maternal age</td><td>1,893 subjects returned the questionnaire</td></tr>
<tr><td>↓</td><td>↓</td><td>↓</td><td>↓</td><td>↓</td></tr>
<tr><td>Study 1:</td><td>Study 2:</td><td>Study 3:</td><td>Study 4:</td><td>Questionnaire Study:</td></tr>
<tr><td>12,363 subjects
6,506 men and 5,857 women</td><td>8,889 subjects
4,689 men and 4,200 women</td><td>12,747 subjects
6,704 men and 6,043 women</td><td>12,734 subjects
6,697 men and 6,037 women</td><td>202 subjects
116 men and 86 women</td></tr>
</table>

Figure 1. Sample sizes and subjects lost due to attrition in the different studies.

3.3 Child Evacuations during World War II

3.3.1 National Archives

During World War II, Finland fought two wars with the Soviet Union: the Winter War from November 1939 until March 1940, and the Continuation War from June 1941 until September 1944. To protect the Finnish children from the hazards of war, over 70,000 children with various socioeconomic backgrounds were evacuated abroad, mainly to Sweden and Denmark, unaccompanied by their parents. Since these evacuations were voluntary, the likelihood of a Finnish child being evacuated was influenced by an unpredictable interplay of political and familial factors (Kavén, 2010; Pesonen et al., 2007). Siblings were commonly placed in different foster families to promote learning the new language faster. Our data suggests that 18.4 % of the separated children had siblings with them in the foster family while 81.6 % did not. The context of and the reasons for the evacuations varied among the different children. Nevertheless, all of the evacuated children were sent abroad without either of their parents and temporary separation from parents was hence experienced by all the evacuated children.

Data on separation from parents, on the age at first separation (some children were separated more than once), and on the duration of the separations were extracted from a register in the Finnish National Archives, which fully documents the 48,628 children evacuated by the Finnish Government through the Ministry of Social Affairs and Health between 1939 and 1946 (Pesonen et al., 2007, 2010).

In the final study sample of 12,747 subjects on the studies on parental separation, there were 1,719 individuals who had been separated from their parents in childhood and 11,028 non-separated individuals. Furthermore, two separated and 13 non-separated subjects had no data on maternal age at childbirth or parity, and the analyses adjusted also for these factors included 1,717 separated and 11,017 non-separated individuals.

Among these 1,717 separated individuals, the mean age at first separation was 4.7 years (*SD* = 2.4, Median = 4.4 years) and the average duration of the separation was 1.8 years (*SD* = 1.1, Median = 1.5 years). Data on age at separation were missing for 10.1 % and on separation duration for 12.9 % of the separated participants. To examine the possible moderating effects of the age at first separation, the participants were grouped

into individuals who had been separated before five years of age (n = 898) and to those separated thereafter (n = 646). Furthermore, to assess the moderating effects of separation duration, the participants were grouped by the median duration of the separation (1.5 years; n = 778 for below the median and n = 718 for above the median).

3.3.2 Questionnaire Data on the Separation Experiences

Between 2009 and 2010, a psychological questionnaire was administered to a HBCS subsample comprising 4,147 subjects (3,072 men and 1,075 women). Of these subjects, 709 had died, 312 declined participation, and 193 lived abroad or had an unknown address. Hence, 2,935 subjects (1,981 men and 954 women) were still traceable, and 1,893 of them (1,095 men and 798 women) (64.5% of the traceable subjects) returned the questionnaire (Tuovinen et al., in press; Figure 1).

This questionnaire survey included questions assessing the stressfulness of the experiences during the separations and in childhood more generally. Among the 1,893 respondents to the questionnaire study, there were 202 separated subjects [Figure 1; 116 (57.4 %) men 86 (42.6 %) women)] who had responded to questions on their separation exposure and on other childhood experiences at a mean age of 71.0 years [Standard Deviation (*SD*) = 2.7 years]. To assess the separation experience more thoroughly, we present here data from this questionnaire study among the separated children.

The questionnaire comprised one question assessing the overall experience of separation, assessed on a scale from 0 (very negative) to 10 (very positive), and 14 questions on the stressfulness of the different aspects of the child`s life before, during or after the separation. These 14 questions each had a scale of 1-7, where a score of 3 indicated an exposure experienced “not at all stressful” and a score of 7 indicated an exposure experienced as “extremely stressful”. A score of 1 was given when an exposure had not happened, and a score of 2 was given when the subject did not remember how stressful the particular exposure was. Three of these questions assessed emotional and physical maltreatment at different stages in childhood (before, during, or after the separation). We recoded the answers to these questions so that any exposures that were assessed at all stressful were encoded as exposure to maltreatment, and a score of 1 as no exposure to maltreatment. Other responses were encoded as missing.

Maltreatment variables were used as binary variables, and also a variable combining these questions “any exposure to maltreatment” was formed. The other 11 questions, concerning the experiences of separation from biological and foster parents, life before, during, and after separation, and difficulties with language at these different stages, were assessed in terms of their stressfulness; response options 1 and 2 were encoded as missing.

Among the separated children, we assessed the overall stressfulness of the separation, the associations of separation and childhood experiences to the length and the duration of the separation, and how particular experiences during the separation and at other time periods in childhood were experienced. In addition, we examined the associations between these childhood experiences and dimensionally evaluated antisocial personality disorder traits in adulthood.

In conjunction with the separation experience questionnaire, the subjects filled in the Older-Adult Self-Report (Achenbach System of Empirically Based Assessment) (OASR ASEBA; Achenbach, Newhouse, Rescorla, 2004) questionnaire, which assesses diverse aspects of psychological functioning in older adults. This questionnaire includes scales on adaptive functioning, on psychiatric syndromes, and on DSM-oriented diagnoses. Here we report the associations between the stressfulness of the different childhood exposures and scores on the DSM-oriented OASR scale on antisocial personality related problems. All the 202 separated subjects with questionnaire data of childhood experiences had also fulfilled the OASR ASEBA antisocial personality scale.

Because there was only one separated subject with questionnaire-based data on the separation experience who had been hospitalised for personality disorders, we present the associations between the stressfulness of childhood exposures only to this less severe type of personality pathology assessed via self-report questionnaire.

3.4 The Diagnoses of Mental Disorders: Finnish Hospital Discharge- and Causes of Death Registers

We extracted the diagnoses on hospitalisations for mental disorders from the national Hospital Discharge Register (HDR) that has data on the primary and up to three subsidiary discharge diagnoses of all hospitalisations in Finland. We also extracted

mental disorder diagnoses contributing to death from the national Causes of Death Register (CDR) that has data on the primary, underlying, and contributory diagnoses identified as causes of death.

In 1969, all Finnish residents were allocated a personal social security number through which they could be linked with the HDR and the CDR register data. Consequently, the diagnoses had been entered in to the HDR and CDR since 1969, when the subjects were between 24 and 35 years old, until 2004 when they were between 60 and 70 years. The follow-up in the CDR ended on December 31, 2003, and that in the HDR lasted until December 31, 2004.

Diagnoses have been entered into the HDR and to the CDR according to the ICD-8 until 1986, according to ICD-9 with DSM-III-R criteria until 1995, and according to the ICD-10 since 1996. Although there were subjects with other mental disorders that were identified solely based on the CDR, all the subjects with personality disorders in the current study cohort were identified from the HDR.

The HDR is a valid and reliable tool for epidemiological research (Keskimäki & Aro, 1991). Since there are no published validity studies on the diagnoses of personality disorder in the HDR, the validity and reliability of these diagnoses is still unproven. However, evidence from the validity of other psychiatric diagnoses, namely the diagnoses of schizophrenia (Mäkikyrö, Isohanni et al., 1998), bipolar disorder (Kieseppä, Partonen, Kaprio, & Lönnqvist, 2000), and of any psychotic disorder (Perälä et al., 2007) in this register support its validity and suitability for psychiatric research purposes, showing that all these diagnoses demonstrate high levels of specificity in the register. The validity of ICD-8 diagnoses of alcohol dependence and alcohol psychosis has also gained support in research (Poikolainen, 1983).

Although the validity of the HDR diagnoses of personality disorder diagnoses is unproven, the reliability of the DSM-III-R and ICD-10 personality disorder diagnoses that have been used in Finland between 1987 and 1995, and from 1996 onwards, respectively, has been assessed. While concerns have been raised about the reliability of some of the specific ICD personality disorder diagnoses (Bronisch & Mombour, 1994), studies on the reliability of the diagnoses of any personality disorder indicate acceptable levels of inter-rater and test-retest reliability for the diagnostic criteria which have been used in Finland (Bronisch & Mombour, 1994, Muhs & Ori, 1995). Consequently, we

concentrated on this broader diagnostic category as our primary diagnostic outcome. Since dramatic personality disorders are most consistently associated with early life adversity (e.g. Kantojärvi et al., 2004; Neugebauer et al., 1999; Widom et al., 2009), we also assessed specific effects on these disorders severe enough to require hospitalisation.

The diagnoses registered in the HDR are mostly based on clinical observations made during a several weeks long hospital period. In typical cases, several diagnostic procedures have contributed to the diagnosis entered in the HDR, sometimes also a structured clinical interview. Diagnoses are often consensus diagnoses, agreed upon by several physicians contributing to the care of the inpatient in question, which can be seen as improving their reliability.

There were some differences in our definition of personality disorder across studies. In the studies on pre- and postnatal growth and personality disorders, schizotypal personality disorder was included in the personality disorders diagnostic group. However, in the studies on the effects of parental separation, which assessed all the main diagnostic categories of ICD-10, schizotypal personality disorder was included in the psychotic disorders diagnostic group. As stated, this diagnostic category is included in personality disorders in the DSM-IV but not in the ICD-10 (APA, 2000; WHO, 1992). In the studies on growth and personality disorders, we wanted to follow the DSM classifications as closely as possible to justify our use of the personality disorder cluster approach. This approach is also more comparable to most previous studies, since the DSM is more often used in research. On the other hand, the studies on parental separation assessed also other mental disorders diagnosed with the ICD approach. Hence, an approach corresponding more to the categories of this diagnostic system was assessed more justified.

Furthermore, in the studies on pre- and postnatal physical growth, the control group included all subjects without a diagnosis of personality disorder, whereas the studies on childhood parental separation differentially compared the risks to individuals without any mental disorder and to those with other, non-personality mental disorders. In the studies on pre- and postnatal growth, a schizophrenia spectrum disorder (identified with the ICD 8 and DSM-III-R codes 2950-2954, 2956-2959 and 297 and with ICD-10 codes F20, F22, F24, and F25), when comorbid with eccentric personality disorder, was used as an exclusion criteria: subjects with both disorders were excluded from the sample.

No such exclusion was done in the studies on childhood parental separation and personality disorders.

Table 2 shows the diagnostic codes used to identify the different mental disorders. Table 3 shows the particular codes for any, cluster-specific, and particular personality disorders and the number of subjects hospitalised for any personality disorder, disorders in each personality disorder cluster, and for the specific personality disorders in each study.

In the total sample, there were 202 individuals (1.5 %; 114 men and 88 women) who had been hospitalised for personality disorders according to the classification used in studies III-IV and 198 subjects (1.5 %; 110 men and 88 women) according to the classification of studies I and II. There were 77 individuals (0.6 %; 45 men and 32 women) who had been hospitalized for dramatic personality disorders. In all the studies, age at first hospitalisation for personality disorder varied between 24 and 63 years. The median age at first hospitalisation for personality disorder was 40.9 years in study I and 40.7 years in studies II-IV.

Table 2. International Classification of Disease diagnostic codes on mental disorders severe enough to warrant or contribute to hospital treatment (Finnish Hospital Discharge Register) or to be the underlying, intermediate or contributing cause of death (Finnish Causes of Death Register).

Mental disorders:	**International Classification of Diseases 8th (ICD-8; in use between 1969-1986), 9th (ICD-9; in use between 1987-1995), and 10th (ICD-10; in use 1996-present) revision diagnostic codes:**
Any [a]	**ICD-8:** 291, 295, 296-305, 306.4-306.5, 306.8, 306.98, 307 **ICD-9:** 291-292, 295-298, 300-304, 305, 3071A, 3074, 3075A-3075B, 3078A, 3079X, 3090A, 3092C-3099X, 312 **ICD-10:** F1-F6
Substance Use (ICD-10: Mental and behavioral disorders due to psychoactive substance use)	**ICD-8:** 291, 303-304 **ICD-9:** 291-292, 303-305 **ICD-10:** F10-F19
Psychotic (ICD-10: Schizophrenia, schizotypal, and delusional disorders)	**ICD-8:** 295, 297, 298.10-299.99 **ICD-9:** 295, 297-298 **ICD-10:** F20-F29
Mood [ICD-10: Mood (affective)]	**ICD-8:** 296, 298.00, 300.40, 300.41, 301.10 **ICD-9:** 296, 3004A, 3011D **ICD-10:** F30-F39
Anxiety (ICD-10: Neurotic, stress-related and somatoform disorders)	**ICD-8:** 300.00-300.30, 300.50-300.99, 305, 306.80, 307.99 **ICD-9:** 3000A-3003A, 3006A-3009X, 3078A, 309 **ICD-10:** F40-F48
Personality (ICD-10: Specific and mixed personality disorders)	**ICD-8:** 301.00, 301.20-301.99 **ICD-9:** 3010A, 3012A-3015A, 3016A-3018X **ICD-10:** F60-F61

Note. [a] The diagnoses (corresponding to codes F50-F59 or F62-F69 in ICD-10) were included in the Any mental disorder –category, but due to heterogeneity and small sample size, we were not able to treat it as a separate category.

Table 3. The prevalence of and the diagnostic codes for personality Disorders.

	Diagnostic Codes			Study I: (n=12363)	Study II: (n=8889)	Studies III-IV (n=12747/ 12734)
Diagnosis	**ICD-8**	**ICD-9/ DSM-IIIR**	**ICD-10**	**Number (%) of Cases**		
Any Personality Disorder	295.5, 301.0, 301.2-301.9	3010A, 3012-3014, 3015A, 3016-3018	F60-F61 (F21)	182 (1.5 %)	149 (1.7 %)	194 (1.5%)
Cluster A: Eccentric Personality Disorders	295.5, 301.0, 301.2	3010, 3012	F21, F60.0, F60.1	14 (0.1 %)	9 (0.1 %)	20 (0.2 %)
Paranoid	301.00	3010A	F60.0	3 (0.2 %)	3 (0.3 %)	6 (0.05%)
Schizoid	301.20	3012A	F60.1	10 (0.1 %)	7 (0.1 %)	14 (0.1%)
Schizotypal*	295.50	3012C	F21	4 (0.03 %)	2 (0.02%)	NA*
Cluster B: Dramatic Personality Disorders	301.3, 301.5 301.7, 301.88	3015A, 3017A, 3018B, 3018D	F60.2-F60.4	71 (0.6%)	63 (0.7 %)	77 (0.6 %)
Antisocial	301.70	3017A	F60.2	13 (0.1 %)	11 (0.1 %)	13 (0.1%)
Borderline	301.30, 301.88	3018D	F60.3	59 (0.5 %)	51 (0.6 %)	64 (0.5 %)
Narcissistic	NA	3018B	NA	6 (0.05%)	5 (0.1 %)	6 (0.05%)
Histrionic	301.50	3015A	F60.4	2 (0.02 %)	1 (0.1 %)	3 (0.02%)
Cluster C: Fearful Personality Disorders	301.4, 301.6	3014A, 3016A, 3018C	F60.5-F60.7	12 (0.1%)	11 (0.1 %)	12 (0.1 %)
Avoidant	NA	3018C	F60.6	1 (0.01%)	0 (0 %)	1 (0.01 %)
Dependent	301.60	3016A	F60.7	10 (0.1 %)	9 (0.1 %)	11
Obsessive-Compulsive	301.40	3014A	F60.5	4 (0.03 %)	3 (0.3 %)	3 (0.02%)
Personality Disorder Not Otherwise Specified	301.80, 301.99	3018X, 3018E	F60.8-F60.9, F61	104 (0.8%)	84 (0.9 %)	101 (0.8%)

* Note. Schizotypal Personality Disorder is not included as a personality disorder in ICD-10.

3.5 Sociodemographic and Perinatal Covariates

Data on sex and on year of birth were extracted from birth records. We defined socioeconomic position in childhood based on father´s occupational status, data on which was derived from school, child welfare, and birth records. There were differences across studies on the weight given to these different registers because of the differing study questions. While in the studies concerning fetal and childhood growth, highest emphasis was given to school records from which most data was available, on the studies examining the predictive role of parental separation, highest attained occupational status from any of these registers was used as a proxy of socioeconomic position in childhood. This indicator is more independent of the effects of the war and reflects better the overall socioeconomic position of the family. The encoding of independent workers, a category comprising different kinds of professions, varied across studies. While these were coded as missing information in studies I and II, in the studies III and IV they belonged to the "higher clerical" –group. We repeated our analyses of studies I and II with the definition of socioeconomic position used in the latter studies on parental separation, and there were no changes to our findings.

Data on maternal age at childbirth and on parity were extracted from birth records. These factors were adjusted for in the analyses of parental separation and severe personality disorders. The original manuscript on prenatal growth and severe personality disorders did not assess whether these factors possibly mediated the associations between body size at birth, length of gestation and any and dramatic personality disorders. However, these analyses were now repeated adjusting for maternal age and parity, which led to no changes in the previously significant findings of the associations between body size at birth and any or dramatic personality disorder (all *p*-values remained < .05).

3.6 Statistical Analyses

The associations of the independent and dependent variables to the sociodemographic and perinatal covariates were examined with the use of *t*-, χ^2-, and Univariate analysis of variance -analyses. The associations between pre- and postnatal growth and

hospitalisation for personality disorders were examined with logistic regression analyses. Cox Proportional Hazards Models were used to examine the associations between parental separation in childhood and any severe mental and particularly any and dramatic personality disorders.

Sex, year of birth, and socioeconomic position in childhood were treated as confounders in all the analyses; sex and year of birth were stratified for in the Cox Proportional Hazards models and adjusted for in the logistic regression analyses. Socioeconomic position in childhood was adjusted for in all the analyses. The analyses of body size at birth were further adjusted for length of gestation and those of childhood parental separation and serious mental and particularly personality disorders for maternal age at childbirth and parity, due to the reasons stated above.

Because of accumulating evidence suggesting possibly sex-specific effects of early life adversity and physical growth (Khalife et al., 2012; J. Lahti et al., 2009; Monfils Gustafsson et al., 2009; Murray et al., 2012; Mäki, Hakko et al., 2003; Sauvola et al., 2002) on personality disorders, all the analyses were repeated for men and women separately. Furthermore, due to the possible modifying role of socioeconomic position in childhood on the effects of parental separation on adult mental health (Tieman et al., 2005), its possible modifying role on the effects of parental separation on mental and personality disorders were assessed with interaction terms. In all the analyses, *p*-values of $\leq .05$ were used to indicate statistical significance.

To assess the effects of co-morbid psychopathology, the analyses on the effects of postnatal growth on personality disorders were repeated adjusting for concurrent mood disorders. To assess the specificity of possible effects of parental separation on any and on dramatic personality disorders, the analyses were run both in comparison to healthy controls and among patients with any severe mental disorder.

For the analyses on the associations of linear differences in body size at certain ages, attained body size at each age was converted to *z*-scores by sex. A *z*-score represents the difference from the mean value of all the girls and all the boys participating in the HBCS, and is expressed in *SD* units.

We examined the associations between the neonatal characteristics and hospitalisation for any and for dramatic personality disorders also with nonlinear (quadratic) terms as the independent variables. These models included also linear terms.

The linear effects are reported from models without the quadratic terms. For the analyses of quadratic associations, the birth size measures were centered.

The postnatal growth variables were standardized residuals from linear regression models of weight, height, and BMI, where body size at each age was regressed upon corresponding measures at all earlier ages. This created completely uncorrelated residuals reflecting growth conditional on previous history (Barker et al., 2005; Osmond et al., 2007). We also examined the associations between attained body size at birth and at each aforementioned age in infancy and in childhood and hospitalisation for personality disorders.

The associations of the retrospectively self-reported stressfulness of the separation exposure and of the other childhood experiences with antisocial personality traits in adulthood were examined with linear regression analyses. Scores on antisocial personality traits were rank-normalized due to deviations from normal distribution and are expressed in *SD* units. Age, sex, socioeconomic position in childhood [66.8 % laborer, 20.3 % lower middle, 10.4 % upper middle, and 2.5 % (five subjects) with missing data in this subsample] and own attained educational level in adulthood (39.1 % basic, 24.3 % upper secondary, 28.2 % lower tertiary, and 8.4 % upper tertiary) were controlled for in these analyses. Associations between the stressfulness of the childhood exposures and the age at and the duration of separation were assessed with Pearson correlation analyses.

4. RESULTS

4.1 Prenatal Growth and Severe Personality Disorders (Study I)

There was a nonlinear, quadratic effect of head circumference at birth in predicting the risk of any severe personality disorder (p = .005). Namely, subjects with a small head circumference (z < -1) were at a significantly increased, 1.64 -fold risk of hospitalisation for personality disorders compared to subjects with a medium size head circumference (-1≤ z ≤ 1; 95 % Confidence Interval (CI) = 1.11-2.41, p = .01; Figure 2) while individuals with a large head circumference at birth (z > 1) had a slightly but non-significantly increased risk compared to individuals with a medium size head circumference (Odds Ratio (*OR*) = 1.14, 95 % CI = 0.74-1.75, p = .55; Figure 2).

The nonlinear pattern was more pronounced and statistically significant among men (Table 4). Men with a small (z < -1) head circumference at birth had a 1.83-fold (95 % CI = 1.06-3.14, p = .03), significantly increased risk of hospitalization for personality disorders compared to men with medium size (-1 ≤ z ≤ 1) head circumference at birth. Also among men, a smaller head circumference to length -ratio at birth linearly predicted an increased risk of hospitalisation for personality disorder (Table 4).

In contrast, hospitalisation for dramatic personality disorders was linearly predicted by a smaller placental surface area at birth (*OR* for each *SD* unit decrease in placental surface area = 1.32, 95% CI = 1.03-1.69, p = .03). This association was especially evident and statistically significant among women (Table 5), while no significant associations between body size at birth or length of gestation and any severe personality disorder emerged among women (Table 4).

Table 4. Neonatal characteristics and personality disorders: Linear and curvilinear (quadratic) effects.

	Men			**Women**		
Neonatal Characteristic	**Odds Ratio [a] (95% CI)**	***p* linear [b]**	***p* quadratic**	**Odds Ratio [a] (95% CI)**	***p* linear [b]**	***p* quadratic**
Birth Weight [c]	0.98 (0.79-1.22)	.88	.47	1.00 (0.79-1.27)	1.00	.84
Length at Birth [c]	0.88 (0.71-1.09)	.25	.32	1.13 (0.89-1.42)	.32	.72
Ponderal Index [c]	1.14 (0.93-1.40)	.20	.71	0.89 (0.71-1.11)	.29	1.00
Head Circumference [c]	1.12 (0.91-1.38)	.27	.01	1.14 (0.90-1.44)	.27	.12
Length of Gestation [d]	1.08 (0.89-1.31)	.45	.97	1.09 (0.88-1.36)	.42	.70
Head Circumference /Length –ratio [c]	1.26 (1.03-1.52)	.02	.31	1.01 (0.81-1.27)	.90	.26
Placental Weight [c]	0.86 (0.71-1.05)	.14	.32	1.07 (0.85-1.35)	.56	.14
Placental Area [c]	0.92 (0.76-1.12)	.40	.20	1.12 (0.89-1.40)	.35	.52

[a] Odds ratios and 95 % confidence intervals (CI) for each *SD* unit decrease in these variables.

[b] The linear p-values are from analyses examining only linear effects and are not adjusted for the quadratic terms

[c] Adjusted for gestational age, socioeconomic position in childhood, and year of birth

[d] Adjusted for socioeconomic position in childhood and year of birth

Table 5. Neonatal characteristics and dramatic personality disorders: Linear and curvilinear (quadratic) effects.

	Men			Women		
Neonatal Characteristic	**Odds Ratio (95% CI)** [a]	***p* linear** [b]	***p* quadratic**	**Odds Ratio** [a] **(95% CI)**	***p* linear** [b]	***p* quadratic**
Birth Weight [c]	1.10 (0.78-1.54)	.59	.71	1.00 (0.68-1.48)	.99	.06
Length at Birth [c]	1.04 (0.75-1.45)	.81	.84	1.09 (0.74-1.60)	.66	.053
Ponderal Index [c]	1.11 (0.81-1.53)	.52	.57	0.88 (0.61-1.27)	.50	.30
Head Circumference [c]	1.25 (0.91-1.72)	.17	.57	1.17 (0.80-1.71)	.43	.48
Length of Gestation [d]	1.14 (0.86-1.53)	.36	.49	1.09 (0.76-1.56)	.65	.17
Head Circumference /Length –ratio [c]	1.23 (0.91-1.67)	.18	.19	1.09 (0.76-1.57)	.62	.83
Placental Weight [c]	0.97 (0.71-1.33)	.83	.90	1.13 (0.77-1.66)	.52	.29
Placental Area [c]	1.21 (0.88-1.67)	.25	.86	1.48 (1.00-2.18)	.048	.53

[a] Odds ratios and 95 % CI:s for each *SD* unit decrease in these variables

[b] The linear p-values are from analyses examining only linear effects and are not adjusted for the quadratic terms

[c] Adjusted for gestational age, socioeconomic position in childhood, and year of birth

[d] Adjusted for socioeconomic position in childhood and year of birth

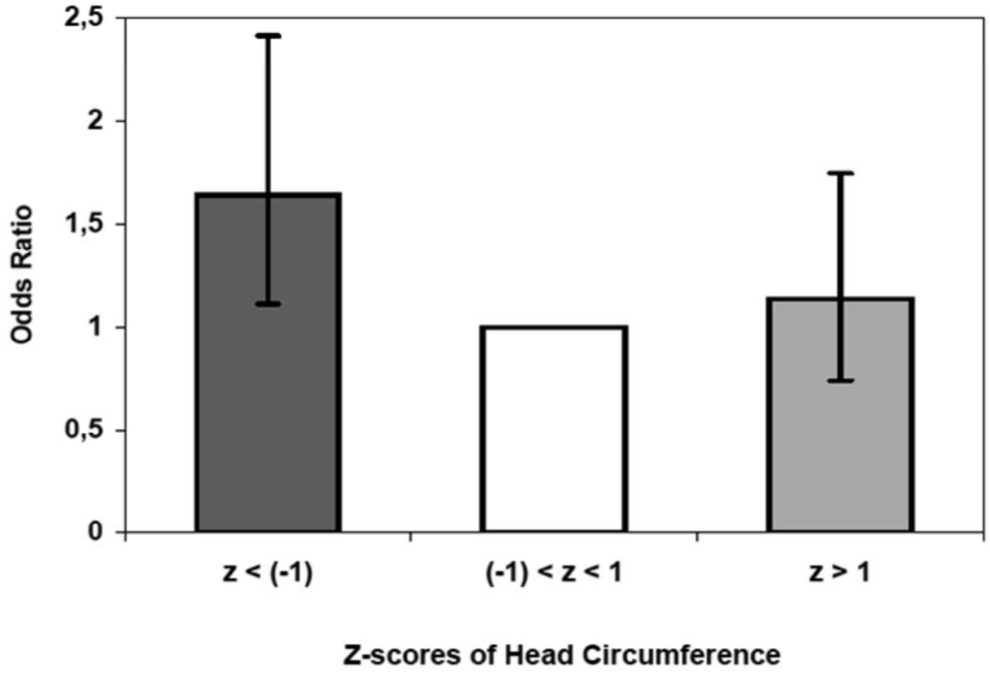

Figure 2: The association between head circumference at birth and personality disorders in adulthood. The bars represent odds ratios for personality disorders for three groups defined by head-circumference *z* -scores: $z < -1$; $-1 \leq z \leq 1$; and $z > 1$. The odds ratios are adjusted for sex, socioeconomic position of childhood, year of birth, and length of gestation. The error bars represent 95 % CI: s.

4.2 Infancy and Childhood Growth and Severe Personality Disorders (Study II)

In the whole sample, the risk of hospitalisation for personality disorders was predicted by slower height growth between two and seven years of age (*OR* for each *SD* unit increase in growth conditional on previous growth = 0.81, 95 % CI = 0.68-0.95, $p = .01$) and slower weight (*OR* = 0.78, 95 % CI = 0.66-0.93, $p = .005$) and BMI (OR = 0.75, 95 % CI = 0.63-0.88, $p = .001$) gains between seven and 11 years of age. All these associations remained significant after adjustment for concurrent mood disorders (*p* -values = .04, = .01, and = .008, respectively).

There was a significant interaction of sex by weight gain between six months and one year of age ($p = .01$) in predicting the risk of severe personality disorders. Further sex-specific analyses showed that among men, slower gain in BMI between birth and six months of age, faster gains in weight and in BMI between six months and one year,

and slower gains in weight and in BMI between seven and 11 years of age each predicted an increased risk of hospitalisation for personality disorders (Table 6a, Figure 3a). Among men, lower attained BMI at six months (*OR* = 0.78, *p* = .03) and again at 11 years of age (*OR* = 0.77, *p* = .02) also associated with an increased risk of hospitalisation for personality disorders. All these findings remained significant after further adjustment for the presence of mood disorders.

Among women, slower height growth between two and seven years of age was associated with an increased risk of personality disorders (Table 6b, Figure 3b). This association was, however, no longer significant after adjustments for co-morbid mood disorders. Likewise to Study I, in the sample of Study II, neither birth weight nor BMI nor length at birth associated with the risk of hospitalisation for any or for dramatic personality disorders among either sex (all *p*-values ≥ .41).

Table 6a. Odds Ratios and 95 % CI: s Representing Associations of Growth from Birth to 11 Years of Age with Hospitalisation for Personality Disorders in Adulthood among Men.

	Weight (n=4685)			Length/Height (n=4646)			Body Mass Index (n=4637)		
	Adjusted model 1 [a]		Fully adj. [b]	Adjusted model 1 [a]		Fully adj. [b]	Adjusted model 1 [a]		Fully adj. [b]
Growth from: [c]	Odds Ratio (95 % CI)	*p*	*p*	Odds Ratio (95 % CI)	*p*	*p*	Odds Ratio (95 % CI)	*p*	*p*
Birth to 6 months	0.86 (0.69-1.08)	.19	.26	1.02 (0.81-1.27)	.88	.47	0.81 (0.65-1.01)	.06	.04
6 months to 1 year	1.36 (1.10-1.68)	.004	.005	1.08 (0.87-1.34)	.47	.38	1.27 (1.04-1.56)	.02	.05
1 to 2 years	0.93 (0.74-1.17)	.54	.14	1.08 (0.88-1.32)	.48	.46	0.90 (0.73-1.11)	.33	.13
2 to 7 years	0.92 (0.74-1.15)	.45	.66	0.84 (0.67-1.06)	.14	.26	1.07 (0.87-1.33)	.51	.82
7 to 11 years	0.70 (0.55-0.89)	.004	.008	1.02 (0.82-1.27)	.89	.93	0.68 (0.54-0.85)	.001	.003

[a] Adjusted for father's occupational status in childhood and for year of birth.
[b] Adjusted also for the presence of a mood disorder
[c] Expressed as a standardized residual of regression of body size at each age regressed on corresponding measures at all earlier ages creating completely uncorrelated residuals reflecting growth conditional on previous history.

Table 6b. Odds Ratios and 95 % CI: s Representing Associations of Growth from Birth to 11 Years of Age with Hospitalisation for Personality Disorders in Adulthood among Women.

	Weight (n=4197)			Length/Height (n=4151)			Body Mass Index (n=4141)		
	Adjusted model 1 [a]		Fully adj. [b]	Adjusted model 1 [a]		Fully adj. [b]	Adjusted model 1 [a]		Fully adj. [b]
Growth from: [c]	Odds Ratio (95 % CI)	*p*	*p*	Odds Ratio (95 % CI)	*p*	*p*	Odds Ratio (95 % CI)	*p*	*p*
Birth to 6 months	1.10 (0.87-1.39)	.44	.18	1.14 (0.90-1.44)	.29	.47	1.09 (0.86-1.38)	.49	.31
6 months to 1 year	0.88 (0.69-1.11)	.28	.36	0.97 (0.76-1.23)	.78	.96	0.95 (0.75-1.21)	.67	.73
1 to 2 years	0.99 (0.79-1.24)	.93	.46	0.95 (0.76-1.20)	.68	.79	0.97 (0.77-1.23)	.80	.69
2 to 7 years	0.81 (0.63-1.04)	.10	.10	0.76 (0.59-0.97)	.03	.17	0.93 (0.73-1.20)	.58	.65
7 to 11 years	0.89 (0.69-1.15)	.37	.74	0.99 (0.77-1.26)	.92	.70	0.85 (0.67-1.08)	.19	.41

[a] Adjusted for father's occupational status in childhood and for year of birth.

[b] Adjusted also for the presence of a mood disorder

[c] Expressed as a standardized residual of regression of body size at each age regressed on corresponding measures at all earlier ages creating completely uncorrelated residuals reflecting growth conditional on previous history.

Figure 3a.

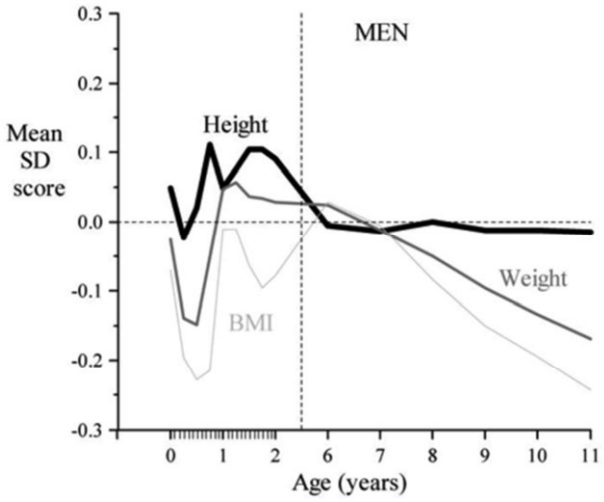

Figure 3b.

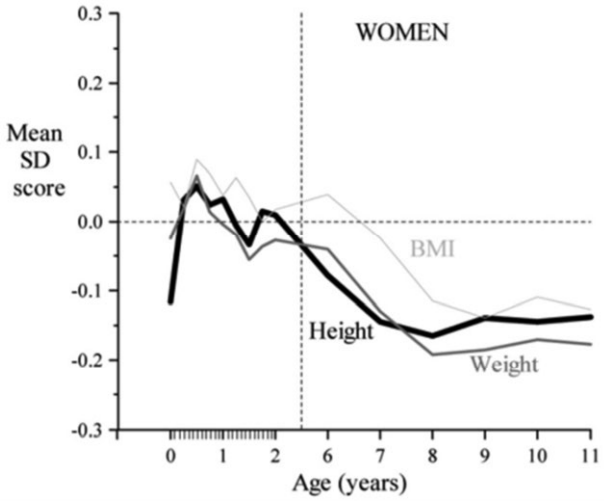

Figure 3a and Figure 3b. Unadjusted mean z scores of trimonthly estimates of weight, length/height, and BMI from birth to two years and annual estimates from six to 11 years for men (Figure 3a) and women (Figure 3b) hospitalised for personality disorders. The mean values for all the boys and all the girls are set at zero with deviations from the mean expressed as standard deviations.

Additional analyses of growth effects on dramatic personality disorders, not reported in the original manuscript, showed that subjects hospitalised for dramatic personality disorders gained less weight (*OR* = 0.73, 95 % CI = 0.56-0.95, *p* = .02) and BMI (*OR* =

0.66, 95 % CI = 0.51-0.85, p = .001) between seven and 11 years of age. The association of weight gain was rendered marginally significant after adjustment for concurrent mood disorders (p = .09). In contrast, slower BMI gain between seven and 11 years was still a significant predictor of hospitalisation for dramatic personality disorders after this adjustment (p = .01).

Sex-specific analyses showed that among men, most of the aforementioned effects of postnatal growth on personality disorders were particularly characteristic of dramatic personality disorders: Men hospitalised for dramatic personality disorders gained faster in weight and in BMI between six months and one year, slower in BMI between one and two years, and slower in BMI and marginally slower in weight between seven and 11 years of age (Table 7a). In contrast, no significant associations between infancy or childhood growth and severe dramatic personality disorders emerged among women (Table 7b). Furthermore, there were no significant associations between attained body size at any specific age and dramatic personality disorders (all p-values ≥ .06).

Table 7a. Odds Ratios and 95 % CI: s Representing Associations of Growth from Birth to 11 Years of Age with Hospitalisation for Dramatic Personality Disorders in Adulthood among Men.

	Weight (n=4640)			Length/Height (n=4601)			Body Mass Index (n=4592)		
	Adjusted model 1 [a]		Fully adj. [b]	Adjusted model 1 [a]		Fully adj. [b]	Adjusted model 1 [a]		Fully adj. [b]
Growth from: [d]	Odds Ratio (95 % CI)	*p*	*p*	Odds Ratio (95 % CI)	*p*	*p*	Odds Ratio (95 % CI)	*p*	*p*
Birth to 6 months	0.77 (0.56-1.08)	.13	.21	0.93 (0.66-1.31)	.68	.98	0.81 (0.58-1.12)	.20	.16
6 months to 1 year	1.36 (1.00-1.85)	.05	.02	0.97 (0.70-1.33)	.83	.96	1.40 (1.04-1.88)	.03	.03
1 to 2 years	0.80 (0.56-1.14)	.22	.06	1.10 (0.83-1.46)	.51	.52	0.76 (0.57-1.02)	.07	.03
2 to 7 years	0.97 (0.70-1.34)	.86	.97	0.85 (0.61-1.19)	.34	.45	1.12 (0.81-1.54)	.50	.71
7 to 11 years	0.71 (0.50-1.00)	.05	.09	1.04 (0.76-1.44)	.79	.70	0.66 (0.48-0.93)	.02	.05

[a] Adjusted for father's occupational status in childhood and for year of birth.

[b] Adjusted also for the presence of a mood disorder

[d] Expressed as a standardized residual of regression of body size at each age regressed on corresponding measures at all earlier ages creating completely uncorrelated residuals reflecting growth conditional on previous history.

Table 7b. Odds Ratios and 95 % CI: s Representing Associations of Growth from Birth to 11 Years of Age with Hospitalisation for Dramatic Personality Disorders in Adulthood among Women.

	Weight (n=4155)			Length/Height (n=4109)			Body Mass Index (n=4099)		
	Adjusted model 1 [a]		Fully adj. [b]	Adjusted model 1 [a]		Fully adj. [b]	Adjusted model 1 [a]		Fully adj. [b]
Growth from: [c]	Odds Ratio (95 % CI)	*p*	*p*	Odds Ratio (95 % CI)	*p*	*p*	Odds Ratio (95 % CI)	*p*	*p*
Birth to 6 months	1.00 (0.68-1.47)	.998	.59	1.25 (0.85-1.82)	.25	.22	0.87 (0.59-1.28)	.48	.73
6 months to 1 year	1.03 (0.70-1.52)	.88	.66	0.99 (0.67-1.45)	.95	.92	1.06 (0.72-1.56)	.77	.59
1 to 2 years	1.00 (0.69-1.46)	.98	.79	0.83 (0.56-1.22)	.33	.30	1.18 (0.82-1.71)	.37	.28
2 to 7 years	1.05 (0.72-1.54)	.80	.78	1.07 (0.72-1.60)	.74	.44	1.01 (0.68-1.49)	.97	.88
7 to 11 years	0.80 (0.52-1.21)	.29	.51	1.23 (0.84-1.80)	.28	.16	0.68 (0.45-1.02)	.06	.13

[a] Adjusted for father's occupational status in childhood and for year of birth.

[b] Adjusted also for the presence of a mood disorder

[c] Expressed as a standardized residual of regression of body size at each age regressed on corresponding measures at all earlier ages creating completely uncorrelated residuals reflecting growth conditional on previous history.

4.3 Temporary Separation from Parents and Severe Mental and Particularly Personality Disorders (Studies III-IV)

Temporary separation from parents in childhood predicted an increased risk of any severe mental disorder and in particular the risks of severe substance use and personality disorders (Table 8).

Table 8. Risk of severe mental disorders according to separation status.

Disorders:	*N*	Non-separated, % [a]	Separated, %[a]	Hazard Ratio[b] (95 % CI) [c]	*p*
No disorder *vs.*	11258				
Any	1489[d] (13, 9, 9)[e]	11.4	13.2	1.18 (1.01 to 1.38)	.04
Substance use	800 (13, 9, 8)	6.4	8.1	1.30 (1.06 to 1.59)	.01
Psychotic	311 (0, 0, 0)	2.6	3.3	1.28 (0.92 to 1.79)	.15
Mood	550 (0, 0, 1)	4.6	5.1	1.10 (0.84 to 1.44)	.48
Anxiety	310 (0, 0, 0)	2.6	3.3	1.28 (0.91 to 1.80)	.16
Personality	194 (0, 0, 0)	1.6	2.4	1.59 (1.05 to 2.42)	.03

[a] % refers to the prevalence of severe mental disorders according to separation status derived from models adjusting for sex, year of birth and childhood socioeconomic background.

[b] Hazard models are stratified for sex and year of birth and adjusted for childhood socioeconomic background. [c] 95% CI refers to 95% confidence interval.

[d] The N of specific severe mental disorders does not sum up to having any disorder, because of change in diagnostic symptoms over time and/or co-morbidity.

[e] The sample size in parenthesis refers to cases identified from the Finnish Causes of Death Register for whom the diagnosis is the primary, intermediate or contributing cause of death, respectively.

Furthermore, the increased risk of severe personality disorders among the separated children was specific to these disorders; that is, the risk for personality disorders was significantly increased also among subjects hospitalised for any severe mental disorder. The risk for personality disorders was 1.6-fold in comparison to having no mental disorder and 1.5-fold in comparison to those with other severe mental disorders (Table 9). Table 9 also shows that the parental separation effects on personality disorders were independent of parity and of maternal age at childbirth.

Compared to the non-separated subjects, children separated before five years of age were at a particularly increased risk of hospitalisations for personality disorders. This significantly increased risk for personality disorders among those with early separations

was found both when the comparison outcome group comprised individuals with no severe mental disorder [*HR* = 1.66 (95 % CI = 1.01-2.73), Figure 4a] and when comparing the risk for personality disorders among individuals with any mental disorder [*HR* = 1.68 (95 % CI = 1.03-2.76), Figure 4a]. Those separated at later ages did not differ in their risks from the non-separated controls (all *p*-values ≥ .70; Figure 4a). Separation duration did not play a moderating role, and when we divided the subjects to groups by the median of separation duration (1.5 years), neither group differed significantly from the non-separated control participants (all *p*-values ≥ .052).

Furthermore, compared to the non-separated individuals, the children separated before five years of age were at a particularly increased risk of severe dramatic personality disorders. Among these individuals with parental separation in early childhood, the risk for dramatic personality disorders in adulthood was significantly increased both when the comparison outcome group comprised healthy individuals (*HR* = 2.10, 95 % CI = 1.01-4.40; Figure 4b) and also when the risk for dramatic personality disorders was assessed among individuals with any mental disorder (*HR* = 2.09, 95 % CI = 1.00-4.37; Figure 4b).

Table 9. Temporary separation from parents and hospitalisation for any and dramatic personality disorders. Hazard ratios and 95 % CI: s.

Comparison group:	Healthy Controls (*N* =11247)		Subjects with Any Non-Personality Mental Disorder (*n* = 1293)	
Diagnostic outcome	Any Personality Disorder (*n* = 194)	Dramatic Personality Disorder (*n* = 77)	Any Personality Disorder (*n* = 194)	Dramatic Personality Disorder (*n* = 77)
Separated vs. Non-Separated	Hazard Ratio (95 % CI) [a]	Hazard Ratio (95 % CI) [a]	Hazard Ratio (95 % CI) [a]	Hazard Ratio (95 % CI) [a]
All subjects	1.58 (1.04-2.41) *	1.83 (0.97-3.44)	1.53 (1.00-2.32) *	1.74 (0.92-3.28)
Women	1.68 (0.90-3.12)	1.01 (0.29-3.56)	1.98 (1.06-3.69) *	1.01 (0.28-3.70)
Men	1.48 (0.84-2.63)	2.37 (1.13-5.00) *	1.34 (0.76-2.38)	2.27 (1.08-4.80) *

[a] Hazard Ratios and 95 % CI:s for models stratified for sex and year of birth and adjusted for socioeconomic position in childhood, maternal age at childbirth, and parity

*$p < .05$

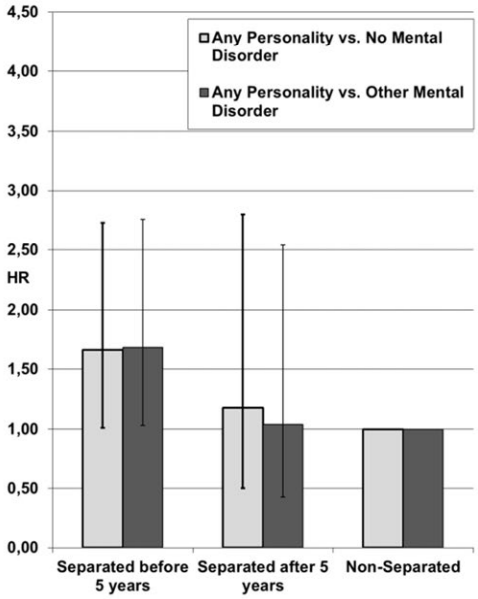

Figure 4a. Age at separation and personality disorders.

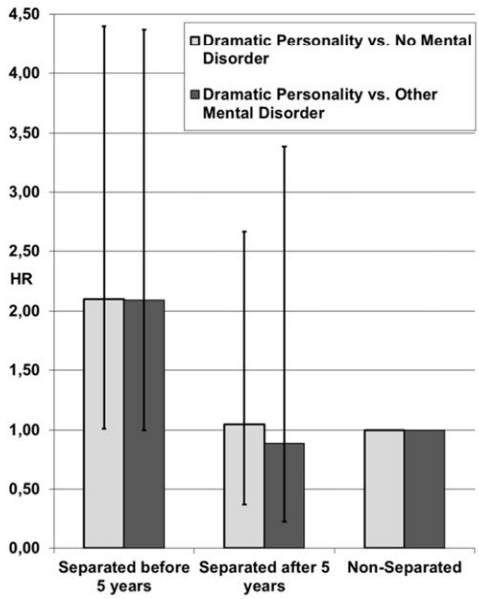

Figure 4b. Age at Separation and Dramatic Personality Disorders

Figure 4a and Figure 4b. Age at first separation and any and dramatic personality disorders, respectively. The figures show the hazard ratios and their 95 % Confidence Intervals of the associations between age at first separation and risk of hospitalisation for any and for dramatic personality disorders**.**

Sex-specific analyses showed that the association of parental separation to any severe personality disorder was more characteristic of women, who had a significantly increased risk of personality disorders in comparison to other mental disorders (Table 9). This risk was particularly characteristic of women separated before the age of five years (*HR* = 2.49, 95 % CI = 1.15-5.37). On the other hand, the separated men (Table 9), especially men separated before five years of age [*HR* = 3.15 (95 % CI = 1.38-7.15), compared to healthy controls and *HR* = 2.82 (95 % CI = 1.24-6.39), among individuals with any mental disorder)] were at a significantly increased risk of hospitalisation for dramatic personality disorders.

4.4 Socioeconomic Position in Childhood and Severe Mental and Personality Disorders: Independent and Interaction Effects with other Adversities

Compared to all the other subjects, individuals from the lowest childhood socioeconomic position (fathers as manual workers) group were at an increased risk of any severe mental disorder (p = .04) and of substance use disorders (p = .01). Further analyses showed that individuals with higher clerical worker fathers had a lower risk of any mental disorder (*HR* = 0.84, 95 % CI = 0.73-0.97), and the offspring of both senior (*HR* = 0.77, 95 % CI = 0.64-0.95) and junior (*HR* = 0.83, 95 % CI = 0.70-0.99) clerical workers had lower risks of substance use disorders than the offspring of manual worker fathers. In contrast, no significant effects of socioeconomic position in childhood on hospitalisation for any or for dramatic personality disorders emerged in the whole sample or among either sex (all p-values $\geq$ .12).

Furthermore, Table 10 shows that there were significant interactions of parental separation by socioeconomic position in childhood (upper vs. lower socioeconomic status) in predicting the risk of any mental disorder (p = .009) and of substance use disorders (p = .03). Namely, the increased risk among the separated children was particularly characteristic of subjects whose fathers were upper clerical workers. Among these subjects, temporary separation from parents was associated with an increased risk of any mental, substance use, mood, psychotic, and personality disorders. In contrast, among subjects with lower socioeconomic background, the separation did not add significantly to the already increased risks associated with the lower socioeconomic position in the family of origin. For personality disorders, there was no interaction by socioeconomic position in childhood but the risk among the separated was most heightened among those from the highest social class in crude hazard ratio comparisons (Table 10).

Table 10. The risk of severe mental disorders according to separation status and childhood upper *vs.* lower socioeconomic background. [a]

Disorders:	**Lower socioeconomic background *n* = 2010 (separated) *vs.* 6317 (non-separated)**			**Upper socioeconomic background *n* = 187 (separated) *vs.* 1152 (non-separated)**		
	% [b]	Hazard Ratio[c] (95% CI)	*p*	% [b]	Hazard Ratio[c] (95% CI)	*p*
Any						
Separated	13.0	1.40 (1.11 to 1.75)	.004	18.7	1.94 (1.32 to 2.84)	.001
Non-Separated	12.1	1.26 (1.08 to 1.47)	.003	9.9	Referent	
Separated vs. non-separated		1.08 (0.89 to 1.31)	.42		2.12 (1.41 to 3.20)	.001
Substance use						
Separated	8.0	1.69 (1.25 to 2.29)	.001	11.8	2.25 (1.35 to 3.73)	.002
Non-Separated	7.0	1.39 (1.12 to 1.73)	.003	5.3	Referent	
Separated vs. non-separated		1.18 (0.92 to 1.52)	.20		2.57 (1.49 to 4.45)	.001
Psychotic						
Separated	3.0	1.36 (0.82 to 2.23)	.23	5.0	2.22 (0.99 to 4.99)	.054
Non-Separated	2.8	1.25 (0.89 to 1.75)	.21	2.3	Referent	
Separated vs. non-separated		1.05 (0.69 to 1.61)	.81		2.64 (1.13 to 6.13)	.025
Mood						
Separated	4.7	1.08 (0.74 to 1.58)	.70	8.4	1.88 (1.02 to 3.48)	.04
Non-Separated	4.7	1.09 (0.85 to 1.40)	.48	4.3	Referent	
Separated vs. non-separated		0.96 (0.68 to 1.34)	.80		2.17 (1.12 to 4.20)	.02
Anxiety						
Separated	2.9	1.08 (0.66 to 1.76)	.76	4.7	1.54 (0.66 to 3.62)	.32
Non-Separated	2.5	0.88 (0.65 to 1.21)	.43	2.8	Referent	
Separated vs. non-separated		1.17 (0.75 to 1.81)	.50		1.87 (0.77 to 4.57)	.17
Personality						
Separated	2.0	1.24 (0.67 to 2.30)	.49	4.3	2.71 (1.11 to 6.62)	.028
Non-Separated	1.6	0.94 (0.63 to 1.41)	.78	1.7	Referent	
Separated vs. non-separated		1.26 (0.73 to 2.19)	.41		3.03 (1.14 to 8.04)	.025

[a] The interactions between 'separation status x upper *vs.* middle childhood socioeconomic background' were not significant in the analyses of mental disorders and therefore hazard ratios and prevalence of mental disorders in the middle childhood socioeconomic background are not presented.

[b] % refers to the prevalence of severe mental disorders according to separation status derived from models adjusting for sex and year of birth.

[c] Hazard models are stratified for sex and year of birth.

4.5 Retrospectively Reported Stressful Experiences in Childhood among the Separated and Their Long-Term Consequences

According to the retrospective questionnaire study, the overall assessments of the separation experience were, on average, positive. On a scale of 0-10 of positivity of the experience, the mean score was 7.71. However, there was large variation between subjects, as indicated by the *SD* being 2.34.

Pairwise *t*-test comparisons were conducted among subjects with valid data on a particular type of childhood exposure to compare differences in the stressfulness of the different exposures before, during, and after the separations. The following significant differences were found: Separation from foster parents was experienced as more stressful than that from biological parents (Mean Difference (*MD*) = -0.47, *df* = 58, *p* = .04). Life in the foster family was experienced as less stressful than life at home before (*MD* = 0.29, *p* = .05, *n* = 73) and after (*MD* = 0.69, *df = 144, p* = .001) the separation. Also the financial situation of the foster family was experienced as less stressful than that at home before (*MD* = 1.00, *df* = 76, *p* < .001) and after (*MD* = 1.03, *df* = 82, *p* < .001) the separation. The subjects reported having been exposed to childhood maltreatment more often after returning home than before leaving home or during the separation (*p*-values < .001 for both).

Women experienced separation from foster parents (*MD* = 0.70, *df* = 95, 95 % CI = 0.11-1.30) and returning home (*MD* = 0.62 *df* = 112.8, 95 % CI = 0.16-1.17) as more stressful than men. Life before leaving home was also rated more stressful by women (*MD* = 0.49, *df* = 58.3, 95 % CI = 0.08-0.90). On the other hand, a lower socioeconomic position in the family of origin was associated with a more stressful financial situation after returning home subsequent to the separation [*F* (2, 150) = 5.11, *p* = .007].

4.5.1 Age and Length of Separation and Separation Experience

Subjects separated at a younger age experienced separation from foster parents (*r* = -.28, *df* = 88, *p* = .007), returning home (*r* = -.32, *df* = 88, *p* < .001), and life after returning

home (r = -.33, df = 151, p < .001) as more stressful. They also experienced more stressful language difficulties when returning home (r = -.23, df = 141, p = .006) than subjects evacuated at older ages.

Longer separations associated with more positive overall assessments of the separation experience (r = .20, df = 180, p = .007), with less stressful separation from biological parents (r = -.26, df = 84, p = .02), and, in contrast, with more stressful experiences of separation from foster parents (r = .44, df = 87, p < .001) and of returning home (r = .34, df = 138, p < .001). Longer separation duration also associated with higher stressfulness of language problems when returning home (r = .29, df = 137, p = .001), and with higher stressfulness of life after returning home (r = .44, df = 147, p < .001). Also the stressfulness of the financial situation before the separation (r = .34, df = 77, p = .002) and after returning home (r = .24, df = 140, p = .003) associated positively with separation duration. Subjects with a longer separation duration also self-reported more often stressful experiences of maltreatment at any time in childhood (OR = 1.64, p = .009, n = 132) and particularly after returning home (OR = 1.70, p = .008, n = 95).

4.5.2 Separation Experience and Antisocial Personality Traits

Self-reported exposure to childhood maltreatment modified the long-term consequences of the separation exposure on adult antisocial personality traits. Compared to not being exposed to maltreatment, having a stressful maltreatment exposure at any time (either before, during, or after separation) in childhood was associated with significantly higher antisocial personality traits in adulthood (β = 0.23, p = .02, n = 114). In particular, exposure to maltreatment in foster care (β = 0.28, p = .03, n = 74) and after the separation (β = 0.28, p = .006, n = 102) were both significantly associated with increased antisocial traits. Also a stressful financial situation in the foster family (β = 0.21, p = .01, n = 139) and after returning home (β = 0.18, p = .03, n = 153) were associated with higher antisocial traits in adulthood.

5. DISCUSSION

This thesis examined the early life developmental origins of severe personality disorders. Our findings highlight the important role played by early life developmental factors, those reflected in early life growth, both prenatally, in infancy, and later in childhood as well as those of temporary separation from parents, especially in early childhood before five years of age in the etiology of personality disorders severe enough to justify hospitalisation. The effects of these early developmental factors were especially salient in the development of dramatic cluster personality disorders. Early separation from parents exerted specific effects on personality disorders also in comparison to other types of psychopathology. All these longitudinal study findings strongly support previous evidence, based mostly on retrospective accounts, that early life developmental adversity sets forth an increased risk for personality disorders in adulthood.

5.1 Pre- and Postnatal Growth and Personality Disorders

Among men, a small head circumference and a smaller head-to-length ratio at birth predicted an increased risk of severe personality disorders in adulthood. In conjunction with these findings, a recent study found that a small head circumference at birth differentiated adult offenders with personality disorder from control subjects in the general population with no severe mental disorder (Fazel et al., 2012). Earlier studies have also suggested that a smaller head circumference at one year of age may predict antisocial symptoms of violent offending among men (Ikäheimo et al., 2007) and schizotypal personality disorder symptoms among women (J. Lahti et al., 2009). Although not directly assessing head circumference at birth, these findings also suggest that reduced head growth either prenatally or in infancy is associated with personality disorder symptoms. A smaller head circumference at birth and a smaller head-to-length ratio have also been shown to predict increased ADHD symptoms in childhood (Heinonen et al., 2011; J. Lahti et al., 2006), which, in turn, predict the risk of personality disorders in adulthood (Biederman et al., 2010). Both a small head circumference and a small head-to-length ratio have been shown to reflect reduced fetal

brain growth (Lindley, Benson, Grimes, Cole, & Herman 1999), the latter also in comparison to trunk growth. Hence, together these findings suggest that brain development during the fetal period may exert programming effects on personality dysfunction in adulthood.

The association of head circumference at birth and hospitalisation for personality disorders was nonlinear: The smallest babies showed the highest risks, and those with medium and large head circumference did not differ significantly from each other in their risks. Previous studies have shown that body size at birth may exert nonlinear effects on schizophrenia (Gunnell et al., 2003; Moilanen et al., 2010) and on temperament trait harm avoidance (J. Lahti et al., 2008), that associates with the risk of personality disorders (Joyce et al., 2003). The potential nonlinearity may be explained, among other things, by some pregnancy disorders such as gestational diabetes leading to macrosomia (Fadl, Östlund, Magnuson, & Hanson, 2010; Gasim, 2012), and setting forth an increased risk also among the biggest babies. Although other studies suggest linear effects of birth size on psychopathology (Abel et al., 2010), our findings highlight the importance of assessing also nonlinear effects when examining the effects of birth size at least on personality dysfunction.

Especially among women, a smaller placental surface area at birth predicted an increased risk of hospitalisation for dramatic personality disorders. While the author knows of no other studies on adult psychopathology in association to placental surface area, a recent study found that, in contrast to our findings, larger placental surface area and larger placental weight in comparison to birth weight associated with higher antisocial personality and ADHD symptoms among eight-year old boys and also with higher levels of overall psychiatric morbidity (Khalife et al., 2012). Before the adjustment for birth size, there was no significant association of placental surface area with psychiatric morbidity, however, and no associations were found among women. These partially contradictory findings to the current ones may be explained by the younger age of the subjects in the other study (Khalife et al., 2012) and by them assessing less severe forms of psychopathology than was done in the current thesis.

On the other hand, a smaller placental surface area at birth has recently been associated with the risk of CHD (Eriksson, Kajantie, Thornburg, Osmond, & Barker, 2011), chronic heart failure (Barker, Gelow et al., 2010), and hypertension (Barker,

Thornburg, Osmond, Kajantie, & Eriksson, 2010; van Abeelen et al., 2011). As dramatic cluster personality disorders predict the risk of hypertension (El-Gabalawy et al., 2010) and cardiovascular disease (El-Gabalawy et al., 2010; Lee et al., 2010), our findings of a smaller placental surface area predicting severe dramatic personality disorders may implicate possible shared etiological origins for these cardiovascular outcomes and dramatic personality disorders. Etiological factors implicated in the associations between a smaller placental surface area and dramatic cluster personality disorders may include, among others, exposure to pre-eclampsia and prenatal malnutrition, since a smaller placental surface area has been found as a consequence of both these prenatal adversities (Kajantie, Thornburg, Eriksson, Osmond, & Barker, 2010; Roseboom, Painter, de Rooij, et al., 2011).

The study among offenders found that also preterm birth and being born SGA and with LBW each predicted an increased risk of personality disorders (Fazel et al., 2012), with prematurity exerting particularly strong effects. A large study showed that being born SGA and preterm predicted an increased risk of hospitalisation for personality disorders among men (Monfils Gustafsson et al., 2009). Likewise to the current study, that study found no effects of prenatal growth on any severe personality disorder among women. In contrast to the other studies, however, the current study did not find significant linear or quadratic effects of birth weight or gestation length on personality disorders among either sex. Our sample was born much earlier, and the rarity of live preterm, especially preterm SGA births between 1934 and 1944 precluded corresponding analyses to those of the previous studies here in our cohort. On the other hand, the study by Monfils Gustafsson and colleagues (2009) did not report associations to any other prenatal growth measures than birth weight and prematurity and assessed hospitalisations for personality disorders only until young adulthood, while our follow-up extended to older adulthood. Furthermore, neither of the Swedish studies assessed particular effects on dramatic cluster personality disorders (Fazel et al., 2012; Monfils Gustafsson et al., 2009). Nevertheless, both these previous studies and the current one suggest that suboptimal prenatal growth may predict severe personality disorders, effects which may be especially salient among men.

Relative gain in BMI and in weight in infancy and later in childhood predicted the risk of personality disorders among men. Thinness at six months and again at 11 years

of age were both also associated with personality disorders among men. Among women, slower height growth between two and seven years of age predicted an increased risk of severe personality disorders. The findings among men were independent of co-morbid mood disorders. Further analyses showed that these associations found among men were mostly typical of personality disorders of the dramatic cluster.

These current findings appear to be novel. They suggest that it is not only the adversities of the prenatal period that affect risk of severe personality disorders, but that factors reflected in growth in infancy and in childhood may also be predictive. Particularly relevant periods of growth were growth in the first six months, growth between six months and one year, and between seven and 11 years among men, and growth between two and seven years among women. The sex-specificity of the findings was highlighted by significant interactions by sex for infancy growth in predicting personality disorders.

A few previous studies have examined attained body size in infancy and in adolescence in relation to personality disorders and related symptoms (Hebebrand et al., 1996; Ikäheimo et al., 2007). Firstly, higher BMI at one year of age was associated with an increased risk of violent offending, an antisocial personality disorder -related symptom, in young adulthood among men (Ikäheimo et al., 2007). In our study, body size at one year of age was not predictive of personality disorders, although smaller size at six months and faster growth between six months and one year were. While both these studies suggest that size in infancy may be predictive of later personality psychopathology among men, the difference in the specifically relevant size patterns may have to do with the differences in the type of dysfunction assessed, and the age differences between the samples studied. Furthermore, the earlier study on infancy size and violent offending did not assess growth between particular ages, only attained body size at a certain age (Ikäheimo et al., 2007).

The findings of slower gains in weight and in BMI between seven and 11 years leading to thinness at 11 years of age predicting the risk of severe personality disorders among men correspond well to those of Hebebrand and colleagues (1997), who found that schizoid personality disorder associated with thinness among adolescent boys. However, that study had a small patient group, concentrated only on schizoid personality disorder, and assessed these associations in a cross-sectional study setting,

not longitudinally, as was done here. On the other hand, previous longitudinal studies have suggested that thinness between seven and 15 years of age may also predict adult risk of schizophrenia (Wahlbeck et al., 2001), and thinness in adolescence may predict suicide risk (Batty et al., 2010; Magnusson et al., 2006; Osler et al., 2008). Such findings may be seen as possibly suggesting conjoint developmental pathways leading to these often co-occurring psychopathological outcomes that would be reflected in lower body mass in late childhood and adolescence.

Slower height growth in childhood, particularly between ages two and seven years, was associated with the risk of severe personality disorders among women. However, this association was not significant after adjustment for concurrent mood disorders, perhaps suggesting effects confounded by comorbidity. On the other hand, it is of note that the vast majority of women with personality disorders also had mood disorders, and thus this adjustment can in a way be seen as over-adjustment. In the sample as a whole, slower childhood height growth predicted personality disorders even after adjusting for comorbid mood disorders, although there was no significant association among men. I know of no earlier studies on childhood growth and personality disorders among women. These findings are hence novel. They nevertheless suggest that women with severe personality disorders may be characterized by slower height growth in childhood.

The effects of early growth on personality disorders were thus different among men and women. The potential underlying mechanisms contributing to the associations between growth and personality disorders generally and those related specifically to the sex differences will be discussed in detail in later sections of this discussion. These chapters will focus more generally on the potential mechanistic pathways underlying the effects of early life adversity on personality disorders and on the sex differences in these associations. Briefly, the potential explanations for the associations between growth and personality disorders include the contribution of both genetic and environmental factors (e.g. Silventoinen et al., 2008), and the mechanisms underlying the sex-specificity of the findings may involve, for example, sex differences in brain development leading to the developing brain being more vulnerable to the effects of environmental adversities at a particular age among either men or women (Goel & Bale, 2009; Lombardo et al., 2012).

5.2 Temporary Separation from Parents and Severe Personality Disorders

Our longitudinal study showed that temporary parental separation in childhood predicted an increased risk of personality disorders requiring hospitalisation in adulthood. Especially among men, increased risks were found particularly for dramatic cluster personality disorders. The risks for any and for dramatic personality disorders were most elevated among children separated in early childhood, before five years of age, while children separated at later ages did not differ in their risks from the non-separated children. These findings closely correspond to those of Crawford and colleagues (2009), who in their longitudinal study found an effect of parental separation particularly before five years of age on borderline personality disorder symptoms, and to those of the longitudinal study that found that parental separation before three years of age prospectively predicted an increased risk of psychopathic personality disorder (Gao et al., 2010). Also corresponding to our findings, in the NFBC, hospitalisation for any and particularly for dramatic personality disorders was predicted by single parenthood at birth (Kantojärvi, Joukamaa et al., 2008; Mäkikyrö, Sauvola et al., 1998), and children separated from one parent due to parental divorce were also at an increased risk of personality disorders.

The increased risk among the separated, particularly those separated before five years of age, was specific to personality disorders and especially to dramatic personality disorders in that it emerged also in comparison to other severe mental disorders, not only when comparing individuals with personality disorders to healthy controls. No previous longitudinal studies have assessed such specificity of effects directly, although one longitudinal study in a small sample reported no difference in the rates of parental separation among individuals with borderline personality disorder and those with other mental disorders (Helgeland & Torgersen, 2004). However, three retrospective studies did find higher rates of parental separation among individuals with personality disorder compared to the rates found among schizophrenia patients (Byrne et al., 1990; Gibbon et al., 2009; Pert et al., 2004), and are in line with our findings, while one study among depressed subjects found no association between borderline personality disorder and parental separation (Weaver & Clum, 1993).

Together these findings suggest that parental separation particularly in early childhood may predict the risk of personality disorders and especially of dramatic cluster personality disorders. The findings further suggest that parental separation in early childhood may have particularly strong effects on personality disorders also in comparison to other types of psychopathology. This finding is not surprising, considering that parental separation associates with insecure attachment and with interpersonal difficulties in later life (Gao et al., 2010; Woodward, Fergusson, & Belsky, 2000) and both of these features are highly characteristic of patients with personality disorders (Bakermans-Kranenburg & van IJzendoorn, 2009; Hill et al., 2011).

Compared to the previous studies on parental separation and personality disorders, it is, however, of note that the current study had a larger sample size than the majority of them, was a longitudinal study based on objective measures of parental separation and personality psychopathology, and assessed the effects of this early life adversity on personality disorders across adulthood onwards to later life, while many earlier studies have had follow-ups only to young adulthood. Although thus supportive of most previous findings, ours give strong credence to the hypothesis that early life interpersonal adversity in the form of separation from parents in early childhood may play an etiological role in the development of severe personality disorders.

In addition to personality disorders, previous longitudinal studies have shown that the risks of substance use (Mäkikyrö, Sauvola et al., 1998; Veijola et al., 2008) and mood (Mäkikyrö, Sauvola et al., 1998; Pesonen et al., 2007; Veijola et al., 2004) disorders may also be increased among individuals exposed to temporary separation from their parents. The current study replicated these findings in terms of the increased risk found among the separated children for substance use disorders, but for mood disorders, an increased risk was found for the separated children only in the highest socioeconomic classes.

Previous studies in the HBCS have shown that the children separated from their parents also show, in late adulthood, altered vulnerability to stress, as indicated by altered functioning of the HPA axis (Pesonen et al., 2010), higher systolic blood pressure (Alastalo et al., 2012b) and higher levels of subclinical depressive symptoms (Pesonen et al., 2007) than their non-separated counterparts. Across adult life, they show poorer cognitive functioning (Pesonen, Räikkönen, Kajantie, Heinonen,

Henriksson, et al., 2011), less social mobility to higher socioeconomic classes (Pesonen, Räikkönen, Heinonen, Kajantie, Osmond, et al., 2011), and a heightened risk of CHD (Alastalo et al, 2009; 2012a). The reproductive functioning of the separated children is altered, with women showing earlier age at menarche and having more children by late adulthood, and men having their first children born earlier and having shorter inter-birth intervals for their children (Pesonen et al., 2008). Overall, these findings correspond well to the DOHaD framework (Barker, 2004, 2009) and to the life cycle model of stress (Lupien et al., 2009), since the separated children, as a consequence of their early life stress exposure, show altered central and peripheral vulnerability to stress, and their risk of somatic illnesses and mental disorders in adult life is increased, particularly in terms of disorders and illnesses known to be associated with changes in the functioning of the stress system (R. Reynolds et al., 2010; Stetler & Miller, 2011).

5.3 Modifying Effects of Sex: Different Etiological Precursors for Personality Disorders among Men and Women?

The vast majority of the current significant findings were more evident among one or the other sex. A small head circumference at birth, and infancy and childhood gains in weight and in BMI predicted any severe personality disorder among men, while parental separation and childhood height growth played a predictive role among women. Dramatic personality disorders, on the other hand, were predicted by parental separation among men, among whom also infancy and childhood weight and body mass gains were predictive. A smaller placental surface area at birth predicted severe dramatic personality disorders among women. Generally, more effects of growth on personality disorders emerged among men than among women, while parental separation exerted more evident effects on different types of personality disorders among the two sexes.

The current findings correspond to previous studies suggesting differential effects of prenatal and infancy growth on personality disorders and related traits for men and women (Khalife et al., 2012; J. Lahti et al., 2009; Monfils Gustafsson et al., 2009). Childhood body size or growth had not been studied among women in relation to personality disorders but the current findings suggest that gains in weight and in BMI are more important among men and height growth among women.

According to the current findings, there seemed to be different developmental vulnerability periods for the effects of growth on personality disorders among men and women. Growth prenatally, in the first year of life and between seven and 11 years predicted later risk of personality disorders among men, while growth between two and seven years was especially relevant among women. As stated, a potential explanation for these sex-specific vulnerability periods is sex differences in brain development at certain ages, leading to the developing brain being more vulnerable among men or among women, depending on the age at question (Goel & Bale, 2009). While the findings are still somewhat uncertain, recent studies indeed suggest that there may be sex differences in brain development during the sensitivity periods when growth predicted personality disorders differentially among the two sexes (Goel & Bale, 2009; Lombardo et al., 2012; Sumich et al., 2012; Uematsu et al., 2012). Sex differences are evident also in the development of the brain areas implicated in the stress system, such as the HPA axis (Goel & Bale, 2009; Lombardo et al., 2012), amygdala (Lombardo et al., 2012; Uematsu et al., 2012), and hippocampus (Uematsu et al., 2012), the functioning of which are all affected in personality disorders (Ruocco et al., 2012; D. Zimmerman & Choi-Kain, 2009). While these findings suggest that differences in brain development at different ages in early life may possibly underlie the sex-specificity of the findings, based on the current knowledge such speculation is tentative. Further studies directly assessing such changes in relation to the associations between personality disorders and growth are needed.

The effect of parental separation on any severe personality disorder, at least in comparison to other mental disorders, being more relevant among women is a novel finding. The NFBC studies did not find interactions by sex nor report sex-specific effects (Kantojärvi et al., 2008). On the other hand, in line with the current findings, dramatic personality disorders and their symptoms have also previously been more strongly associated with parental separation among men than among women (Murray et al., 2012; Mäki, Hakko et al., 2003; Sauvola et al., 2002), suggesting that early parental separation may more evidently predict this type of personality psychopathology among men. On a neurobiological level, the effects of early life adversity on the development of the HPA axis have been shown to differ by sex (DeSantis et al., 2011; Goel & Bale, 2009; Mueller & Bale, 2011), and sex differences in the development of the functioning

of these brain areas may potentially be underlying contributory factors to the differential associations of both parental separation and growth to the different types of personality disorders among the two sexes.

Together the current findings thus highlight the importance of studying sex as a possible modifier of the effects of early life developmental adversity in the etiology of severe personality disorders. However, it is of note that significant interactions by sex were found only for infancy gain in weight, thus precluding any strong conclusions about the potential sex-specificity of the etiological pathways.

5.4 Other Modifying Factors on the Effects on Parental Separation: Socioeconomic Adversity and Stressful Experiences in Childhood

5.4.1 Socioeconomic Position in Childhood

Childhood socioeconomic position did not exert main effects on severe personality disorders, which is in line with some (Kantojärvi, Joukamaa et al., 2008; Widom et al., 2009) but not all (Anglin et al., 2008; Cohen et al., 2008; Crawford et al., 2009; Lahey et al., 2005) previous studies. However, most of the studies with significant effects of childhood socioeconomic position assessed the symptoms of personality disorder (Anglin et al., 2008; Cohen et al., 2008; Crawford et al., 2009), while for more severe types of personality dysfunction justifying a diagnosis the evidence on such predisposing effects is scantier.

Although there was no interaction of socioeconomic position with parental separation in predicting personality disorders, childhood socioeconomic position interacted with parental separation in predicting the risks of any mental and substance use disorders requiring hospitalisation or contributing to death. The effects of parental separation on any mental disorder and on substance use disorders were especially salient among individuals from a higher socioeconomic background in the family of origin. While overall children from poorer socioeconomic circumstances had heightened risks of any mental disorder and of substance use disorders, being separated seemed to nullify the protective effects of higher socioeconomic position but did not add to the increased

risk already found among those from poorer socioeconomic circumstances. Furthermore, in spite of the lack of significant interaction effects, when comparing the hazard ratios, the effects of temporary parental separation on severe personality disorders were most evident and statistically significant among individuals with the highest socioeconomic position of family of origin. These highlighted effects of parental separation in the highest childhood socioeconomic classes are in line with the findings of a study of intercountry adoptees (Tieman et al., 2005), that found that adopted children in the highest socioeconomic classes differed most from their non-adopted socioeconomically matched counterparts. However, it is of note that in the adoption study the assessed socioeconomic position was that of the adoptee family, while we had socioeconomic data only on the family of origin where the children also returned to after the separation.

Possibly the change in the developmental circumstances as a consequence of the separation was more drastic for those children who came from a family of origin with a higher socioeconomic position and this mismatch in the developmental circumstances then made these individuals most vulnerable to the deleterious effects of separation. This would be in line with The Mismatch Hypothesis of the origins of mental disorders, which states that when an individual is developmentally (either genetically or environmentally) programmed to counter certain types of environmental circumstances, any strong changes to these circumstances would then exert predisposing effects on mental disorders (M. Schmidt, 2011). In line with the DOHaD hypothesis (Barker, 2007; Gluckman et al., 2011), the Mismatch Hypothesis considers the developing child to elicit information from the environment from the prenatal period onwards, and program its brain development based on this information (M. Schmidt, 2011). When this information goes awry in prediction, such as in the case of children from higher socioeconomic position being separated from their parents to circumstances that may vary randomly, a mismatch occurs, and the child is left predisposed to psychopathology as her/his brain is not prepared to the circumstances it encounters (M. Schmidt, 2011).

5.4.2 Stressful Exposures in Childhood among the Separated Children

Although parental separation predicted an increased risk of any mental, personality, and substance use disorders, our retrospective questionnaire study among the separated

children showed that the separated children had, as adults, overall, rather positive recollections of their separation experience. However, there were several modifying factors that influenced the stressfulness of the separation and life in childhood among the separated children. Younger age at separation was associated with more stressful childhood experiences. Particularly separation from foster parents, returning home, and life after returning home were rated as more stressful by those with earlier separation. Individuals with an early separation also had more language difficulties when returning home. On the other hand, individuals separated for longer periods of time experienced the factors associated with the time when they were separated more positively and life after returning home and separation from foster parents more negatively.

The separation experience may thus have been more stressful for some children depending on the age at and the duration of separation. This may be seen as suggesting that the modifying effects of age at separation on personality disorders that we found may also have to do with a generally more stressful environment in childhood among those with early separation. Furthermore, individuals separated at early ages may actually have had to endure two separations that affected their interpersonal development. Returning home was also experienced as more stressful by those with longer separations. Individuals with early and longer separations may have had time to form two attachment bonds (Bowlby, 1969), during the time the plasticity of interpersonal development was at its highest (Delius, Bovenschen, & Spangler, 2008), that were then disrupted. New interpersonal bonds may have been formed with the foster family, making the second separation a very stressful exposure. Furthermore, the children separated at early ages and for longer durations may, after the relatively longer time of being separated from their family of origin, have alienated from their biological family, and returning together with them may have been a stressful experience. However, based on the current data, such mechanism considerations remain speculative.

Although the questionnaire data on these exposures is open to the bias of retrospective recall (Hardt & Rutter, 2004), it suggested that particular aspects of the childhood environment may have influenced the long-term effects of the separation on adult antisocial personality traits. Both circumstances before, and especially during and after the separation associated with antisocial personality traits. Generally, the findings suggest that among the separated children, a stressful early life environment exerted

predisposing effects on the development of antisocial traits. Especially exposure to childhood maltreatment and financial difficulties in childhood played a relevant role in predicting individual differences in antisocial personality traits among the separated children. Hence, early life adversities previously associated with personality dysfunction (Crawford et al., 2009; Johnson et al., 1999; Widom et al., 2009) also seemed to modify the long-term effects of separation on antisocial personality traits.

In addition to sex, socioeconomic position in childhood, and age at first separation, which were found in the register-based studies to possibly modify the effects of the separation on mental and especially personality disorders, the findings of this questionnaire study thus suggest that particular facets of the childhood environment may also have been important modifiers. Having more detailed and prospectively gathered information on them may have led to more exact identification of individuals particularly left vulnerable by the separation, as by no means all separated children developed mental or personality disorders. Generally, the questionnaire-based findings correspond well, however, with earlier research findings and with the DOHaD- (Barker, 2009) and the life cycle model- (Lupien et al., 2009) frameworks in that the more stressful the childhood environment, the more harmful its effects on personality development. They also fit the attachment theory (Bowlby, 1969, 1988) in that earlier separations were experienced as more stressful. No causality claims can be inferred from these correlational associations obtained with retrospective measures, however.

5.5 Potential Underlying Mechanisms for Associations between Early Life Growth, Parental Separation, and Severe Personality Disorders

5.5.1 Environmental Contributors to the Associations between Growth and Personality Disorders

As stated, body size at birth and length of gestation reflect the combined effects of genetic predispositions (Jones et al., 2010; Silventoinen et al., 2008, 2011), and of environmental factors occurring prenatally, which include among others maternal nutrition (Stein, Zybert, van de Bor, & Lumey, 2004), substance use (Durmus et al.,

2011; Erickson & Arbour, 2012; Feldman et al., 2012; Gavin, Thompson, Rue, & Guo, 2012; Jaddoe et al., 2007), and psychosocial stress [for example, maternal depression (Grote et al., 2010; Henrichs et al., 2010), anxiety (Henrichs et al., 2010) and post-traumatic stress disorder symptoms (Engel, Berkowitz, Wolff, & Yehuda, 2005), general distress (Rondo et al., 2003) and exposure to traumatic events (Dancause et al., 2011; Lederman et al., 2004; Xiong et al., 2008)] and maternal illnesses such as pre-eclampsia and hypertension (Kajantie, Eriksson, Osmond, Thornburg, & Barker, 2009; Kajantie et al., 2010; Masoura et al., 2012), infectious illness (Jones et al., 2010; Wenstrom et al., 1998) and gestational diabetes (Fadl et al., 2010; Gasim, 2012) during pregnancy. Primiparity (Shah, 2010) and younger maternal age at conception (Gibbs et al., 2012) also predict LBW and prematurity risk in the offspring.

Previous studies have shown that of these different prenatal environmental adversities, maternal smoking during pregnancy (Ekblad et al., 2010) and prenatal malnutrition (Hoek et al., 1996; Neugebauer et al., 1999) are associated with the risk of offspring personality disorders in adulthood. Prenatal malnutrition has also been associated with a smaller head circumference (Stein et al., 2004) and with a smaller placental surface area (Roseboom, Painter, de Rooij, et al., 2011) at birth, the birth size measures particularly associated with severe personality disorders. Maternal smoking during pregnancy has also been shown to predict smaller head circumference at birth (Durmus et al., 2011). On the other hand, maternal psychosocial stress (Rice et al., 2010; Winsper et al., 2012) and prenatal exposure to influenza (Machon et al., 2002; Venables, 1996) have been shown to predict personality disorder traits, while no studies have assessed their associations to personality pathology severe enough to justify a personality disorder diagnosis. In contrast, in the HBCS, neither maternal hypertension during pregnancy nor pre-eclampsia predicted hospitalisations for personality disorders (Tuovinen et al., 2012), although hypertension during pregnancy predicted an increased risk of any severe mental disorder. Neither did pre-eclampsia or eclampsia associate significantly with severe personality disorders in a recent Swedish study (Fazel et al., 2012). Being born to multiparous and to younger mothers have both previously been associated with the risk of personality disorders (Fazel et al., 2012), but they did not mediate the effects of birth size or of parental separation here.

Hence, though scanty, the findings so far suggest that prenatal malnutrition and exposure to maternal smoking during pregnancy and possibly also psychosocial stress during pregnancy and prenatal exposure to influenza may be particularly relevant prenatal adversities in the development of personality disorders, and may possibly underlie our findings of suboptimal prenatal growth predicting severe personality disorders.

Infancy and childhood growth also reflect the conjoint effects of genetics and environmental factors operating throughout development (e.g. Silventoinen et al., 2012). Suboptimal postnatal growth is an indicator of early living conditions (Grantham-McGregor et al., 2007; Kang Sim et al., 2012; Osmond et al., 2007; Uljaszek, 2006), and may reflect the effects of malnutrition (Becker, Black, & Brown, 1991), of inflammatory (Marcovecchio, Mohn, & Chiarelli, 2012) and infectious (Becker et al., 1991; Checkley et al., 2008; Newell, Borja, Peckham, & European Collaborative Study, 2003) diseases which divert nutrition away from growth, and of poorer economic circumstances (Grantham-McGregor et al., 2007; Kang Sim et al., 2012) and sub-optimal parenting (Fuemmeler et al., 2012; Kang Sim et al., 2012). Childhood maltreatment (Uljaszek, 2006) and (lack of) breastfeeding (Arenz, Rückerl, Koletzko, & von Kries, 2004) may also predict postnatal growth.

Poorer parenting (Johnson et al., 2006) and childhood maltreatment (Johnson et al., 1999; Luntz & Widom, 1994; Widom et al., 2009) have also been shown to prospectively increase the risk of personality disorders. As stated, childhood maltreatment, though retrospectively reported, also associated with higher antisocial personality traits in the current study. Although the current study did not find main effects of socioeconomic position in childhood on personality disorders, some earlier studies suggest that impoverished conditions in childhood may increase the risk of personality dysfunction (Anglin et al., 2008; Cohen et al., 2008; Crawford et al., 2009; Lahey et al., 2005). Furthermore, in the current questionnaire study on antisocial traits, a financially stressful early life environment was associated with higher antisocial symptoms. Hence, these and the other aforementioned factors affecting growth can all be seen as potential contributors to the associations found between infancy and childhood growth and personality disorders.

5.5.2 Genetics

Genetic factors affect growth across the lifespan with effect sizes increasing with increasing age (Silventoinen et al., 2007, 2008). There are also significant genetic effects on head circumference at birth (Silventoinen et al., 2011). Particular genetic vulnerabilities have also been shown to predict personality disorders (e.g. Garcia et al., 2010; Li et al., 2012, Ni et al., 2009; Tadić et al., 2009). Hence, genetic predispositions affecting both growth and the risk of personality disorders offer one possible explanation for our findings on the associations between pre- and postnatal growth and personality disorders.

Furthermore, the largely heritable temperament traits, that predict the risk of personality disorders (Carlson et al., 2009; Caspi et al., 1996; Glenn et al., 2007), may also have influenced the choice of parents regarding which children they selected to be sent abroad to be evacuated. Thus, the associations between the separations caused by these evacuations and personality disorders may have emerged as a consequence of gene-environment correlations: same genetic predispositions, reflected in temperament traits, leading to an increased likelihood of being separated from parents, and to an increased risk of severe personality disorders. However, previous studies do suggest environmental rather than genetic mediation of parental separation effects on personality disorder related psychopathology (Burt et al., 2008).

Nevertheless, we cannot exclude the possibility that some genetic vulnerability may underlie our findings. Studies with genetically informed designs are needed to elucidate whether genes or environmental factors, or perhaps the interactions among them, as suggested by many studies (Belsky et al., 2012; Caspi et al., 2002; Kim-Cohen et al., 2006; Wilson et al., 2012), were the most influential. In terms of gene-environment interactions, genetic predispositions may also have influenced which children were the most affected by the separation or of the environmental adversities reflected in growth.

5.5.3 Parental Separation, Insecure Attachment, and Personality Disorders

Parental separation may also lead to personality disorders by influencing attachment development. According to the attachment theory (Bowlby, 1969), an infant needs to

relate securely to at least one primary caregiver in early development to enable adaptive socio-emotional development. The cognitive theory of attachment further states that during the sensitive periods of attachment development in early childhood, an infant/child forms an internal working model of social interaction based upon the early interpersonal experiences with her/his caregiver(s) (Bowlby, 1969, Delius, Bovenschen, & Schangler, 2008), and these subjective theories of attachment then direct the developing individual's expectations, cognitions, emotions, and ways of reacting in interpersonal relationships throughout development.

Parental separation in childhood is associated with insecure attachment, especially when the separation occurs early in development (Foster, Davies, & Steele, 2003; Woodward et al., 2000). Supporting such a vulnerability period, a prospective study showed that parental separations had most evident effects on attachment development when the separation occurred in the first five years of life (Woodward et al., 2000).

The current study thus found that severe personality disorders are predicted by parental separation particularly in those ages when its effects are strongest on attachment development, suggesting that early parental separation leading to insecure attachment and thereby affecting personality development may be one mechanism underlying our findings. Supporting this framework, in a prospective study, attachment disorganization at 12-18 months of age predicted borderline personality disorder symptoms in adulthood (Carlson et al., 2009). Other prospective studies have showed that maladaptive parenting behaviors more generally, assessed in childhood, predicted an increased risk of personality disorders in adulthood (Johnson et al., 2006) and their symptoms among both mono- and dizygotic twins in childhood (Belsky et al., 2012). Adaptive parenting behaviors contributed to lower scores on personality disorder traits in adult offspring (Johnson, Liu, & Cohen, 2011). Together these studies suggest that one pathway through which temporary parental separation in early childhood may influence the risk of personality disorders is via disruptive influences on attachment development.

5.5.4 Possible Underlying Neurobiological Pathways from Early Life Growth and from Parental Separation to Personality Disorders

According to the current findings, vulnerability for personality disorders was programmed by developmental factors prenatally and during the first 11 years of life. Parental separation played an especially relevant role if it occurred in the first five years. On a neurobiological level, in accordance with the DOHaD hypothesis and the life cycle model of stress, parental separation (Tyrka et al., 2008; Pesonen et al., 2010), other forms of early life stress such as childhood maltreatment (Dannlowski et al., 2012; McCrory et al., 2011; Teicher et al., 2012), and alterations in pre- (Kajantie et al., 2003; R. Reynolds et al., 2005) and postnatal (Fernald, Grantham-McGregor, Manandhar, & Costello, 2003) growth have been shown to be associated with altered structure and functioning of the HPA axis, hippocampus, amygdala, and prefrontal cortex; the brain areas implicated in the stress system, suggesting that one pathway, through which early developmental adversity may exert its long-term effects, is via leading to permanent changes in the individuals` vulnerability to stress, and thereby predisposing to later psychopathology. The functioning of the stress system may possibly be particularly affected by adversities in early life, since developmental plasticity of the brain areas regulating this system is at its highest then (Lupien et al., 2009; Uematsu et al., 2012). This may help in explaining the evident predictive role played by early life developmental factors for well-being in adult life.

Furthermore, the effects of prenatal developmental adversities such as maternal psychosocial stress on birth size may be mediated by developmental programming by maternal glucocorticoids. Direct associations of maternal cortisol levels during pregnancy with head circumference at birth (Li et al., 2012) and with infant cortisol levels (O'Connor, Bergman, Sarkar, & Glover, 2012) have been shown. Also particular prenatal exposures such as overexposure to maternal glucocorticoids as a consequence of glycyrrhizin in diet (Räikkönen et al., 2010) or to maternal psychosocial stress during pregnancy (Entringer et al., 2009) have been shown to alter offspring HPA axis function.

As stated, neurobiological changes in the functioning of the brain areas implicated in the stress system (Brunner et al., 2010; Carrasco et al., 2012; Carvalho Fernando et al., 2012; Herpertz et al., 2001; Nunes et al., 2009; Ruocco et al., 2012; Soloff et al., 2008;

Wolf et al., 2012: D. Zimmerman & Choi-Kain, 2009) are also evident among patients with personality disorders, and may thus underlie the associations found in the current studies. Hence, early life adversities, parental separation and the adversities reflected in both pre- and postnatal growth may lead to long-term changes in the functioning of the stress system, in particular in the glucocorticoid functioning of the HPA axis, and thereby set forth an increased risk of personality disorders in adulthood.

Also altered functioning of growth hormone-insulin like growth factor -axis (D'Ercole, Ye, Calikoglu, & Gutierrez- Ospina, 1996; Geary, Pringle, Rodeck, Kingdom, & Hindmarsh, 2003; Gerra et al., 2003; Hochberg & Albertsson-Wikland, 2008; Juul, 2001; Veldhuis et al., 2005) and of sex steroids (Aluja & García, 2007; Geary et al., 2003; Goel & Bale, 2009; Hines, 2008; Juul, 2001; Lombardo et al., 2012) may be possible underlying neurobiological factors essential for explaining our findings, especially those on early life growth and personality disorders. Both growth and sex hormones play an important role in explaining individual (Hochberg & Albertsson-Wikland, 2008; Juul, 2001; Veldhuis et al., 2005) and sex (Geary et al., 2003; Juul, 2001) differences in growth, and in brain development in early life (D'Ercole et al., 1996; Goel & Bale, 2009; Hines, 2008; Lombardo et al., 2012). Their functioning is also markedly associated with the functioning of the stress system (Charmandari et al., 2005; Goel & Bale, 2009, Goel, Plyler, Daniels, & Bale, 2011). Both sex steroids and growth hormones have also been shown to play a possible predictive role in the etiology of antisocial personality disorder (Aluja & García, 2007; Gerra et al., 2003). Consequently, altered functioning of these hormones may have contributed to our findings of early life growth predicting severe personality disorders, and to explaining the sex-specificity of the majority of our findings.

The effects of early life adversity on personality disorders, both of parental separation in particular and of the adversities reflected in growth may be epigenetic in nature; changes in gene expression as a consequence of early life adversity. Prenatal adversities may affect growth for example via their effects on HSD11B2 gene expression in the placenta encoding the 11βHSD-2 enzyme (e.g. Jensen Peña et al., 2011), possibly via leaving the fetus more vulnerable to maternal glucocorticoids. Specific epigenetic changes have also been associated with early life growth (Marsit et al., 2012; Menon et al., 2012; Michels et al., 2012; Wyrwoll et al., 2011), and are

evident as a consequence of prenatal malnutrition (Heeijmans et al., 2008) that also may predispose to personality disorders (Hoek et al., 1996; Neugebauer et al., 1999), and have been shown to emerge as a consequence of parental separation in childhood (Tyrka et al., 2012). Epigenetic changes are also found among patients with personality disorder (Dammann et al., 2011), and have been shown to mediate the effects of early life stress on personality dysfunction (Beach et al., 2011). Thus, epigenetic changes as a consequence of early life adversity leading to an increased vulnerability for personality disorders offer one plausible molecular genetic mechanism for all the associations found in the current study between early life developmental factors and personality disorders.

5.6 Generalizability of our Findings: Differences between Individuals with Personality Disorders in the General Population and Individuals Hospitalised for Personality Disorders

The patient group studied comprised subjects with personality disorders severe enough to require hospitalisation. This is a patient group of special public health importance as severe cases need more treatment and associate with greater disability (Yang et al., 2010). A methodological question concerns their representativeness of personality disorder patients in general: what kinds of differences are there between hospitalised and non-hospitalised cases? This question was directly assessed in the NFBC (Kantojärvi et al., 2004). Firstly, that study suggested that hospitalisation for personality disorders is more common among men than women. Other studies support such an association also in the general population (Coid et al., 2006; Jackson & Burgess, 2000; Huang et al., 2009), while in the NFBC, there was no sex difference in personality disorder prevalence in the population-based sample (Kantojärvi et al., 2004). The current study found no sex difference in the prevalence of hospitalisation for personality disorders. Furthermore, while cluster C personality disorders were the most prevalent in the general population, cluster B personality disorders were by far the most common among hospitalised cases in the NFBC (Kantojärvi et al., 2004), and also in the current study cohort.

Interestingly, the available etiological studies mostly suggest shared etiological factors for personality disorders in general and for those requiring hospitalisation (Crawford et al., 2009; Fazel et al., 2012; Kantojärvi, Joukamaa et al., 2008; Mäkikyrö, Sauvola et al., 1998). The resemblance of the etiological findings is not surprising, since most of the studies on the etiology of personality disorders have focused on the disorders of the dramatic cluster, and dramatic cluster disorders most often lead to hospitalisation (Kantojärvi et al., 2004).

Furthermore, Cox Proportional Hazards analyses among 13,288 participants of our study cohort suggested that, in comparison to all the other subjects in the sample, all-cause mortality was 3.54-fold (95 % CI = 2.80-4.49), CHD mortality 4.40-fold (95 % CI = 2.65-7.30), and the risk of suicide 9.58-fold (95 % CI = 5.54-16.54) among the individuals hospitalised for personality disorders (unpublished data). The hospitalised personality disorder patients were also more often separated/divorced or unmarried (all *p*-values < .001) and had lower attained educational level in adulthood (p = .02) than individuals with no severe personality disorder. Furthermore, antisocial personality disorder was present only among men in our cohort. This resemblance of the etiological precursors, sociodemographic correlates, and the interpersonal and public health consequences of personality disorders requiring hospitalisation and those in the general population supports the convergent validity of the HDR diagnoses of personality disorders.

However, the findings of studies conducted among hospitalised individuals with personality disorders are best generalized to severe personality disorders and especially to the disorders of the dramatic cluster that most often require hospitalisation. More caution must be used in generalizing such findings to personality disorders in the general population and to the disorders of the fearful cluster that are underrepresented among hospitalised cases (Kantojärvi et al., 2004). The results of this thesis indeed suggest that many of the effects of early life adversity on severe personality disorders are particularly characteristic of dramatic cluster personality disorders.

5.7 Strengths and Limitations of the Studies

Strengths of the current studies include the longitudinal study design, the large sample-size, the objective, record- and register-based data on the predictor and on the outcome variables, and the diagnostic follow-up extending for over 35 years. This follow-up is longer than in the other prospective studies on early life adversity and personality disorders, and this thesis shows that the effects of early life adversity on severe personality disorders extend across adult lifespan. The health record- and register-based data allows us to draw firmer conclusions on the possible predictive role played by early life factors than could be concluded based on the majority of previous studies that relied on retrospective reports of early life developmental adversity. The large sample size and the more than 200 individuals diagnosed with personality disorder in the current study cohort enabled studying personality pathology justifying a diagnosis, not concentrating only on personality disorder symptoms as the majority of the other longitudinal studies have done. The current findings support previous ones in many instances, but they additionally highlight that the effects of early developmental, environmental adversity extend to personality dysfunction justifying a diagnosis and leading to hospitalisation.

However, there are also limitations. Firstly, the validity of the personality disorder diagnoses in the HDR has not been studied. Nevertheless, as stated, according to the evidence available, they tend to show convergent, ecological and predictive validity (e.g. Crawford et al., 2009; Fazel et al., 2012; Kantojärvi, Joukamaa et al., 2008).

Limitations of the current study also include that there were no data on paternal age at conception, which has recently been shown to predict different types of psychopathology (Buizer-Voskamp et al., 2011; Hultman, Sandin, Levine, Lichtenstein, & Reichenberg, 2011; Kuja-Halkola et al., 2012; Torrey et al., 2009). Genetic explanations for the current findings could not be confirmed or excluded, since there were no genetic data available, and because the HDR follow-up started only in 1969, there were neither data on parental psychopathology. Neither could we assess gene-environment interactions that have repeatedly been shown to be relevant for personality disorders (e.g. Kim-Cohen et al., 2006), or examine the possibly explanatory role played by epigenetics. Such epigenetic analysis is, however, currently underway in a subsample of this cohort. On the other hand, since we had no growth data from

adolescence, we could not assess the possible predictive role played by pubertal growth in the development of personality disorders. Furthermore, since the diagnostic data were based on hospital discharge- and causes of death- registers, the generalizability of the findings to less severe forms of psychopathology is questionable.

There was a marked attrition in the study on infancy and childhood growth and personality disorders, mostly due to missing data on growth. The possibility that an attrition bias may have influenced the findings on growth and personality disorders cannot be excluded, although growth in the particular periods associated with severe personality disorders among men or women were not associated with attrition.

The subsample of evacuated participants who had self-report data on the stressfulness of their separation and on other childhood experiences was quite small and may possibly be biased. These subjects were alive and healthy enough to fill in the questionnaire at an average age of 71 years. It is also possible that participants with the more positive memories of the separation exposure were the ones most likely to complete the questionnaire. These factors limit the conclusions that can be made of the generally rather positive recollections of the separation experience. Nevertheless, significant associations between different childhood environmental stressors and antisocial personality disorder traits were found also in this subsample. Indeed, the questionnaire data suggested that assessing the particular experiences of the separated children may have yielded more detailed information for which children the separation was particularly stressful.

All the study subjects were born in state hospitals, which led to lower childhood socioeconomic classes being overrepresented in the study sample. This may possibly compromise the generalizability of the findings to the general population. Since the subjects were born between 1934 and 1944, the generalizability of the findings to the present days` surroundings is questionable. Nevertheless, studies in more recent cohorts have mostly suggested similar risk factors for personality disorders and related symptoms than was found here (e.g. Crawford et al., 2009; Fazel et al., 2012; Kantojärvi, Joukamaa et al., 2008).

5.8 Implications of the Findings

Whether the underlying causal factors are genetic or environmental, the findings of this thesis do suggest that the risk of severe adult personality disorders is evident in early life. The identified longitudinal predictors of personality disorders (small body size at birth, particular suboptimal patterns of infancy and childhood growth, and separation from parents in early childhood) can help in identifying those individuals particularly at risk for developing these long-lasting mental disorders known to exert disabling consequences on multiple aspects of adult functioning.

Such identification may help in developing preventive interventions (Gluckman et al., 2011) that may be especially crucial in the treatment of personality disorders, especially disorders such as antisocial personality disorder, for treatment of which the therapeutic and pharmaceutical interventions in adulthood currently show little promise (Gibbon et al., 2010; Khalife et al., 2010). Findings so far indeed suggest that early life preventive interventions based on psychosocial stimulation and on nutritional, education-based, and exercise stimulation can be beneficial in preventing antisocial psychopathology in adolescence and adulthood among growth-retarded (Walker, Chang, Vera-Hernandez, &McGregor, 2011) and malnourished (Raine, Mélange, Liu, Venables, & Mednick, 2003) individuals, respectively. The latter intervention benefited malnourished individuals also in terms of leading to reduced schizotypal personality disorder symptoms in adulthood (Raine et al., 2003), while the psychosocial intervention, focusing on the interaction between the primary caregiver and the growth-retarded infant, resulted in improvements in multiple aspects of psychosocial well-being (Walker et al., 2011). Furthermore, a recent study found that an early wide-scale educational, preschool- and family-focused intervention targeting individuals of impoverished conditions had long-term effects on multiple aspects of psychological well-being in adulthood, and these effects extended also to the intervention children less often having criminal convictions (A. Reynolds, Temple, Our, Artigas, & White, 2011). The identification of several early life risk markers for severe personality disorders in the studies of this thesis may help in targeting preventive work by specifying those individuals most in need of preventive measures.

By highlighting the important etiological role of early life factors, the findings of this thesis may also increase the understanding of personality disorder patients for the clinicians working with them. Already some of the most effective psychotherapeutic treatments for borderline personality disorder patients take their difficult developmental history considerably into account (Bateman & Fonagy, 2010; Kellogg & Young, 2006), and the current findings implicate the reasonability of such efforts and highlight additional aspects of early life development that may be of particular relevance.

5.9 Directions for Future Research

In addition to the current categorical model of personality disorders, the future revisions of the DSM diagnostic system will include a dimensional model of personality dysfunction, assessed with the five traits of negative affectivity, detachment, antagonism, disinhibition, and of psychoticism (Hopwood et al., 2012). All the personality disorders in DSM-IV can also be conceptualized in terms of maladaptive distributions of scores on these personality dimensions (Hopwood et al., 2012; Samuel & Widiger, 2008). Further studies on the etiology of personality dysfunction will benefit from including both the categorical and the dimensional assessments of personality pathology.

Further studies should also assess interactions between the genetic and environmental factors possibly contributing to personality disorders and the direct neurobiological mechanisms through which these factors exert their effects. A prospective study design including genome- and epigenome wide data, data on HPA axis function and documented data of different early life stressors will help in identifying the possible etiological roles played by each of these factors and the interactions among them. Mediating and moderating roles of different etiological contributors could also be simultaneously assessed. Including functional brain imaging methods will help in identifying the abnormalities in brain functioning associated with these disorders characterized by reduced brain growth already in prenatal life.

It would also be interesting to identify developmental predictors of prognosis among personality disorder patients; which patients are most affected by their personality dysfunction and which etiological factors predict poorer prognosis among these patients

with an increased all-cause and cardiovascular mortality and particularly heightened suicide risk. Some such studies have been conducted, suggesting that patients with exposure to early life adversity in the form of childhood maltreatment may have the poorest prognosis (Gunderson et al., 2006; Zanarini, Frankenburg, Hennen, Reich, & Silk, 2006). However, these studies used retrospective accounts of early life adversity.

5.10 Conclusions

This longitudinal study showed that several different early life factors contribute to the risk of severe personality disorders. Identified developmental precursors included a smaller head circumference and a smaller head-to-length ratio at birth, slower BMI gain between birth and six months, faster weight and BMI gains between six months and one year, and slower gains in weight and in BMI between seven and 11 years of age among men, and slower height growth between two and seven years among women. Dramatic personality disorders were among women predicted by a smaller placental surface area at birth, and the effects of infancy and childhood growth found among men were mostly characteristic of men with dramatic cluster personality disorders.

Temporary parental separation in early childhood, particularly before five years of age, predicted an increased risk of any severe personality disorder and among men, especially of dramatic personality disorders. The effects of early parental separation were especially salient on personality disorders also in comparison to other types of psychopathology, suggesting that these disorders characterized by severe interpersonal dysfunction are especially predicted by separation from parents in early life. Socioeconomic position in childhood and the stressfulness of the childhood environment emerged as possible modifiers of the long-term effects of parental separation.

To conclude, the vulnerability for any and particularly for dramatic personality disorders severe enough to justify hospitalisation is developmentally programmed in early life.

6 REFERENCES

Abel, K. M., Wicks, S., Susser, E. S., Dalman, C., Pedersen, M. G., Mortensen, P. B., & Webb, R. T. (2010). Birth weight, schizophrenia, and adult mental disorder: is risk confined to the smallest babies? *Archives of General Psychiatry, 67,* 923-930.

Achenbach T., Newhouse, P. A., & Rescorla, L. A. (2004). *Manual for the ASEBA Older Adult Forms & Profiles.* Burlington, VT: University of Vermont, Research Center for Children, Youth, and Families.

Agrawal, H. R., Gunderson, J., Holmes, B. M., & Lyons-Ruth, K. (2004). Attachment studies with borderline patients: a review. *Harvard Review of Psychiatry, 12,* 94-104.

Alastalo, H., Räikkönen, K., Pesonen, A. K., Osmond, C., Barker, D. J., Heinonen, K., … Eriksson, J. G. (2012a). Cardiovascular morbidity and mortality in finnish men and women separated temporarily from their parents in childhood--a life course study. *Psychosomatic Medicine, 74,* 583-587.

Alastalo, H., Räikkönen, K., Pesonen, A. K., Osmond, C., Barker, D. J., Heinonen, K., … Eriksson, J. G. (2012b). Early life stress and blood pressure levels in late adulthood. *Journal of Human Hypertension.* Advance online Publication. doi: 10.1038/jhh.2012.6

Alastalo, H., Räikkonen, K., Pesonen, A. K., Osmond, C., Barker, D. J., Kajantie, E., … Eriksson, J. G. (2009). Cardiovascular health of Finnish war evacuees 60 years later. *Annals of Medicine, 41,* 66-72.

Alati, R., Lawlor, D. A., Mamun, A. A., Williams, G. M., Najman, J. M., O'Callaghan, M., & Bor, W. (2007). Is there a fetal origin of depression? Evidence from the Mater University Study of Pregnancy and its outcomes. *American Journal of Epidemiology, 165,* 575-582.

Allin, M., Rooney, M., Cuddy, M., Wyatt, J., Walshe, M., Rifkin, L., & Murray, R. (2006). Personality in young adults who are born preterm. *Pediatrics,* 117, 309-316.

Aluja, A., & García, L. F. (2007). Role of sex hormone-binding globulin in the relationship between sex hormones and antisocial and aggressive personality in inmates. *Psychiatry Research, 152,* 189-196.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders (4th ed., text rev.).* Washington, DC. Author.

Andersen, L. G., Angquist, L., Eriksson, J. G., Forsen T, Gamborg M, Osmond C., … Sørensen, T. I. (2010). Birth weight, childhood body mass index and risk of coronary heart disease in adults: combined historical cohort studies. *PLoS One, 5,* e14126.

Anderson, S. E., Cohen, P., Naumova, E. N., Jacques, P. F., & Must, A. (2007). Adolescent obesity and risk for subsequent major depressive disorder and anxiety disorder: prospective evidence. *Psychosomatic Medicine, 69,* 740-747.

Anderson, S. E., Cohen, P., Naumova, E. N., & Must, A. (2006). Association of depression and anxiety disorders with weight change in a prospective community-based study of children followed up into adulthood. *Archives of Pediatrics & Adolescent Medicine, 160,* 285-291.

Anglin, D. M., Cohen, P. R., & Chen, H. (2008). Duration of early maternal separation and prediction of schizotypal symptoms from early adolescence to midlife. *Schizophrenia Research, 103,* 143-150.

Arenz, S., Rückerl, R., Koletzko, B., & von Kries, R. (2004). Breast-feeding and childhood obesity--a systematic review. *International Journal of Obesity, 28,* 1247-1256.

Bagot, R. C., & Meaney, M. J. (2010). Epigenetics and the biological basis of gene x environment interactions. *Journal of the American Academy of Child and Adolescent Psychiatry, 49,* 752-771.

Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2009). The first 10,000 Adult Attachment Interviews: distributions of adult attachment representations in clinical and non-clinical groups. *Attachment & Human Development, 11,* 223-263.

Bandelow, B., Krause, J., Wedekind, D., Broocks, A., Hajak, G., & Rüther, E. (2005). Early traumatic life events, parental attitudes, family history, and birth risk factors in patients with borderline personality disorder and healthy controls. *Psychiatry Research, 134,* 169-179.

Banerjee, S.B., Arterbery, A.S,. Fergus, D.J., & Adkins-Regan, E. (2012). Deprivation of maternal care has long-lasting consequences for the hypothalamic-pituitary-adrenal axis of zebra finches. *Proceedings. Biological Sciences /The Royal Society, 279,* 759-766.

Barker, D. J. (1995). Fetal origins of coronary heart disease. *British Medical Journal, 311,* 171-174.

Barker, D. J. (2004). The developmental origins of well-being. *Philosophical transactions of the Royal Society of London, 359,* 1359-1366.

Barker, D. J., Osmond, C., Kajantie, E., & Eriksson, J. G. (2009). Growth and chronic disease: findings in the Helsinki Birth Cohort. *Annals of Human Biology, 36,* 445-458.

Barker, D. J., Osmond, C., Golding, J., Kuh, D., & Wadsworth, M. E. (1989). Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *British Medical Journal, 298,* 564-567.

Barker, D. J. (2007). The origins of the developmental origins theory. *Journal of Internal Medicine, 261,* 412-417.

Barker, D. J., Gelow, J., Thornburg, K., Osmond, C., Kajantie, E., Eriksson, J. G. (2010). The early origins of chronic heart failure: impaired placental growth and initiation of insulin resistance in childhood. *European Journal of Heart Failure, 12,* 819-825.

Barker, D. J., Osmond, C., Rodin, I., Fall, C. H., & Winter, P. D. (1995). Low weight gain in infancy and suicide in adult life. *British Medical Journal, 311,* 1203.

Barker, D. J., Thornburg, K. L., Osmond, C., Kajantie, E., & Eriksson, J. G. (2010). The surface area of the placenta and hypertension in the offspring in later life. *The International Journal of Developmental Biology, 54,* 525-530.

Basoglu, C., Oner, O., Ates, A., Algul, A., Bez, Y., Cetin, M., … Munir, K. M. (2011). Synaptosomal-associated protein 25 gene polymorphisms and antisocial personality disorder: association with temperament and psychopathy. *Canadian Journal of Psychiatry, 56,* 341-347.

Bateman, A., & Fonagy, P. (2010). Mentalization based treatment for borderline personality disorder. *World Psychiatry, 9,* 11-15.

Battle, C. L., Shea, M. T., Johnson, D. M., Yen, S., Zlotnick, C., Zanarini, M. C., … Morey, L. C. (2004). Childhood maltreatment associated with adult personality disorders: findings from the Collaborative Longitudinal Personality Disorders Study. *Journal of Personality Disorders, 18,* 193-211.

Batty, G. D., Whitley, E., Kivimäki, M., Tynelius, P., & Rasmussen, F. (2010). Body mass index and attempted suicide: Cohort study of 1,133,019 Swedish men. *American Journal of Epidemiology, 172,* 890-899.

Beach, S. R., Brody, G. H., Todorov, A. A., Gunter, T. D., & Philibert, R. A. (2011). Methylation at 5HTT Mediates the Impact of Child Sex Abuse on Women's Antisocial Behavior: An Examination of the Iowa Adoptee Sample. *Psychosomatic Med*icine, *73,* 83-87.

Becker, S., Black, R. E., & Brown, K. H. (1991). Relative effects of diarrhea, fever, and dietary energy intake on weight gain in rural Bangladeshi children. *American Journal of Clinical Nutrition, 53,* 1499-1503.

Belsky, D. W., Caspi, A., Arseneault, L., Bleidorn, W., Fonagy, P., Goodman, M., …Moffitt, T. E. (2012). Etiological features of borderline personality related characteristics in a birth cohort of 12-year-old children. *Development and Psychopathology, 24,* 251-265.

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological Bulletin, 135,* 885-908.

Biederman, J., Petty, C. R., Monuteaux, M. C., Fried, R., Byrne, D., Mirto, T., … Faraone, S. V. (2010). Adult psychiatric outcomes of girls with attention deficit hyperactivity disorder: 11-year follow-up in a longitudinal case-control study. *American Journal of Psychiatry, 167,* 409-417.

Black, D. W., Gunter, T., Loveless, P., Allen, J., & Sieleni, B. (2010). Antisocial personality disorder in incarcerated offenders: Psychiatric comorbidity and quality of life. *Annals of Clinical Psychiatry, 22,* 113-120.

Bornovalova, M. A., Hicks, B. M., Iacono, W. G., & McGue, M. (2009). Stability, change, and heritability of borderline personality disorder traits from adolescence to adulthood: a longitudinal twin study. *Development and Psychopathology, 21,* 1335-1353.

Bowlby, J. (1969). *Attachment. Attachment and Loss.* Vol. I. London: Hogarth.

Bowlby, J. (1988). *A Secure Base: Clinical Applications of Attachment Theory*. London: Routledge.

Bowlby, J. Miller, E. & Winnicott., D.W. (1939). Evacuation of small children. *British Medical Journal, 2,* 1202.

Boyle, M. H., Miskovic, V., Van Lieshout, R., Duncan, L., Schmidt, L. A., Hoult, L., … Saigal, S. (2011). Psychopathology in young adults born at extremely low birth weight. *Psychological Medicine, 41,* 1763-1774.

Brennan, P. A., Grekin, E. R., & Mednick, S. A. (1999). Maternal smoking during pregnancy and adult male criminal outcomes. *Archives of General Psychiatry, 56,* 215-219.

Brennan, P. A., Grekin, E. R., Mortensen, E. L., & Mednick, S. A. (2002). Relationship of maternal smoking during pregnancy with criminal arrest and hospitalization for substance abuse in male and female adult offspring. *American Journal of Psychiatry, 159,* 48-54.

Bronisch, T., & Mombour, W. (1994). Comparison of a diagnostic checklist with a structured interview for the assessment of DSM-III-R and ICD-10 personality disorders. *Psychopathology, 27,* 312-320.

Brunner, R., Henze, R., Parzer, P., Kramer, J., Feigl, N., Lutz, K., … Stieltjes, B. (2010). Reduced prefrontal and orbitofrontal gray matter in female adolescents with borderline personality disorder: is it disorder specific? *Neuroimage, 49*, 114-120.

Buizer-Voskamp, J. E., Laan, W., Staal, W. G., Hennekam, E. A., Aukes, M. F., Termorshuizen, F., …, Ophoff, R. A. (2011). Paternal age and psychiatric disorders: findings from a Dutch population registry. *Schizophrenia Research, 129,* 128-132.

Burnett, A. C., Anderson, P. J., Cheong, J., Doyle, L. W., Davey, C. G., & Wood, S. J. (2011). Prevalence of psychiatric diagnoses in preterm and full-term children, adolescents and young adults: a meta-analysis. *Psychological Medicine, 20,* 1-12.

Burt, S. A., Barnes, A. R., McGue, M., & Iacono, W. G. (2008). Parental divorce and adolescent delinquency: Ruling out the impact of common genes. *Developmental Psychology, 44,* 1668-1677.

Byrne, C. P., Velamoor, V. R., Cernovsky, Z. Z., Cortese, L., & Losztyn, S. (1990). A comparison of borderline and schizophrenic patients for childhood life events and parent-child relationships. *Canadian Journal of Psychiatry, 35,* 590-595.

Cannon, M., Jones, P. B. &, Murray, R.M. (2002). Obstetric complications and schizophrenia: historical and meta-analytic review. *American Journal of Psychiatry, 159,* 1080-1092.

Carlson, E. A., Egeland, B., & Sroufe, L. A. (2009). A prospective investigation of the development of borderline personality symptoms. *Developmental Psychopathology, 21,* 1311-1334.

Carrasco, J. L., Tajima-Pozo, K., Díaz-Marsá, M., Casado, A., López-Ibor, J. J., Arrazola, J., & Yus, M. (2012). Microstructural white matter damage at orbitofrontal areas in borderline personality disorder. *Journal of Affective Disorders, 139,* 149-153.

Carvalho Fernando, S., Beblo, T., Schlosser, N., Terfehr, K., Otte, C., Löwe, B., … Wingenfeld, K. (2012). Associations of childhood trauma with hypothalamic-pituitary-adrenal function in borderline personality disorder and major depression. *Psychoneuroendocrinology, 37,* 1659-1668.

Caspi, A., McClay, J., Moffitt, T. E., Mill, J., Martin, J., Craig, I. W., & Poulton, R. (2002). Role of genotype in the cycle of violence in maltreated children. *Science, 297,* 851-854.

Caspi, A., Moffitt, T. E., Newman, D. L., & Silva, P. A. (1996). Behavioral observations at age 3 years predict adult psychiatric disorders. Longitudinal evidence from a birth cohort. *Archives of General Psychiatry, 53,* 1033-1039.

Caspi, A., Roberts, B. W., & Shiner. R. L. (2005). Personality development: stability and change. *Annual Review of Psychology, 56,* 453-484.

Cederblad, M., Dahlin, L., & Hagnell, O. (1988). The Lundby project: Do psychiatric risk factors in childhood influence mental health in adulthood? *Läkartidningen, 85,* 4317-4318, 4321.

Charmandari, E., Tsigos, C., & Chrousos, G. (2005). Endocrinology of the stress response. *Annual Review of Physiology, 67,* 259-284.

Chawarska, K., Campbell, D., Chen, L., Shic, F., Klin, A., & Chang, J. (2011). Early generalized overgrowth in boys with autism. *Archives of General Psychiatry, 68,* 1021-1031.

Checkley, W., Buckley, G., Gilman, R. H., Assis, A. M., Guerrant, R. L., Morris, S. S., … Childhood Malnutrition and Infection Network. (2008). Multi-country analysis of the effects of diarrhoea on childhood stunting. *International Journal of Epidemiology, 37,* 816-830.

Cheng, H., Huang, Y., Liu, B., & Liu, Z. (2010). Familial aggregation of personality disorder: epidemiological evidence from high school students 18 years and older in Beijing, China. *Comprehensive Psychiatry, 51,* 524-530.

Cnattingius, S., Svensson, T., Granath, F., & Iliadou, A. (2011).Maternal smoking during pregnancy and risks of suicidal acts in young offspring. *European Journal of Epidemiology, 26,* 485-492.

Cohen, P., Chen, H., Gordon, K., Johnson, J., Brook, J., & Kasen, S. (2008). Socioeconomic background and the developmental course of schizotypal and borderline personality disorder symptoms. *Development and Psychopathology, 20,* 633-650.

Coid, J., Yang, M., Tyrer, P., Roberts, A., & Ullrich, S. (2006). Prevalence and correlates of personality disorder in Great Britain. *British Journal of Psychiatry, 188,* 423-431.

Congdon, E., Service, S., Wessman, J., Seppänen, J. K., Schönauer, S., Miettunen, J., … Freimer, N. B. (2012). Early environment and neurobehavioral development predict adult temperament clusters. *PLoS One, 7,* e38065.

Copeland, W. E., Shanahan, L., Costello, E. J., & Angold, A. (2009). Childhood and adolescent psychiatric disorders as predictors of young adult disorders. *Archives of General Psychiatry, 66,* 764-772.

Costello, E. J., Worthman, C., Erkanli, A., & Angold, A. (2007). Prediction from low birth weight to female adolescent depression: a test of competing hypotheses. *Archives of General Psychiatry, 64,* 338-344.

Courchesne, E., Carper, R., & Akshoomoff, N. (2003). Evidence of brain overgrowth in the first year of life in autism. *The Journal of the American Medical Association, 290,* 337-344.

Crawford, T. N., Cohen, P., & Brook, J. S. (2001). Dramatic-erratic personality disorder symptoms: I. Continuity from early adolescence into adulthood. *Journal of Personality Disorders, 15,* 319-335.

Crawford, T. N., Cohen, P. R., Chen, H., Anglin, D. M., & Ehrensaft, M. (2009). Early maternal separation and the trajectory of borderline personality disorder symptoms. *Developmental Psychopathology, 21,* 1013-1030.

Crawford, T. N., Shaver, P. R., Cohen, P., Pilkonis, P. A., Gillath, O., & Kasen, S. (2006). Self-reported attachment, interpersonal aggression, and personality disorder in a prospective community sample of adolescents and adults. *Journal of Personality Disorders, 20,* 331-351.

Crump, C., Sundquist, K., Sundquist, J., & Winkleby, M. A. (2011). Gestational age at birth and mortality in young adulthood. *The Journal of the American Medical Association, 306,* 1233-1240.

Cutajar, M. C., Mullen, P. E., Ogloff, J. R., Thomas, S. D., Wells, D. L., & Spataro, J. (2010). Psychopathology in a large cohort of sexually abused children followed up to 43 years. *Child Abuse & Neglect, 34,* 813-822.

Dammann, G., Teschler, S., Haag, T., Altmüller, F., Tuczek, F., & Dammann, R. H. (2011). Increased DNA methylation of neuropsychiatric genes occurs in borderline personality disorder. *Epigenetics, 6,* 1454-1462.

Dancause, K. N., Laplante, D. P., Oremus, C., Fraser, S., Brunet, A., & King, S. (2011). Disaster-related prenatal maternal stress influences birth outcomes: project Ice Storm. *Early Human Development, 87*, 813-820.

Danese, A., Moffitt, T. E., Harrington, H., Milne, B. J., Polanczyk, G., Pariante, C. M.,… Caspi, A. (2009). Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. *Archives of Pediatrics & Adolescent Medicine, 163*, 1135-1143.

Dannlowski, U., Stuhrmann , A., Beutelmann, V., Zwanzger, P., Lenzen, T., Grotegerd, D., … Kugel, H. (2012). Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biological Psychiatry, 71*, 286-293.

Danziger, P. D., Silverwood, R., & Koupil, I. (2011). Fetal growth, early life circumstances, and risk of suicide in late adulthood. *European Journal of Epidemiology, 26*, 571-581.

Davis, E. P., Waffarn, F., & Sandman, C. A. (2011). Prenatal treatment with glucocorticoids sensitizes the hpa axis response to stress among full-term infants. *Developmental Psychobiology, 53*, 175-183.

Dean, K., Stevens, H., Mortensen, P. B., Murray, R. M., Walsh, E., & Pedersen, C. B. (2010). Full spectrum of psychiatric outcomes among offspring with parental history of mental disorder. *Archives of General Psychiatry, 67*, 822-829.

Decuyper, M., De Fruyt, F., & Buschman, J. (2008). A five-factor model perspective on psychopathy and comorbid Axis-II disorders in a forensic-psychiatric sample. *International Journal of Law and Psychiatry, 31*, 394-406.

Depue, R. A. (2009). Genetic, environmental, and epigenetic factors in the development of personality disturbance. *Development and Psychopathology, 21*, 1031-1063.

de Jong, F., Monuteaux, M. C., van Elburg, R. M., Gillman, M. W., & Belfort, M. B. (2012). Systematic review and meta-analysis of preterm birth and later systolic blood pressure. *Hypertension, 59*, 226-234.

Delius, A., Bovenschen, I., & Spangler, G. (2008). The inner working model as a "theory of attachment": development during the preschool years. *Attachment and Human Development, 10*, 395-414.

Dempster, E. L., Pidsley, R., Schalkwyk, L. C., Owens, S., Georgiades, A., Kane, F., … Mill, J. (2011). Disease-associated epigenetic changes in monozygotic twins discordant for schizophrenia and bipolar disorder. *Human Molecular Genetics, 20*, 4786-4796.

D'Ercole, A. J., Ye, P., Calikoglu, A. S., & Gutierrez-Ospina, G. (1996). The role of the insulin-like growth factors in the central nervous system. *Molecular Neurobiology, 13*, 227-255.

Distel, M. A., Carlier, A., Middeldorp, C. M., Derom, C. A., Lubke, G. H., & Boomsma, D. I. (2011). Borderline personality traits and adult attention-deficit hyperactivity disorder symptoms: A genetic analysis of comorbidity. *American Journal of Medical Genetics, 156*, 817-825.

Distel, M. A., Rebollo-Mesa, I., Willemsen, G., Derom, C. A., Trull, T. J., Martin, N. G., & Boomsma, D. I. (2009). Familial resemblance of borderline personality disorder features: genetic or cultural transmission? *PLoS One, 4*, e5334.

Distel, M. A., Trull, T. J., Derom, C. A., Thiery, E. W., Grimmer, M. A., Martin, N. G., & Boomsma, D. I. (2008). Heritability of borderline personality disorder features is similar across three countries. *Psychological Medicine, 38,* 1219-1229.

D'Onofrio, B. M., Singh, A. L., Iliadou, A., Lambe, M., Hultman, C. M., Grann, M., … Lichtenstein, P. (2010). Familial confounding of the association between maternal smoking during pregnancy and offspring criminality: a population-based study in Sweden. *Archives of General Psychiatry, 67,* 529-538.

Douglas, K., Chan, G., Gelernter, J., Arias, A. J., Anton, R. F., Poling, J., … Kranzler, H. R. (2011). 5-HTTLPR as a potential moderator of the effects of adverse childhood experiences on risk of antisocial personality disorder. *Psychiatric Genetics, 21*, 240-248.

Durmus, B., Kruithof, C. J., Gillman, M. H., Willemsen, S. P., Hofman, A., Raat, H., … Jaddoe, V. W. (2011). Parental smoking during pregnancy, early growth, and risk of obesity in preschool children: the Generation R Study. *American Journal of Clinical Nutrition, 94,* 164-171.

Ekblad, M., Gissler, M., Lehtonen, L., & Korkeila, J. (2010). Prenatal smoking exposure and the risk of psychiatric morbidity into young adulthood. *Archives of General Psychiatry, 67,* 841-849.

El-Gabalawy, R., Katz, L. Y., & Sareen, J. (2010). Comorbidity and associated severity of borderline personality disorder and physical health conditions in a nationally representative sample. *Psychosomatic Medicine, 72,* 641-647.

Elgen, I. B., Holsten, F., & Odberg, M. D. (2012). Psychiatric disorders in low birthweight young adults. Prevalence and association with assessments at 11 years. *European Psychiatry.* Advance online publication. doi: 10.1016/j.eurpsy.2012.06.002

Elonheimo, H., Niemelä, S., Parkkola, K., Multimäki, P., Helenius, H., Nuutila, A. M., & Sourander, A. (2007). Police-registered offenses and psychiatric disorders among young males: the Finnish "From a boy to a man" birth cohort study. *Social Psychiatry and Psychiatric Epidemiology, 42,* 477-484.

Engel, S. M., Berkowitz, G. S., Wolff, M. S., & Yehuda, R. (2005). Psychological trauma associated with the World Trade Center attacks and its effect on pregnancy outcome. *Paediatric and Perinatal Epidemiology, 19,* 334-341.

Entringer, S., Kumsta, R., Hellhammer, D. H., Wadhwa, P. D., & Wüst, S. (2009). Prenatal exposure to maternal psychosocial stress and HPA axis regulation in young adults. *Hormones and Behaviour, 55,* 292-298.

Erickson, A. C., & Arbour, L. T. (2012). Heavy smoking during pregnancy as a marker for other risk factors of adverse birth outcomes: a population-based study in British Columbia, Canada. *BMC Public Health, 12,* 102.

Eriksson, J. G., Forsén, T. J., Kajantie, E., Osmond C., & Barker, D. J. (2007). Childhood growth and hypertension in later life. *Hypertension, 49,* 1415-1421.

Eriksson, J. G., Forsén, T., Tuomilehto, J., Winter, P. D., Osmond, C., & Barker, D. J. (1999). Catch-up growth in childhood and death from coronary heart disease: longitudinal study. *British Medical Journal, 318,* 427-431.

Eriksson, J. G., Kajantie, E., Thornburg, K. L., Osmond C., & Barker, D. J. (2011). Mother's body size and placental size predict coronary heart disease in men. *European Heart Journal, 32,* 2297-2303.

Eriksson, J. G., Osmond, C., Kajantie, E., Forsén, T. J., & Barker, D. J. (2006). Patterns of growth among children who later develop type 2 diabetes or its risk factors. *Diabetologia, 49,* 2853-2858.

Ettner, S. L., Maclean, J. C., & French, M. T. (2011). Does having a dysfunctional personality hurt your career? Axis II personality disorders and labor market outcomes. *Industrial Relations, 50,* 149-173.

Fadl, H. E., Östlund, I. K., Magnuson, A. F., & Hanson, U. S. (2010). Maternal and neonatal outcomes and time trends of gestational diabetes mellitus in Sweden from 1991 to 2003. *Diabetic Medicine, 27,* 436-441.

Fan, Z., Zhang, Z. X., Li, Y., Wang, Z., Xu, T., Gong, X., … Zeng, Y. (2010). Relationship between birth size and coronary heart disease in China. *Annals of Medicine, 42,* 596-602.

Farrington, D. P. (2000). Psychosocial predictors of adult antisocial personality and adult convictions. *Behavioural Sciences & The Law, 18,* 605-622.

Fazel, S., Bakiyeva, L., Cnattingius, S., Grann, M., Hultman, C. M., Lichtenstein, P., & Geddes, J. R. (2012). Perinatal Risk Factors in Offenders with Severe Personality Disorder: A Population-based Investigation. *Journal of Personality Disorders, 26,* 737-750.

Feldman, H. S., Jones, K. L., Lindsay, S., Slymen, D., Klonoff-Cohen, H., Kao, K.,… Chambers, C. (2012). Prenatal alcohol exposure patterns and alcohol-related birth defects and growth deficiencies: a prospective study. *Alcohol Clinical and Experimental Research, 36,* 670-676.

Feng, X., Wang, L., Yang, S., Qin, D., Wang, J., Li, C., … Hu, X. (2011). Maternal separation produces lasting changes in cortisol and behavior in rhesus monkeys. *Proceedings of the National Academy of Sciences of the United States of America, 108,* 14312-14317.

Fenoglio, K. A., Brunson, K. L., Avishai-Eliner, S., Chen, Y., & Baram, T. Z. (2004). Region-specific onset of handling-induced changes in corticotropin-releasing factor and glucocorticoid receptor expression. *Endocrinology, 145,* 2702-2706.

Fernald, L. C., Grantham-McGregor, S. M., Manandhar, D. S., & Costello, A. (2003). Salivary cortisol and heart rate in stunted and nonstunted Nepalese school children. *European Journal of Clinical Nutrition, 57,* 1458-1465.

Ferguson, C. J. (2010). A meta-analysis of normal and disordered personality across the life span. *Journal of Personality and Social Psychology, 98,* 659-667.

Fergusson, D. M., Boden, J. M., Horwood, L. J., Miller, A. L., & Kennedy, M. A. (2011). MAOA, abuse exposure and antisocial behaviour: 30-year longitudinal study. *British Journal of Psychiatry, 198,* 457-463.

Forsdahl, A. (1977). Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? *British Journal of Preventive & Social Medicine, 31,* 91-95.

Forsdahl, A. (1978). Living conditions in childhood and subsequent development of risk factors for arteriosclerotic heart disease. The cardiovascular survey in Finnmark 1974-75. *Journal of Epidemiology and Community Health, 32,* 34-37.

Forsén, T., Eriksson, J., Tuomilehto, J., Reunanen, A., Osmond, C., & Barker, D. (2000). The fetal and childhood growth of persons who develop type 2 diabetes. *Annals of Internal Medicine, 133,* 176-182.

Fossati, A., Donati, D., Donini, M., Novella, L., Bagnato, M., & Maffei, C. (2001). Temperament, character, and attachment patterns in borderline personality disorder. *Journal of Personality Disorders, 15,* 390-402.

Foster, D., Davies, S., & Steele, H. (2003). The evacuation of British children during World War II: a preliminary investigation into the long-term psychological effects. *Aging and Mental Health, 7,* 398-408.

Franklin, T. B., Russig, H., Weiss, I. C., Gräff, J., Linder, N., Michalon, A, …, Mansuy, I. M. (2010). Epigenetic transmission of the impact of early stress across generations. *Biological Psychiatry, 68,* 408-415.

Freud, S. (1910). The Origin and Development of Psychoanalysis. *The American Journal of Psychology, 21,* 181-218.

Fuemmeler, B. F., Yang, C., Costanzo, P., Hoyle, R. H., Siegler, I. C., Williams, R. B., & Østbye, T. (2012). Parenting Styles and Body Mass Index Trajectories From Adolescence to Adulthood. *Health Psychology, 31,* 441-449.

Gale, C. R., & Martyn, C. N. (2004). Birth weight and later risk of depression in a national birth cohort. *British Journal of Psychiatry, 184,* 28-33.

Galéra, C., Côté, S. M., Bouvard, M. P., Pingault, J. B., Melchior, M., Michel, G., … Tremblay, R. E. (2011). Early risk factors for hyperactivity-impulsivity and inattention trajectories from age 17 months to 8 years. *Archives of General Psychiatry, 68,* 1267-1275.

Gao, Y., Raine, A., Chan, F., Venables, P. H., & Mednick, S. A. (2010) Early maternal and paternal bonding, childhood physical abuse and adult psychopathic personality. *Psychological Medicine, 40,* 1007-1016.

Garcia, L. F., Aluja, A., Fibla, J., Cuevas, L., & García, O. (2010). Incremental effect for antisocial personality disorder genetic risk combining 5-HTTLPR and 5-HTTVNTR polymorphisms. *Psychiatry Research, 177,* 161-166.

Gasim, T. (2012). Gestational diabetes mellitus: maternal and perinatal outcomes in 220 saudi women. *Oman Medical Journal, 27,* 140-144.

Gavin, A. R., Thompson, E., Rue, T., & Guo Y. (2012). Maternal early life risk factors for offspring birth weight: findings from the add health study. *Prevention Science, 13,* 162-172.

Geary, M. P., Pringle, P. J., Rodeck, C. H., Kingdom, J. C., & Hindmarsh, P. C. (2003). Sexual dimorphism in the growth hormone and insulin-like growth factor axis at birth. *The Journal of Clinical Endocrinology and Metabolism, 88,* 3708-3714.

Gerra, G., Zaimovic, A., Moi, G., Bussandri, M., Delsignore, R., Caccavari, R., & Brambilla, F. (2003). Neuroendocrine correlates of antisocial personality disorder in abstinent heroin-dependent subjects. *Addiction Biology, 8,* 23-32.

Ghadirivasfi, M., Nohesara, S., Ahmadkhaniha, H. R., Eskandari, M. R., Mostafavi, S., Thiagalingam, S., & Abdolmaleky, H. M. (2011). Hypomethylation of the serotonin receptor type-2A Gene (HTR2A) at T102C polymorphic site in DNA derived from the saliva of patients with schizophrenia and bipolar disorder. *American Journal of Medical Genetics, 156B,* 536-545.

Gibbon, S., Duggan, C., Stoffers, J., Huband, N., Völlm, B. A., Ferriter, M., & Lieb, K. (2010). Psychological interventions for antisocial personality disorder. *Cochrane Database of Systematic Reviews*, CD007668. doi: 10.1002/14651858.CD007668.pub2

Gibbon, S. A., Ferriter, M., & Duggan, C. (2009). A comparison of the family and childhood backgrounds of hospitalised offenders with schizophrenia or personality disorder. *Criminal Behaviour and Mental Health, 19,* 207-218.

Gibbs, C. M., Wendt, A., Peters, S., & Hogue, C. J. (2012). The impact of early age at first childbirth on maternal and infant health. *Paediatric and Perinatal Epidemiology, 26,* 259-284.

Glenn, A. L., Raine, A., Venables, P. H., & Mednick, S. A. (2007). Early temperamental and psychophysiological precursors of adult psychopathic personality. *Journal of Abnormal Psychology, 116,* 508-518.

Glover, V., O'Connor, T. G., & O'Donnell, K. (2010). Prenatal stress and the programming of the HPA axis. *Neuroscience and Biobehavioral Reviews, 35,* 17-22.

Gluckman, P. D., Hanson, M. A., & Low, F. M. (2011), The role of developmental plasticity and epigenetics in human health. *Birth Defects Research Part C: Embryo Today: Reviews, 93,* 12-18.

Goel, N., & Bale, T. L. (2009). Examining the intersection of sex and stress in modelling neuropsychiatric disorders. *Journal of Neuroendocrinology, 21,* 415-420.

Goel, N., Plyler, K. S., Daniels, D., & Bale, T. L. (2011). Androgenic influence on serotonergic activation of the HPA stress axis. *Endocrinology, 152,* 2001-2010.

Goldman-Mellor, S., Hamer, M., & Steptoe, A. (2012). Early-life stress and recurrent psychological distress over the lifecourse predict divergent cortisol reactivity patterns in adulthood. *Psychoneuroendocrinology, 37,* 1755-1768.

Grant, B. F., Hasin, D. S., Stinson, F. S., Dawson, D. A., Chou, S. P., Ruan, W. J., & Pickering, R. P. (2004). Prevalence, Correlates, and Disability of Personality Disorders in the United States: Results From the National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of Clinical Psychiatry, 65,* 948-958.

Grantham-McGregor, S., Cheung, Y. B., Cueto, S., Glewwe, P., Richter, L., Strupp, B. & International Child Development Steering Group. (2007). Developmental potential in the first 5 years for children in developing countries. *Lancet, 369,* 60-70.

Green, J. G., McLaughlin, K. A., Berglund, P.A., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2010). Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: associations with first onset of DSM-IV disorders. *Archives of General Psychiatry, 67,* 113-123.

Grigoletti, L., Perini, G., Rossi, A., Biggeri, A., Barbui, C., Tansella, M., & Amaddeo, F. (2009). Mortality and cause of death among psychiatric patients: a 20-year case-register study in an area with a community-based system of care. *Psychological Medicine, 39,* 1875-1884.

Groen-Blokhuis, M. M., Middeldorp, C. M., van Beijsterveldt, C. E., & Boomsma, D. I. (2011). Evidence for a causal association of low birth weight and attention problems. *The Journal of American Academy of Child and Adolescent Psychiatry, 50,* 1247-1254.

Grote, N. K., Bridge, J. A., Gavin, A. R., Melville, J. L., Iyengar, S., & Katon, W. J. (2010). A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. *Archives of General Psychiatry, 67,* 1012-1024.

Guinchat, V., Thorsen, P., Laurent, C., Cans, C., Bodeau, N., Cohen, D. (2012). Pre-, peri- and neonatal risk factors for autism. *Acta Obstetricia & Gynecologica Scandinavica, 91,* 287-300.

Gunderson, J. G., Daversa, M. T., Grilo, C. M., McGlashan, T. H., Zanarini, M. C., Shea, M. T., … Stout, R. L. (2006). Predictors of 2-year outcome for patients with borderline personality disorder. *American Journal of Psychiatry, 163,* 822-826.

Gunderson, J. G., Zanarini, M. C., Choi-Kain, L. W., Mitchell, K. S., Jang, K. L., & Hudson, J. I. (2011). Family study of borderline personality disorder and its sectors of psychopathology. *Archives of General Psychiatry, 68,* 753-762.

Gunnell, D., Harrison, G., Whitley, E., Lewis, G., Tynelius, P., & Rasmussen, F. (2005). The association of fetal and childhood growth with risk of schizophrenia. Cohort study of 720,000 Swedish men and women. *Schizophrenia Research, 79,* 315-322.

Gunnell, D., Rasmussen, F., Fouskakis, D., Tynelius, P., & Harrison, G. (2003). Patterns of fetal and childhood growth and the development of psychosis in young males: a cohort study. *American Journal of Epidemiology, 158,* 291-300.

Gustafsson, P., & Källén, K. (2011). Perinatal, maternal, and fetal characteristics of children diagnosed with attention-deficit-hyperactivity disorder: results from a population-based study utilizing the Swedish Medical Birth Register. *Developmental Medicine and Child Neurology, 53,* 263-268.

Hack, M., Youngstrom, E. A., Cartar, L., Schluchter, M., Taylor, H. G., Flannery, D., … Borawski, E. (2004). Behavioral outcomes and evidence of psychopathology among very low birth weight infants at age 20 years. *Pediatrics, 114,* 932-940.

Hankin, B. L., Barrocas, A. L., Jenness, J., Oppenheimer, C. W., Badanes, L. S., Abela, J. R., … Smolen, A. (2011). Association between 5-HTTLPR and Borderline Personality Disorder Traits among Youth. *Frontiers in Psychiatry, 2,* 6.

Hannerz, H., Borgå, P., & Borritz, M. (2001). Life expectancies for individuals with psychiatric diagnoses. *Public Health, 115,* 328-337.

Hardt, J., & Rutter, M. (2004). Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. *Journal of Child Psychology and Psychiatry, 45,* 260-273.

Harris, A., & Seckl, J. (2011). Glucocorticoids, prenatal stress and the programming of disease. *Hormones and Behaviour, 59,* 279-289.

Hasin, D., Fenton, M. C., Skodol, A., Krueger, R., Keyes, K., Geier, T., …, Grant, B. (2011). Personality disorders and the 3-year course of alcohol, drug, and nicotine use disorders. *Archives of General Psychiatry, 68,* 1158-1167.

Haukka, J., Suvisaari, J., Häkkinen, L., & Lönnqvist, J. (2008). Growth pattern and risk of schizophrenia. *Psychological Medicine, 38,* 63-70.

Hebebrand, J., Henninghausen, K., Nau, S., Himmelmann, G. W., Schulz, E., Schäfer, H., & Remschmidt, H.(1997). Low body weight in male children and adolescents with schizoid personality disorder or Asperger's disorder. *Acta Psychiatrica Scandinavica, 96,* 64-67.

Heijmans, B. T., Tobi, E. W., Stein, A. D., Putter, H., Blauw, G. J., Susser, E. S., … Lumey, L. H. (2008). Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proceedings of the National Academy of Sciences of the United States of America, 105,* 17046-17049.

Heinonen, K., Räikkönen, K., Pesonen, A. K., Andersson, S., Kajantie, E., Eriksson, J. G.,…, Lano, A. (2011). Trajectories of growth and symptoms of attention-deficit/hyperactivity disorder in children: a longitudinal study. *BMC Pediatrics, 11,* 84.

Helgeland, M. I., & Torgersen, S. (2004). Developmental antecedents of borderline personality disorder. *Comprehensive Psychiatry, 45,* 138-147.

Henrichs, J., Schenk, J. J., Roza, S. J., van den Berg, M. P., Schmidt, H. G., Steegers, E.A., …, Tiemeier, H. (2010). Maternal psychological distress and fetal growth trajectories: the Generation R Study. *Psychological Medicine, 40,* 633-643.

Herpertz, S. C., Dietrich, T. M., Wenning, B., Krings, T., Erberich, S. G., Willmes, K., … Sass, H. (2001). Evidence of abnormal amygdala functioning in borderline personality disorder: a functional MRI study. *Biological Psychiatry, 50,* 292-298.

Herva, A., Pouta, A., Hakko, H., Läksy, K., Joukamaa, M., & Veijola, J. (2008). Birth measures and depression at age 31 years: the Northern Finland 1966 Birth Cohort Study. *Psychiatry Research, 160,* 263-270.

Hill, J., Stepp, S. D., Wan, M. W., Hope, H., Morse, J. Q., Steele, M., …, Pilkonis, P. A. (2011). Attachment, borderline personality, and romantic relationship dysfunction. *Journal of Personality Disorders, 25,* 789-805.

Hines, M. (2008). Early androgen influences on human neural and behavioural development. *Early Human Development, 84,* 805-807.

Hjern, A., Lindblad, F., & Vinnerljung, B. (2002). Suicide, psychiatric illness, and social maladjustment in intercountry adoptees in Sweden: a cohort study. *Lancet, 360,* 443-448.

Hochberg, Z., & Albertsson-Wikland, K. (2008). Evo-devo of infantile and childhood growth. *Pediatric Research, 64,* 2-7.

Hoek, H. W., Susser, E. Z., Buck, K., Lumey, L. H., Lin, S. P., & Gorman, J. M. (1996). Schizoid personality disorder after prenatal exposure to famine. *American Journal of Psychiatry, 153,* 1637-1639.

Hopwood, C. J., Thomas, K. M., Markon, K. E., Wright, A. G., & Krueger, R. F. (2012). DSM-5 personality traits and DSM-IV personality disorders. *Journal of Abnormal Psychology, 121,* 424-432.

Hovi, P., Andersson, S., Räikkönen, K., Strang-Karlsson, S., Järvenpää, A. L., Eriksson, J. G., …, Kajantie, E. (2010). Ambulatory blood pressure in young adults with very low birth weight. *Journal of Pediatrics, 156,* 54-59.

Huang, Y., Kotov, R., de Girolamo, G., Preti, A., Angermeyer, M., Benjet, C., … Kessler, R. C. (2009). DSM-IV personality disorders in the WHO World Mental Health Surveys. *British Journal of Psychiatry, 195,* 46-53.

Huang, J., Yang, Y., Wu, J., Napolitano, L. A., Xi, Y., & Cui, Y. (2012). Childhood abuse in chinese patients with borderline personality disorder. *Journal of Personality Disorders, 26,* 238-254.

Hultman, C. M., Sandin, S., Levine, S. Z., Lichtenstein, P., & Reichenberg, A. (2011). Advancing paternal age and risk of autism: new evidence from a population-based study and a meta-analysis of epidemiological studies. *Molecular Psychiatry, 16,* 1203-1212.

Hultman, C. M., Torrång, A., Tuvblad, C., Cnattingius, S., Larsson, J. O., & Lichtenstein, P. (2007). Birth weight and attention-deficit/hyperactivity symptoms in childhood and early adolescence: a prospective Swedish twin study. *The Journal of American Academy of Child and Adolescent Psychiatry. 46,* 370-377.

Huttunen, M. O., & Niskanen, P. (1978). Prenatal loss of father and psychiatric disorders. *Archives of General Psychiatry, 35,* 429-431.

Huxley, R., Owen, C. G., Whincup, P. H., Cook, D. G., Rich-Edwards, J., Smith, G. D., & Collins, R. (2007). Is birth weight a risk factor for ischemic heart disease in later life? *American Journal of Clinical Nutrition, 85,* 1244-1250.

Igarashi, H., Hasui, C., Uji, M., Shono, M., Nagata, T., & Kitamura, T. (2010). Effects of child abuse history on borderline personality traits, negative life events, and depression: a study among a university student population in Japan. *Psychiatry Research, 180,* 120-125.

Ikäheimo, P., Räsänen, P., Hakko, H., Hartikainen, A.-L., Laitinen, J., Hodgins, S., & Tiihonen J. (2007). Body size and violent offending among males in the Northern Finland 1966 birth cohort. *Social Psychiatry and Psychiatric Epidemiology, 42,* 845-850.

Jackson, H. J., & Burgess, P. M. (2000). Personality disorders in the community: A report from the Australian National Survey of Mental Health and Wellbeing. *Social Psychiatry and Psychiatric Epidemiology, 35,* 531-538.

Jaddoe, V. W., Verburg, B. O., de Ridder, M. A., Hofman, A., Mackenbach, J. P., Moll, H. A., … Witteman, J. C. (2007). Maternal smoking and fetal growth characteristics in different periods of pregnancy: the generation R study. *American Journal of Epidemiology, 165,* 1207-1215.

Jaffee, S., Caspi, A., Moffitt, T. E., Belsky, J., & Silva, P. (2001). Why are children born to teen mothers at risk for adverse outcomes in young adulthood? Results from a 20-year longitudinal study. *Development and Psychopathology, 13,* 377-397.

Jensen Peña, C., Monk, C., & Champagne, F. A. (2012). Epigenetic effects of prenatal stress on 11β-hydroxysteroid dehydrogenase-2 in the placenta and fetal brain. *PLoS One, 7,* e39791.

Johnson, B. A., Brent, D. A., Connolly, J., Bridge, J., Matta, J., Constantine, D., … White, T. (1995). Familial aggregation of adolescent personality disorders. *Journal of American Academy of Child and Adolescent Psychiatry, 34,* 798-804.

Johnson, J. G., Cohen, P., Brown, J., Smailes, E. M., & Bernstein, D. P. (1999). Childhood maltreatment increases risk for personality disorders during adulthood. *Archives of General Psychiatry, 56,* 600-606.

Johnson, J. G., Cohen, P., Chen, H., Kasen, S., & Brook, J. S. (2006). Parenting behaviors associated with risk for offspring personality disorder during adulthood. *Archives of General Psychiatry, 63,* 579-587.

Johnson, J. G., Cohen, P., Smailes, E. M., Skodol, A. E., Brown, J., & Oldham, J. M. (2001). Childhood verbal abuse and risk for personality disorders during adolescence and early adulthood. *Comprehensive Psychiatry, 42,* 16-23.

Johnson, J. G., Liu, L., & Cohen, P. (2011). Parenting behaviours associated with the development of adaptive and maladaptive offspring personality traits. *Canadian Journal of Psychiatry, 56,* 447-456.

Johnson, J. G., Smailes, E. M., Cohen, P., Brown, J., & Bernstein, D. P. (2000). Associations between four types of childhood neglect and personality disorder symptoms during adolescence and early adulthood: findings of a community-based longitudinal study. *Journal of Personality Disorders, 14,* 171-187.

Jones, A., Charakida, M., Falaschetti, E., Hingorani, A. D., Finer, N., Masi, S., Donald A. E., … Deanfield, J. E. (2012). Adipose and height growth through childhood and blood pressure status in a large prospective cohort study. *Hypertension, 59,* 919-925.

Jones, N. M., Holzman, C., Friderici, K. H., Jernigan, K., Chung, H., Wirth, J., & Fisher, R. (2010). Interplay of cytokine polymorphisms and bacterial vaginosis in the etiology of preterm delivery. *Journal of Reproductive Immunology, 87,* 82-89.

Jonson-Reid, M., Presnall, N., Drake, B., Fox, L., Bierut, L., Reich, W., … Constantino, J. N. (2010). Effects of child maltreatment and inherited liability on antisocial development: an official records study. *Journal of American Academy of Child and Adolescent Psychiatry, 49,* 321-332.

Joyce, P. R., McKenzie, J. M., Luty, S. E., Mulder, R. T., Carter, J. D., Sullivan, P. F., & Cloninger. C. R. (2003). Temperament, childhood environment and psychopathology as risk factors for avoidant and borderline personality disorders. *The Australian and New Zealand Journal of Psychiatry, 37,* 756-764.

Juul, A. (2001). The effects of oestrogens on linear bone growth. *Human Reproduction Update, 7,* 303-313.

Kajantie, E., Eriksson, J., Barker, D. J., Forsén, T., Osmond, C., Wood, P. J., … Phillips, D. I. (2003). Birthsize, gestational age and adrenal function in adult life: studies of dexamethasone suppression and ACTH1-24 stimulation. *European Journal of Endocrinology, 149,* 569-575.

Kajantie, E., Eriksson, J. G., Osmond, C., Thornburg, K., & Barker, D. J. (2009). Pre-eclampsia is associated with increased risk of stroke in the adult offspring: the Helsinki birth cohort study. *Stroke, 40,* 1176-1180.

Kajantie, E., Barker, D. J., Osmond, C., Forsén, T., & Eriksson, J. G. (2008). Growth before 2 years of age and serum lipids 60 years later: the Helsinki Birth Cohort study. *International Journal of Epidemiology, 37,* 280-289.

Kajantie, E., Osmond, C., Barker, D. J., & Eriksson, J. G. (2010). Preterm birth--a risk factor for type 2 diabetes? The Helsinki birth cohort study. *Diabetes Care, 33,* 2623-2625.

Kajantie, E., & Räikkönen, K. (2010). Early life predictors of the physiological stress response later in life. *Neuroscience and Biobehavioral Reviews, 35,* 23-32.

Kajantie, E., Thornburg, K. L., Eriksson, J. G., Osmond C., Barker, D. J. (2010). In preeclampsia, the placenta grows slowly along its minor axis. *International Journal of Developmental Biology, 54,* 469-473.

Kang Sim, D. E., Cappiello, M., Castillo, M., Lozoff, B., Martinez, S., Blanco, E., & Gahagan, S. (2012). Postnatal Growth Patterns in a Chilean Cohort: The Role of SES and Family Environment. *International Journal of Pediatrics, 2012*, 354060.

Kasen, S., Cohen, P., Skodol, A. E., Johnson, J. G., & Brook, J. S. (1999). Influence of child and adolescent psychiatric disorders on young adult personality disorder. *American Journal of Psychiatry, 156*, 1529-1535.

Kasen, S., Cohen, P., Skodol, A. E., Johnson, J. G., Smailes, E., & Brook, J. S. (2001). Childhood depression and adult personality disorder: alternative pathways of continuity. *Archives of General Psychiatry, 58*, 231-236.

Kavén, P. (2010). *Humanitaarisuuden varjossa: Poliittiset tekijät lastensiirroissa Ruotsiin sotiemme aikana ja niiden jälkeen.* Helsinki, Finland: Faculty of Arts, Department of Philosophy, History, Culture and Art Studies, University of Helsinki.

Kantojärvi, L., Joukamaa, M., Miettunen, J., Läksy, K., Herva, A., Karvonen, J. T.,… Veijola, J. (2008). Childhood family structure and personality disorders in adulthood. *European Psychiatry, 23*, 205-211.

Kantojärvi, L., Miettunen, J., Veijola, J., Läksy, K., Karvonen, J. T., Ekelund, J., … Joukamaa, M. (2008). Temperament profiles in personality disorders among a young adult population. *Nordic Journal of Psychiatry, 62*, 423-430.

Kantojärvi, L., Veijola, J., Läksy, K., Jokelainen, J., Herva, A., Karvonen, J. T., … Joukamaa, M. (2004). Comparison of hospital-treated personality disorders and personality disorders in a general population sample. *Nordic Journal of Psychiatry, 58*, 357-362.

Kellogg, S. H., & Young, J. E. (2006). Schema therapy for borderline personality disorder. *Journal of Clinical Psychology, 62*, 445-458.

Kemppainen, L., Mäkikyrö, T., Jokelainen, J., Nieminen, P., Järvelin, M. R., Isohanni, M. (2000). Is grand multiparity associated with offsprings' hospital-treated mental disorders? A 28-year follow-up of the North Finland 1966 birth cohort. *Social Psychiatry and Psychiatric Epidemiology, 35*, 104-108.

Kendler, K. S., Aggen, S. H., Czajkowski, N., Røysamb, E., Tambs, K., Torgersen, S., … Reichborn-Kjennerud, T. (2008). The structure of genetic and environmental risk factors for DSM-IV personality disorders: a multivariate twin study. *Archives of General Psychiatry, 65*, 1438-1446.

Kendler, K. S., Czajkowski, N., Tambs, K., Torgersen, S., Aggen, S. H., Neale, M. C., & Reichborn-Kjennerud, T. (2006). Dimensional representations of DSM-IV cluster A personality disorders in a population-based sample of Norwegian twins: a multivariate study. *Psychological Medicine, 36*, 1583-1591.

Kendler, K. S., Prescott, C. A., Myers, J., & Neale, M. C. (2003). The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Archives of General Psychiatry, 60*, 929-937.

Kendler, K. S., Aggen, S. H., Knudsen, G. P., Røysamb, E., Neale, M. C., & Reichborn-Kjennerud, T. (2011). The structure of genetic and environmental risk factors for syndromal and subsyndromal common DSM-IV axis I and all axis II disorders. *American Journal of Psychiatry, 168*, 29-39.

Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., … Kendler, K. S. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Archives of General Psychiatry, 51,* 8-19.

Kessler, R. C., McLaughlin, K. A., Green, J. G., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., … Williams, D. R. (2010). Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *British Journal of Psychiatry, 197,* 378-385.

Khalifa, N., Duggan, C., Stoffers, J., Huband, N., Völlm, B. A., Ferriter, M., & Lieb, K. (2010). Pharmacological interventions for antisocial personality disorder. *Cochrane Database of Systematic Reviews,* CD007667. doi: 10.1002/14651858.CD007667.pub2

Khalife, N., Glover, V., Hartikainen, A. L., Taanila, A., Ebeling, H., Järvelin, M. R., & Rodriguez, A. (2012). Placental size is associated with mental health in children and adolescents. *PLoS One, 7,* e40534.

Kieseppä, T., Partonen, T., Kaprio, J., & Lönnqvist, J. (2000). Accuracy of register- and record-based bipolar I diagnoses in Finland – a study of twins. *Acta Neuropsychiatrica, 12,* 106-109.

Kimbrel, N. A., Mitchell, J. T., Hundt, N. E., Robertson, C. D., & Nelson-Gray, R. O. (2012). BIS and BAS interact with perceived parental affectionless control to predict personality disorder symptomatology. *Journal of Personality Disorders, 26,* 203-212.

Kim-Cohen, J., Caspi, A., Taylor, A., Williams, B., Newcombe, R., Craig, I. W., & Moffitt, T. E. (2006). *MAOA,* maltreatment, and gene–environment interaction predicting children's mental health: new evidence and a meta-analysis. *Molecular Psychiatry, 11,* 903-913.

Kuja-Halkola, R., Pawitan, Y., D'Onofrio, B. M., Långström, N., & Lichtenstein, P. (2012). Advancing paternal age and offspring violent offending: A sibling-comparison study. *Developmental Psychopathology, 24,* 739-753.

Knop, J., Penick, E. C., Jensen, P., Nickel, E. J., Gabrielli, W. F., Mednick, S. A., & Schulsinger, F. (2003). Risk factors that predicted problem drinking in Danish men at age thirty. *Journal of Studies on Alcohol, 64,* 745-755.

Lahey, B. B., Loeber, R., Burke, J. D., & Applegate, B. (2005). Predicting Future Antisocial Personality Disorder in Males From a Clinical Assessment in Childhood. *Journal of Consulting and Clinical Psychology, 73,* 389-399.

Lahti, J., Räikkönen, K., Heinonen, K., Pesonen, A. K., Kajantie, E., Forsén, T., … Eriksson, J. G. (2008). Body size at birth and socio-economic status in childhood: implications for Cloninger's psychobiological model of temperament at age 60. *Psychiatry Research, 160,* 167-174.

Lahti, J., Räikkönen, K., Kajantie, E., Heinonen, K., Pesonen, A.-K., Järvenpää, A.-L., & Strandberg, T. (2006). Small body size at birth and behavioural symptoms of ADHD in children aged five to six years. *Journal of Child Psychology and Psychiatry, 47,* 1167-1174.

Lahti, J., Räikkönen, K., Pesonen, A. K., Heinonen, K., Kajantie, E., Forsén, T., … Eriksson, J. G. (2010). Prenatal growth, postnatal growth and trait anxiety in late adulthood - the Helsinki Birth Cohort Study. *Acta Psychiatrica Scandinavica, 121,* 227-235.

Lahti, J., Räikkönen, K., Sovio, U., Miettunen, J., Hartikainen, A. L., Pouta A., … Veijola, J. (2009). Early-life origins of schizotypal traits in adulthood. *British Journal of Psychiatry, 195,* 132-137.

Lawlor, D. A., Ronalds, G., Clark, H., Smith, G. D., & Leon, D. A. (2005). Birth weight is inversely associated with incident coronary heart disease and stroke among individuals born in the 1950s: findings from the Aberdeen Children of the 1950s prospective cohort study. *Circulation, 112,* 1414-1418.

Lederman, S. A., Rauh, V., Weiss, L., Stein, J. L., Hoepner, L. A., Becker, M., & Perera, F. P. (2004). The effects of the World Trade Center event on birth outcomes among term deliveries at three lower Manhattan hospitals. *Environmental Health Perspectives, 112,* 1772-1778.

Lee, H. B., Bienvenu, O. J., Cho, S. J., Ramsey, C. M., Bandeen-Roche, K., Eaton, W. W., & Nestadt, G. (2010). Personality disorders and traits as predictors of incident cardiovascular disease: findings from the 23-year follow-up of the Baltimore ECA study. *Psychosomatics, 51,* 289-296.

Li, D., Zhao, H., Kranzler, H. R., Oslin, D., Anton, R. F., Farrer, L. A., & Gelernter, J. (2012). Association of COL25A1 with comorbid antisocial personality disorder and substance dependence. *Biological Psychiatry, 71,* 733-740.

Lindley, A. A., Benson, J. E., Grimes, C., Cole, T. M., & Herman, A. A. (1999). The relationship in neonates between clinically measured head circumference and brain volume estimated from head CT-scans. *Early Human Development, 56,* 17-29.

Lindström, K., Lindblad, F., & Hjern, A. (2009). Psychiatric morbidity in adolescents and young adults born preterm: a Swedish national cohort study. *Pediatrics, 123,* e47-e53.

Liu, D., Diorio, J., Tannenbaum, B., Caldji, C., Francis, D., Freedman, A., Sharma, S., … Meaney, M. J. (1997). Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. *Science, 277,* 1659-1662.

Losh, M., Esserman, D., Anckarsäter, H., Sullivan, P. F., & Lichtenstein, P. (2012). Lower birth weight indicates higher risk of autistic traits in discordant twin pairs. *Psychological Medicine, 42,* 1091-1102.

Lombardo, M. V., Ashwin, E., Auyeung, B., Chakrabarti, B., Taylor, K., Hackett, G., … Baron-Cohen, S. (2012). Fetal testosterone influences sexually dimorphic gray matter in the human brain. *The Journal of Neuroscience, 32,* 674-680.

Lund, L. K., Vik, T., Skranes, J., Brubakk, A. M., & Indredavik, M. S. (2011). Psychiatric morbidity in two low birth weight groups assessed by diagnostic interview in young adulthood. *Acta Paediatrica, 100,* 598-604.

Luntz, B. K., & Widom, C. S. (1994). Antisocial personality disorder in abused and neglected children grown up. *American Journal of Psychiatry, 151,* 670-674.

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience, 10,* 434-445.

Lyons-Ruth, K., Holmes, B. M., Sasvari-Szekely, M., Ronai, Z., Nemoda, Z., & Pauls, D. (2007). Serotonin transporter polymorphism and borderline or antisocial traits among low-income young adults. *Psychiatric Genetics, 17,* 339-343.

Machón, R. A., Huttunen, M. O., Mednick, S. A., Sinivuo, J., Tanskanen, A., Bunn Watson, J., … Pyhälä, R. (2002). Adult schizotypal personality characteristics and prenatal influenza in a Finnish birth cohort. *Schizophrenia Research, 54,* 7-16.

Masoura, S., Kalogiannidis, I., Margioula-Siarkou, C., Diamanti, E., Papouli, M., Drossou-Agakidou, V., … Agorastos, T. (2012). Neonatal outcomes of late preterm deliveries with pre-eclampsia. *Minerva Ginecologica, 64,* 109-115.

Magnusson, P. K., Gunnell, D., Tynelius, P., Davey Smith, G., & Rasmussen, F. (2005). Strong inverse association between height and suicide in a large cohort of Swedish men: evidence of early life origins of suicidal behavior? *American Journal of Psychiatry, 162,* 1373-1375.

Magnusson, P. K., Rasmussen F, Lawlor, D. A., Tynelius, P., & Gunnell, D. (2006). Association of body mass index with suicide mortality: a prospective cohort study of more than one million men. *American Journal of Epidemiology, 163,* 1-8.

Marcovecchio, M. L., Mohn, A., & Chiarelli, F. (2012). Inflammatory cytokines and growth in childhood. *Current Opinion in Endocrinology, Diabetes & Obesity, 19,* 57-62.

Marsit, C. J., Maccani, M. A., Padbury, J. F., & Lester, B. M. (2012). Placental 11-beta hydroxysteroid dehydrogenase methylation is associated with newborn growth and a measure of neurobehavioral outcome. *PLoS One, 7,* e33794.

Mathiasen, R., Hansen, B. M., Forman, J. L., Kessing, L. V., & Greisen, G. (2011). The risk of psychiatric disorders in individuals born prematurely in Denmark from 1974 to 1996. *Acta Paediatrica, 100,* 691-699.

Matrisciano, F., Tueting, P., Dalal, I., Kadriu, B., Grayson, D. R., Davis, J. M., … Guidotti, A. (2011). Epigenetic modifications of GABAergic interneurons are associated with the schizophrenia-like phenotype induced by prenatal stress in mice. *Human Molecular Genetics, 20,* 4786-4796.

McCrory, E., De Brito, S. A., & Viding, E. (2011). The impact of childhood maltreatment: a review of neurobiological and genetic factors. *Frontiers in Psychiatry, 2,* 48.

McGowan, P. O., Sasaki, A., D'Alessio, A. C., Dymov, S., Labonté, B., Szyf, M., … Meaney, M. J. (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nature Neuroscience, 12,* 342-348.

McGowan, P. O., Suderman, M., Sasaki, A., Huang, T. C., Hallett, M., Meaney, M. J., & Szyf, M. (2011). Broad epigenetic signature of maternal care in the brain of adult rats. *PLoS One, 6,* e14739.

McLaughlin, K. A., Breslau, J., Green, J. G., Lakoma, M. D., Sampson, N. A., Zaslavsky, A. M, & Kessler, R. C. (2011). Childhood socio-economic status and the onset, persistence, and severity of DSM-IV mental disorders in a US national sample. *Social Science & Medicine, 73,* 1088-1096.

Meaney, M. J. (2001). Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annual Review of Neuroscience, 24,* 1161-1192.

Menon, R., Conneely, K. N., & Smith, A. K. (2012). DNA methylation: an epigenetic risk factor in preterm birth. *Reproductive Sciences, 19,* 6-13.

Michels, K. B., Harris, H. R., & Barault, L. (2011). Birthweight, maternal weight trajectories and global DNA methylation of LINE-1 repetitive elements. *PLoS One, 6,* e25254.

Miller, C. J., Flory, J. D., Miller, S. R., Harty, S. C., Newcorn, J. H., & Halperin, J. M. (2008). Childhood attention-deficit/hyperactivity disorder and the emergence of personality disorders in adolescence: a prospective follow-up study. *Journal of Clinical Psychiatry, 69,* 1477-1484.

Miller, J. D., & Lynam, D. R. (2012). An Examination of the Psychopathic Personality Inventory's Nomological Network: A Meta-Analytic Review. *Personality Disorders, 3,* 305-326.

Mishra, G., Osmond, C., Power, C., Rich-Edwards, J. W., Roseboom, T. J., Sachdev, H. S., … Yarbrough, D. E. (2008). Birth weight and risk of type 2 diabetes: a systematic review. *The Journal of the American Medical Association, 300,* 2886-2897.

Mitrou, F., Gaudie, J., Lawrence, D., Silburn, S. R., Stanley, F. J., & Zubrick, S. R. (2010). Antecedents of hospital admission for deliberate self-harm from a 14-year follow-up study using data-linkage. *BMC Psychiatry, 10,* 82.

Mittendorfer-Rutz, E., Wasserman, D., & Rasmussen, F. (2008). Fetal and childhood growth and the risk of violent and non-violent suicide attempts: a cohort study of 318,953 men. *Journal of Epidemiology and Community Health, 62,* 168-173.

Moilanen, K., Jokelainen, J., Jones, P. B., Hartikainen, A. L., Järvelin, M. R., & Isohanni, M. (2010). Deviant intrauterine growth and risk of schizophrenia: a 34-year follow-up of the Northern Finland 1966 Birth Cohort. *Schizophrenia Research, 124,* 223-230.

Monfils Gustafsson, W., Josefsson, A., Ekholm Selling, K., & Sydsjö, G. (2009). Preterm birth or foetal growth impairment and psychiatric hospitalization in adolescence and early adulthood in a Swedish population-based birth cohort. *Acta Psychiatrica Scandinavica, 119,* 54-61.

Moran, P., Stewart, R., Brugha, T., Bebbington, P., Bhugra, D., Jenkins, R., & Coid, J. W. (2007). Personality disorder and cardiovascular disease: results from a national household survey. *Journal of Clinical Psychiatry, 68,* 69-74.

Mueller, B. R., & Bale, T. L. (2008). Sex-specific programming of offspring emotionality after stress early in pregnancy. *The Journal of Neuroscience, 28,* 9055-9065.

Muhs, A., & Ori, C. (1995). Concepts of neurotic and personality disorders in ICD-10: Results of the research criteria study *Psychotherapy and Psychosomatics, 63,* 99-111.

Mulder, R. T., Joyce, P. R., & Cloninger, C. R. (1994). Temperament and early environment influence comorbidity and personality disorders in major depression. *Comprehensive Psychiatry, 35,* 225-233.

Murray, J., & Farrington, D. P. (2005). Parental imprisonment: effects on boys' antisocial behaviour and delinquency through the life-course. *Journal of Child Psychology and Psychiatry, 46,* 1269-1278.

Murray, J. Farrington, D. P., & Sekol, I. (2012). Children's antisocial behavior, mental health, drug use, and educational performance after parental incarceration: A systematic review and meta-analysis. *Psychological Bulletin, 138,* 175-210.

Mäki, P., Hakko, H., Joukamaa, M., Läärä E, Isohanni, M., & Veijola, J. (2003). Parental separation at birth and criminal behaviour in adulthood--a long-term follow-up of the Finnish Christmas Seal Home children. *Social Psychiatry and Psychiatric Epidemiology, 38,* 354-359.

Mäki, P., Veijola, J., Joukamaa, M., Läärä, E., Hakko, H., Jones, P. B., & Isohanni, M. (2003). Maternal separation at birth and schizophrenia--a long-term follow-up of the Finnish Christmas Seal Home Children. *Schizophrenia Research, 60,* 13-19.

Mäki, P., Veijola, J., Räsänen, P., Joukamaa, M., Valonen, P., Jokelainen, J., & Isohanni, M. (2003). Criminality in the offspring of antenatally depressed mothers: a 33-year follow-up of the Northern Finland 1966 Birth Cohort. *Journal of Affective Disorders, 74,* 273-278.

Mäkikyrö, T., Isohanni, M., Moring, J., Hakko, H., Hovatta, I., & Lönnqvist, J. (1998). Accuracy of register-based schizophrenia diagnoses in a genetic study. *European Psychiatry, 13,* 57-62.

Mäkikyrö, T., Sauvola, A., Moring, J., Veijola, J., Nieminen, P., Järvelin, M. R., & Isohanni, M. (1998). Hospital-treated psychiatric disorders in adults with a single- parent and two-parent family background: A 28-year follow-up of the 1966 Northern Finland birth cohort. *Family Process, 37,* 335-344.

Neugebauer, R., Hoek, H. W., & Susser, E. (1999). Prenatal exposure to wartime famine and development of antisocial personality disorder in early adulthood. *The Journal of the American Medical Association, 282,* 455-462.

Newell, M. L., Borja, M. C., Peckham, C., & European Collaborative Study. (2003). Height, weight, and growth in children born to mothers with HIV-1 infection in Europe. *Pediatrics, 111,* e52-e60.

Newton-Howes, G., Tyrer, P., & Johnson, T. (2006). Personality disorder and the outcome of depression: meta-analysis of published studies. *British Journal of Psychiatry, 188,* 13-20.

Ni, X., Chan, K., Bulgin, N., Sicard, T., Bismil, R., McMain, S., & Kennedy, J. L. (2006). Association between serotonin transporter gene and borderline personality disorder. *Journal of Psychiatric Research, 40,* 448-453.

Ni, X., Chan, D., Chan, K., McMain, S., & Kennedy, J. L. (2009). Serotonin genes and gene-gene interactions in borderline personality disorder in a matched case-control study. *Progress in Neuropsychopharmacolocogy & Biological Psychiatry, 33,* 128-133.

Ni, X., Sicard, T., Bulgin, N., Bismil, R., Chan, K., McMain, S., & Kennedy, J. L. (2007). Monoamine oxidase a gene is associated with borderline personality disorder. *Psychiatric Genetics, 17,* 153-157.

Niemi, L. T., Suvisaari, J. M., Haukka, J. K., & Lönnqvist, J. K. (2005). Childhood growth and future development of psychotic disorder among Helsinki high-risk children. *Schizophrenia Research, 76,* 105-112.

Nilsson, E. Stålberg, G. Lichtenstein, P., Cnattingius, S. Olausson, P. O., & Hultman, C. M. (2005). Fetal growth restriction and schizophrenia: a Swedish twin study. *Twin Research and Human Genetics, 8,* 402-408.

Norman, M. (2008). Low birth weight and the developing vascular tree: a systematic review. *Acta Paediatrica, 97,* 1165-1172.

Nomura, Y., Brooks-Gunn, J., Davey, C., Ham, J., & Fifer, W. P. (2007). The role of perinatal problems in risk of co-morbid psychiatric and medical disorders in adulthood. *Psychological Medicine, 37,* 1323-1334.

Norris, S. A., Osmond, C., Gigante, D., Kuzawa, C. W., Ramakrishnan, L., Lee, N. R., … COHORTS Group. (2012). Size at birth, weight gain in infancy and childhood, and adult diabetes risk in five low- or middle-income country birth cohorts. *Diabetes Care, 35,* 72-79.

Nunes, P. M., Wenzel, A., Borges, K. T., Porto, C. R., Caminha, R. M., & de Oliveira, I. R. (2009). Volumes of the hippocampus and amygdala in patients with borderline personality disorder: a meta-analysis. *Journal of Personality Disorders, 23,* 333-345.

Oberlander, T. F., Weinberg, J., Papsdorf, M., Grunau, R., Misri, S., & Devlin, A. M. (2008). Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics, 3,* 97-106.

O'Connor, T. G., Ben-Shlomo, Y., Heron, J., Golding, J., Adams, D., & Glover, V. (2005). Prenatal anxiety predicts individual differences in cortisol in pre-adolescent children. *Biological Psychiatry, 58,* 211-217.

O'Connor, T. G., Bergman, K., Sarkar, P., & Glover, V. (2012). Prenatal cortisol exposure predicts infant cortisol response to acute stress. *Developmental Psychobiology*. Advance online Publication. doi: 10.1002/dev.21007.

Olesen, J., Gustavsson, A., Svensson, M., Wittchen, H.-U., & Jönsson, B., on behalf of the CDBE2010 study group and the European Brain Council. (2012). The economic cost of brain disorders in Europe. *European Journal of Neurology, 19,* 155-162.

Osler, M., Nybo Andersen, A. M., & Nordentoft, M. (2008). Impaired childhood development and suicidal behaviour in a cohort of Danish men born in 1953. *Journal of Epidemiology and Community Health, 62,* 23-28.

Osmond, C., Kajantie, E., Forsén, T. J., Eriksson, J. G., & Barker, D. J. (2007). Infant growth and stroke in adult life: the Helsinki birth cohort study. *Stroke, 38,* 264-270.

Pascual, J. C., Soler, J., Barrachina, J., Campins, M. J., Alvarez, E., Pérez, V., … Baiget, M. (2008). Failure to detect an association between the serotonin transporter gene and borderline personality disorder. *Journal of Psychiatric Research, 42,* 87-88.

Perez-Rodriguez, M. M., Weinstein, S., New, A. S., Bevilacqua, L., Yuan, Q., Zhou, Z., … Siever, L. J. (2010). Tryptophan-hydroxylase 2 haplotype association with borderline personality disorder and aggression in a sample of patients with personality disorders and healthy controls. *Journal of Psychiatric Research, 44,* 1075-1081.

Perrin, M. A., Chen, H., Sandberg, D. E., Malaspina, D., & Brown, A. S. (2007). Growth trajectory during early life and risk of adult schizophrenia. *British Journal of Psychiatry, 191,* 512-520.

Perälä, J., Suvisaari, J., Saarni, S. I., Kuoppasalmi, K., Isometsä, E., Pirkola, S., … Lönnqvist, J. (2007): Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Archives of General Psychiatry, 64,* 19-28.

Pert, L., Ferriter, M., & Saul, C. (2004). Parental loss before the age of 16 years: a comparative study of patients with personality disorder and patients with schizophrenia in a high secure hospital's population. *Psychology and Psychotherapy, 77,* 403-407.

Pesonen, A. K., Räikkönen, K., Feldt, K., Heinonen, K., Osmond, C., Phillips, D. I., … Kajantie, E. (2010). Childhood separation experience predicts HPA axis hormonal responses in late adulthood: a natural experiment of World War II. *Psychoneuroendocrinology, 35,* 758-767.

Pesonen, A. K., Räikkönen, K., Heinonen, K., Kajantie, E., Forsén, T., & Eriksson, J. G. (2007). Depressive symptoms in adults separated from their parents as children: a natural experiment during World War II. *American Journal of Epidemiology, 166,* 1126-1133.

Pesonen, A. K., Räikkönen, K., Heinonen, K., Kajantie, E., Forsén, T., & Eriksson, J. G. (2008). Reproductive traits following a parent-child separation trauma during childhood: a natural experiment during World War II. *American Journal of Human Biology, 20,* 345-351.

Pesonen, A. K., Räikkönen, K., Kajantie, E., Heinonen, K., Henriksson, M., … Eriksson, J. G. (2011). Intellectual ability in young men separated temporarily from their parents in childhood. *Intelligence, 39,* 335-341.

Pesonen, A. K., Räikkönen, K., Kajantie, E., Heinonen, K., Osmond, C., Barker, D. J., … Eriksson, J. G. (2011). Inter-generational social mobility following early life stress. *Annals of Medicine, 43,* 320-328.

Pesonen, A. K., Räikkönen, K., Kajantie, E., Heinonen, K., Strandberg, T. E., & Järvenpää, A. L. (2006). Fetal programming of temperamental negative affectivity among children born healthy at term. *Developmental Psychobiology, 48,* 633-643.

Pesonen, A. K., Räikkönen, K., Lano, A., Peltoniemi, O., Hallman, M., & Kari, M. A. (2009). Antenatal betamethasone and fetal growth in prematurely born children: implications for temperament traits at the age of 2 years. *Pediatrics, 123,* e31-e37.

Pilgaard, K., Færch, K., Carstensen, B., Poulsen, P., Pisinger, C., Pedersen, O., … Vaag, A. (2010). Low birthweight and premature birth are both associated with type 2 diabetes in a random sample of middle-aged Danes. *Diabetologia, 53,* 2526-2530.

Poikolainen, K. (1983). Accuracy of hospital discharge data: five alcohol-related diseases. *Drug and Alcohol Dependence, 12,* 315-322.

Pompili, M., Girardi, P., Ruberto, A., & Tatarelli, R. (2005). Suicide in borderline personality disorder: a meta-analysis. *Nordic Journal of Psychiatry, 59,* 319-324.

Putkonen, H., Weizmann-Henelius, G., Repo-Tiihonen, E., Lindberg, N., Saarela, T., Eronen, M., & Häkkänen-Nyholm, H. (2010). Homicide, Psychopathy, and Aging—A Nationwide Register-based Case-comparison Study of Homicide Offenders Aged 60 Years or Older. *Journal of Forensic Sciences, 55,* 1552-1556.

Pyhälä, R., Räikkönen, K., Pesonen, A. K., Heinonen, K., Hovi, P., Eriksson, J. G., Järvenpää, A. L., … Kajantie, E. (2009). Behavioral inhibition and behavioral approach in young adults with very low birth weight? The Helsinki study of very low birth weight adults. *Personality and Individual Differences, 46,* 106-110.

Raine, A., Mellingen, K., Liu, J., Venables, P., & Mednick, S. A. (2003). Effects of environmental enrichment at ages 3-5 years on schizotypal personality and antisocial behavior at ages 17 and 23 years. *American Journal of Psychiatry, 160,* 1627-1635.

Ravelli, G. P., Stein, Z. A., & Susser, M. W. (1976). Obesity in young men after famine exposure in utero and early infancy. *New England Journal of Medicine, 295,* 349-353.

Reef, J., van Meurs, I., Verhulst, F. C., & van der Ende, J. (2010). Children's problems predict adults' DSM-IV disorders across 24 years. *Journal of the American Academy of Child and Adolescent Psychiatry, 49,* 1117-1124.

Reichborn-Kjennerud, T., Czajkowski, N., Neale, M. C., Ørstavik, R. E., Torgersen, S., Tambs, K., … Kendler, K. S. (2007). Genetic and environmental influences on dimensional representations of DSM-IV cluster C personality disorders: a population-based multivariate twin study. *Psychological Medicine, 37,* 645-653.

Reynolds, A. J., Temple, J. A., Ou, S. R., Arteaga, I. A., & White, B. A. (2011). School-based early childhood education and age-28 well-being: effects by timing, dosage, and subgroups. *Science, 333,* 360-364.

Reynolds, R. M., Labad, J., Strachan, M. W., Braun, A., Fowkes, F. G., Lee, A. J., … Edinburgh Type 2 Diabetes Study (ET2DS) Investigators. (2010). Elevated fasting plasma cortisol is associated with ischemic heart disease and its risk factors in people with type 2 diabetes: the Edinburgh type 2 diabetes study. *The Journal of Clinical Endocrinology and Metabolism, 95,* 1602-1608.

Reynolds, R. M., Walker, B. R., Syddall, H. E., Andrew, R., Wood, P. J., & Phillips, D. I. (2005). Is there a gender difference in the associations of birthweight and adult hypothalamic-pituitary-adrenal axis activity? *European Journal of Endocrinology, 152,* 249-253.

Rice, F., Harold, G. T., Boivin, J., van den Bree, M., Hay, D. F., Thapar, A. (2010). The links between prenatal stress and offspring development and psychopathology: disentangling environmental and inherited influences. *Psychological Medicine, 40,* 335-345.

Rinne, T., de Kloet, E. R., Wouters, L., Goekoop, J. G., DeRijk, R. H., & van den Brink, W. (2002). Hyperresponsiveness of hypothalamic-pituitary-adrenal axis to combined dexamethasone/corticotropin-releasing hormone challenge in female borderline personality disorder subjects with a history of sustained childhood abuse. *Biological Psychiatry, 52,* 1102-1112.

Risnes, K. R., Vatten, L. J., Baker, J. L., Jameson, K., Sovio, U., Kajantie, E., … Bracken, M. B. (2011). Birthweight and mortality in adulthood: a systematic review and meta-analysis. *International Journal of Epidemiology, 40,* 647-661.

Rondó, P. H., Ferreira, R. F., Nogueira, F., Ribeiro, M. C., Lobert, H., & Artes, R. (2003). Maternal psychological stress and distress as predictors of low birth weight, prematurity and intrauterine growth retardation. *European Journal of Clinical Nutrition, 57,* 266-272.

Rosa, A., Picchioni, M. M., Kalidindi, S., Loat, C. S., Knight, J., Toulopoulou, T., … Craig, I. W. (2008). Differential methylation of the X-chromosome is a possible source of discordance for bipolar disorder female monozygotic twins. *American Journal of Medical Genetics, 147B,* 459-462.

Roseboom, T. J., Painter, R. C., de Rooij, S. R., van Abeelen, A. F., Veenendaal, M. V., Osmond, C., & Barker, D. J. (2011). Effects of famine on placental size and efficiency. *Placenta, 32,* 395-399.

Roseboom, T. J., Painter, R. C., van Abeelen, A. F., Veenendaal, M. V., & de Rooij, S. R. (2011). Hungry in the womb: what are the consequences? Lessons from the Dutch famine. *Maturitas, 70,* 141-145.

Roseboom, T. J., van der Meulen, J. H., Ravelli, A. C., van Montfrans, G. A., Osmond, C., Barker, D. J., & Bleker, O. P. (1999). Blood pressure in adults after prenatal exposure to famine. *Journal of Hypertension, 17,* 325-330.

Ruocco, A. C., Amirthavasagam, S., & Zakzanis, K. K. (2012). Amygdala and hippocampal volume reductions as candidate endophenotypes for borderline personality disorder: A meta-analysis of magnetic resonance imaging studies. *Psychiatry Research, 201,* 245-252.

Räikkönen, K., Pesonen, A. K., Heinonen, K., Lahti, J., Kajantie, E., Forsén, T,, … Eriksson, J. G.. (2008). Infant growth and hostility in adult life. *Psychosomatic Medicine, 70,* 306-313.

Räikkönen, K., Pesonen, A. K., Heinonen, K., Kajantie, E., Hovi, P., Järvenpää, A. L., … Andersson, S. (2008). Depression in young adults with very low birth weight: the Helsinki study of very low-birth-weight adults. *Archives of General Psychiatry, 65,* 290-296.

Räikkönen, K., Pesonen, A. K., Kajantie, E., Heinonen, K., Forsén, T., Phillips, D. I., … Eriksson, J. G. (2007). Length of gestation and depressive symptoms at age 60 years. *British Journal of Psychiatry, 190,* 469-474.

Räikkönen, K., Seckl, J. R., Heinonen, K., Pyhälä, R., Feldt, K., Jones, A., Pesonen, A. K., … Kajantie, E. (2010). Maternal prenatal licorice consumption alters hypothalamic-pituitary-adrenocortical axis function in children, *Psychoneuroendocrinology, 35,* 1587-1593.

Räsänen, P., Hakko, H., Isohanni, M., Hodgins, S., Järvelin, M. R., & Tiihonen, J. (1999). Maternal smoking during pregnancy and risk of criminal behavior among adult male offspring in the Northern Finland 1966 Birth Cohort. *American Journal of Psychiatry, 156,* 857-862.

Sabo, R. T., Lu, Z., Daniels, S., & Sun, S. S. (2012). Serial Childhood BMI and Associations With Adult Hypertension and Obesity: The Fels Longitudinal Study. *Obesity, 20,* 1741-1743.

Sabunciyan, S., Aryee, M. J., Irizarry, R. A., Rongione, M., Webster, M. J., Kaufman, W. E., … Consortium G. (2012). Genome-wide DNA methylation scan in major depressive disorder. *PLoS One, 7,* e34451.

Saleptsi, E., Bichescu, D., Rockstroh, B., Neuner, F., Schauer, M., Studer, K., … Elbert, T. (2004). Negative and positive childhood experiences across developmental periods in psychiatric patients with different diagnoses - an explorative study. *BMC Psychiatry, 4,* 40.

Samuel, D. B., & Widiger, T. A. (2008). A meta-analytic review of the relationships between the five-factor model and DSM-IV-TR personality disorders: a facet level analysis. *Clinical Psychology Review, 28,* 1326-1342.

Samuels, J. (2011). Personality disorders: epidemiology and public health issues. *Internatational Review of Psychiatry, 23,* 223-233.

Samuels, J., Eaton, W. W., Bienvenu, O. J. III, Brown, C. H., Costa Jr, P. T., & Nestadt, G. (2002). Prevalence and correlates of personality disorders in a community sample. *British Journal of Psychiatry, 180,* 536-542.

Sandboge, S., Moltchanova, E., Blomstedt, P. A., Salonen, M. K., Kajantie, E., Osmond, C., … Eriksson, J. G. (2012). Birth-weight and resting metabolic rate in adulthood - sex-specific differences. *Annals of Medicine, 44,* 296-303.

Sansone, R. A., & Sansone, L. A. (2011). Personality Disorders: A Nation-based Perspective on Prevalence. *Innovations in Clinical Neuroscience, 8,* 13-18.

Sauvola, A., Koskinen, O., Jokelainen, J., Hakko, H., Järvelin, M. R., & Räsänen, P. (2002). Family type and criminal behaviour of male offspring: the Northern Finland 1966 Birth Cohort Study. *The International Journal of Social Psychiatry, 48,* 115-121.

Schmidt, L. A., Miskovic, V., Boyle, M. H., & Saigal, S. (2008). Shyness and timidity in young adults who were born at extremely low birth weight. *Pediatrics, 122,* e181-e187.

Schmidt, M. V. (2011). Animal models for depression and the mismatch hypothesis of disease. *Psychoneuroendocrinology, 36,* 330-338.

Scott, K. M., Smith, D. R., & Ellis, P. M. (2010). Prospectively ascertained child maltreatment and its association with DSM-IV mental disorders in young adults. *Archives of General Psychiatry, 67,* 712-719.

Shah, P. S. (2010). Parity and low birth weight and preterm birth: a systematic review and meta-analyses *Acta Obstetricia & Gynecologica Scandinavica, 89,* 862-875.

Shenk, C. E., Noll, J. G., Putnam, F. W., & Trickett, P. K. (2010). A prospective examination of the role of childhood sexual abuse and physiological asymmetry in the development of psychopathology. *Child Abuse & Neglect, 34,* 752-761.

Soloff, P., Nutche, J., Goradia, D., & Diwadkar, V. (2008). Structural brain abnormalities in borderline personality disorder: a voxel-based morphometry study. *Psychiatry Research, 164,* 223-236.

Silventoinen, K., Bartels, M., Posthuma, D., Estourgie-van Burk, G. F., Willemsen, G., van Beijsterveldt, T. C., & Boomsma, D. I. (2007). Genetic regulation of growth in height and weight from 3 to 12 years of age: a longitudinal study of Dutch twin children. *Twin Research and Human Genetics, 10,* 354-363.

Silventoinen, K., Pietiläinen, K. H., Tynelius, P., Sørensen, T. I., Kaprio, J., & Rasmussen, F. (2008). Genetic regulation of growth from birth to 18 years of age: the Swedish young male twins study. *American Journal of Human Biology, 20,* 292-298.

Silventoinen, K., Baker, J. L., Sørensen, T. I. (2012). Growth in height in childhood and risk of coronary heart disease in adult men and women. *PLoS One, 7,* e30476.

Silventoinen, K., Karvonen, M., Sugimoto, M., Kaprio, J., Dunkel, L. and Yokoyama, Y. (2011). Genetics of head circumference in infancy: A longitudinal study of Japanese twins. *American Journal of Human Biology, 23,* 630-634.

Sørensen, H. J., Mortensen, E. L., Reinisch, J. M., & Mednick, S. A. (2006). Height, weight and body mass index in early adulthood and risk of schizophrenia. *Acta Psychiatrica Scandinavica, 114,* 49-54.

Sourander, A., Jensen, P., Davies, M., Niemelä, S., Elonheimo, H., Ristkari, T., … Almqvist, F. (2007). Who is at greatest risk of adverse long-term outcomes? The Finnish From a Boy to a Man study. *Journal of the American Academy of Child and Adolescent Psychiatry, 46,* 1148-1161.

Stein, A. D., Zybert, P. A., van de Bor, M., & Lumey, L. H. (2004). Intrauterine famine exposure and body proportions at birth: the Dutch Hunger Winter. *International Journal of Epidemiology, 33,* 831-836.

Stetler, C., & Miller, G. E. (2011). Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. *Psychosomatic Medicine, 73,* 114-126.

Strang-Karlsson, S., Räikkönen, K., Pesonen, A. K., Kajantie, E., Paavonen, E. J., Lahti, J., … Andersson, S. (2008). Very low birth weight and behavioral symptoms of attention deficit hyperactivity disorder in young adulthood: the Helsinki study of very-low-birth-weight adults. *American Journal of Psychiatry, 165,* 1345-1353.

Sumich, A. L., Sarkar, S., Hermens, D. F., Ibrahimovic, A., Kelesidi, K., Wilson, D., & Rubia, K. (2012). Sex differences in brain maturation as measured using event-related potentials. *Developmental Neuropsychology, 37,* 415-433.

Svrakic, D. M., Draganic, S., Hill, K., Bayon, C., Przybeck, T. R., & Cloninger, C. R. (2002). Temperament, character, and personality disorders: etiologic, diagnostic, treatment issues. *Acta Psychiatrica Scandinavica, 106,* 189-195.

Tadić, A., Elsässer, A., Storm, N., Baade, U., Wagner, S., Başkaya, O., … Dahmen, N. (2010). Association analysis between gene variants of the tyrosine hydroxylase and the serotonin transporter in borderline personality disorder. *World Journal of Biological Psychiatry, 11,* 45-58.

Tadić, A., Victor, A., Başkaya, O., von Cube, R., Hoch, J., Kouti, I., … Dahmen N. (2009). Interaction between gene variants of the serotonin transporter promoter region (5-HTTLPR) and catechol O-methyltransferase (COMT) in borderline personality disorder. *American Journal of Medical Genetics, 150B,* 487-495.

Taylor, A., & Kim-Cohen, J. (2007). Meta-analysis of gene-environment interactions in developmental psychopathology. *Developmental Psychopathology, 19,* 1029-1037.

Teicher, M. H., Anderson, C. M., & Polcari, A. (2012) Childhood maltreatment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum. *Proceedings of the National Academy of Sciences of the United States of America, 109,* E563-E572.

Thomas, K., Harrison, G., Zammit, S., Lewis, G., Horwood, J., Heron, J., … Gunnell, D. (2009). Association of measures of fetal and childhood growth with non-clinical psychotic symptoms in 12-year-olds: the ALSPAC cohort. *British Journal of Psychiatry, 194,* 521-526.

Thompson, C., Syddall, H., Rodin, I., Osmond, C., & Barker, D. J. (2001). Birth weight and the risk of depressive disorder in late life. *British Journal of Psychiatry, 179,* 450-455.

Tidemalm, D., Elofsson, S., Stefansson, C. G., Waern, M., & Runeson, B. (2005). Predictors of suicide in a community-based cohort of individuals with severe mental disorder. *Social Psychiatry and Psychiatric Epidemiology, 40,* 595-600.

Tidemalm, D., Waern, M., Stefansson, C. G., Elofsson, S., & Runeson, B. (2008). Excess mortality in persons with severe mental disorder in Sweden: a cohort study of 12 103 individuals with and without contact with psychiatric services. *Clinical Practice and Epidemiology in Mental Health, 4,* 23.

Tieman, W., van der Ende, J., & Verhulst, F. C. (2005). Psychiatric disorders in young adult intercountry adoptees: an epidemiological study. *American Journal of Psychiatry, 162,* 592-598.

Tijsseling, D., Wijnberger, L. D., Derks, J. B., van Velthoven, C. T., de Vries, W. B., van Bel, F., … Visser, G. H. (2012). Effects of antenatal glucocorticoid therapy on hippocampal histology of preterm infants. *PloS One, 7,* e33369.

Torgersen, S., Czajkowski, N., Jacobson, K., Reichborn-Kjennerud, T., Røysamb, E., Neale, M. C., & Kendler, K. S. (2008). Dimensional representations of DSM-IV cluster B personality disorders in a population-based sample of Norwegian twins: a multivariate study. *Psychological Medicine, 38,* 1617-1625.

Torgersen, S., Kringlen, E., & Cramer, V. (2001) The prevalence of personality disorders in a community sample. *Archives of General Psychiatry, 58,* 590-596.

Torgersen, S., Lygren, S., Oien, P. A., Skre, I., Onstad, S., Edvardsen, J.,… Kringlen, E. (2000). A twin study of personality disorders. *Comprehensive Psychiatry, 41,* 416-425.

Torrey, E. F., Buka, S., Cannon, T. D., Goldstein, J. M.., Seidman, L. J., Liu, T., … Yolken, R. H. (2009). Paternal age as a risk factor for schizophrenia: how important is it? *Schizophrenia Research, 114,* 1-5.

Trull, T. J. (2001a). Relationships of borderline features to parental mental illness, childhood abuse, Axis I disorder, and current functioning. *Journal of Personality Disorders, 15,* 19-32.

Trull, T. J. (2001b). Structural relations between borderline personality disorder features and putative etiological correlates. *Journal of Abnormal Psychology, 110,* 471-481.

Tuovinen S., Eriksson, J. G., Kajantie, E., Lahti, J., Pesonen, A. K., Heinonen, K., … Räikkönen, K. (in press). Maternal hypertensive disorders during pregnancy and self-reported cognitive impairment of the offspring seventy years later: The Helsinki Birth Cohort Study. *American Journal of Obstetrics and Gynecology.*

Tuovinen, S., Räikkönen, K., Pesonen, A. K., Lahti, M., Heinonen, K., Wahlbeck, K., … Eriksson, J. G. (2012). Hypertensive disorders in pregnancy and risk of severe mental disorders in the offspring in adulthood: the Helsinki Birth Cohort Study. *Journal of Psychiatric Research, 46,* 303-310.

Tyrka, A. R., Price, L. H., Marsit, C., Walters, O. C., & Carpenter, L. L. (2012). Childhood adversity and epigenetic modulation of the leukocyte glucocorticoid receptor: preliminary findings in healthy adults. *PLoS One, 7,* e30148.

Tyrka, A. R., Wier, L., Price, L. H., Ross, N., Anderson, G. M., Wilkinson, C. W., & Carpenter, L. L. (2008). Childhood parental loss and adult hypothalamic-pituitary-adrenal function. *Biological Psychiatry, 63,* 1147-1154.

Uematsu, A., Matsui, M., Tanaka, C., Takahashi, T., Noguchi, K., Suzuki, M., & Nishijo, H. (2012). Developmental trajectories of amygdala and hippocampus from infancy to early adulthood in healthy individuals. *PLoS One, 7,* e46970.

Ulijaszek, S. J. (2006). The international growth standard for children and adolescents project: environmental influences on preadolescent and adolescent growth in weight and height. *Food and Nutrition Bulletin, 27,* S279-S294.

van Abeelen, A. F., de Rooij, S. R., Osmond, C., Painter, R. C., Veenendaal, M. V., Bossuyt, P. M., … Roseboom, T. J. (2011). The sex-specific effects of famine on the association between placental size and later hypertension. *Placenta, 32,* 694-698.

van Hasselt, F. N., Cornelisse, S., Zhang, T. Y., Meaney, M. J., Velzing, E. H., Krugers, H. J., & Joëls, M. (2012). Adult hippocampal glucocorticoid receptor expression and dentate synaptic plasticity correlate with maternal care received by individuals early in life. *Hippocampus, 22,* 255-266.

Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., … Bentall, R. P. (2012). Childhood Adversities Increase the Risk of Psychosis: A Meta-analysis of Patient-Control, Prospective- and Cross-sectional Cohort Studies. *Schizophrenia Bulletin, 38,* 661-671.

Vasiliadis, H. M., Buka, S. L., Martin, L. T., & Gilman, S. E. (2010). Fetal growth and the lifetime risk of generalized anxiety disorder. *Depression and Anxiety, 27,* 1066-1072.

Vasiliadis, H. M., Gilman, S. E., & Buka, S. L. (2008). Fetal growth restriction and the development of major depression. *Acta Psychiatrica Scandinavica, 117,* 306-312.

Veijola, J., Mäki, P., Joukamaa, M., Läärä, E., Hakko, H., & Isohanni, M. (2004). Parental separation at birth and depression in adulthood: a long-term follow-up of the Finnish Christmas Seal Home Children. *Psychological Medicine, 34,* 357-362.

Veijola, J., Läärä, E., Joukamaa, M., Isohanni, M., Hakko, H., Haapea, M., … Mäki, P. (2008). Temporary parental separation at birth and substance use disorder in adulthood. A long-term follow-up of the Finnish Christmas Seal Home Children. *Social Psychiatry and Psychiatric Epidemiology, 43,* 11-17.

Veldhuis, J. D., Roemmich, J. N., Richmond, E. J., Rogol, A. D., Lovejoy, J. C., Sheffield-Moore, M., … Bowers, C. Y. (2005). Endocrine control of body composition in infancy, childhood, and puberty. *Endocrine Reviews, 26,* 114-146.

Venables, P. H. (1996). Schizotypy and maternal exposure to influenza and to cold temperature: the Mauritius study. *Journal of Abnormal Psychology, 105,* 53-60.

Vieau, D., Sebaai, N., Léonhardt, M., Dutriez-Casteloot, I., Molendi-Coste, O., Laborie, C., … Lesage, J. (2007). HPA axis programming by maternal undernutrition in the male rat offspring. *Psychoneuroendocrinology, 32,* S16-S20.

Wahlbeck, K., Forsén, T., Osmond, C., Barker, D. J., & Eriksson, J. G. (2001). Association of schizophrenia with low maternal body mass index, small size at birth, and thinness during childhood. *Archives of General Psychiatry, 58,* 48-52.

Wang, X. D., Labermaier, C., Holsboer, F., Wurst, W., Deussing, J. M., Müller, M. B., & Schmidt, M. V. (2012). Early-life stress-induced anxiety-related behavior in adult mice partially requires forebrain corticotropin-releasing hormone receptor 1. *The European Journal of Neuroscience, 36,* 2360-2367.

Walker, S. P., Chang, S. M., Vera-Hernández, M., & Grantham-McGregor, S. (2011). Early childhood stimulation benefits adult competence and reduces violent behavior. *Pediatrics, 127,* 849-857.

Weaver, I. C., Cervoni, N., Champagne, F. A., D'Alessio, A. C., Sharma, S., Seckl, J. R., & Meaney, M. J. (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience, 7,* 847-854.

Weaver, T. L., & Clum, G. A. (1993). Early family environments and traumatic experiences associated with borderline personality disorder. *Journal of Consulting and Clinical Psychology, 61,* 1068-1075.

Weaver, I. C., Meaney, M. J., & Szyf, M. (2006). Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood. *Proceedings of the National Academy of Sciences of the United States of America, 103,* 3480-3485.

Wegelius, A., Tuulio-Henriksson, A., Pankakoski, M., Haukka, J., Lehto, U., Paunio, T., … Suvisaari, J. (2011). An association between high birth weight and schizophrenia in a Finnish schizophrenia family study sample. *Psychiatry Research, 190,* 181-186.

Welham, J., Scott, J., Williams, G., Najman, J., O'Callaghan, M., & McGrath, J. (2009). Growth in young adults who screen positive for non-affective psychosis: birth cohort study. *The Australian and New Zealand Journal of Psychiatry, 43,* 61-67.

Wenstrom, K. D., Andrews, W. W., Hauth, J. C., Goldenberg, R. L., DuBard, M. B., & Cliver, S. P. (1998). Elevated second-trimester amniotic fluid interleukin-6 levels predict preterm delivery. *American Journal of Obstetrics and Gynecology, 178,* 546-550.

Westen, D., Nakash, O., Thomas, C., & Bradley, R. (2006). Clinical assessment of attachment patterns and personality disorder in adolescents and adults. *Journal of Consulting and Clinical Psychology, 74,* 1065-1085.

Westrupp, E. M., Northam, E., Doyle, L. W., Callanan, C., & Anderson, P. J. (2011). Adult psychiatric outcomes of very low birth weight survivors. *The Australian and New Zealand Journal of Psychiatry, 45,* 1069-1077.

Whincup, P. H., Kaye, S. J., Owen, C. G., Huxley, R., Cook, D. G., Anazawa, S., … Yarbrough, D. E. (2008). Birth weight and risk of type 2 diabetes: a systematic review. *The Journal of the American Medical Association, 300,* 2886-2897.

Widom, C. S., Czaja, S. J., & Paris, J. (2009). A prospective investigation of borderline personality disorder in abused and neglected children followed up into adulthood. *Journal of Personality Disorders, 23,* 433-446.

Wilson, S., & Durbin, C. E. (2012). Parental personality disorder symptoms are associated with dysfunctional parent-child interactions during early childhood: A multilevel modeling analysis. *Personality Disorders, 3,* 55-65.

Wilson, S. T., Stanley, B., Brent, D. A., Oquendo, M. A., Huang, Y. Y., Haghighi, F., … Mann, J. J. (2012). Interaction between tryptophan hydroxylase I polymorphisms and childhood abuse is associated with increased risk for borderline personality disorder in adulthood. *Psychiatric Genetics, 22, 15-24.*

Wilson, S. T., Stanley, B., Brent, D. A., Oquendo, M. A., Huang, Y. Y., & Mann, J. J. (2009). Thetryptophan hydroxylase I A218C polymorphism is associated with diagnosis, but not suicidal behavior, in borderline personality disorder. *American Journal of Medical Genetics, 150B,* 202-207.

Winsper, C., Zanarini, M., & Wolke, D. (2012). Prospective study of family adversity and maladaptive parenting in childhood and borderline personality disorder symptoms in a non-clinical population at 11 years. *Psychological Medicine.* Advance online Publication. doi: 10.1017/S0033291712000542

Wolf, R. C., Thomann, P. A., Sambataro, F., Vasic, N., Schmid, M., & Wolf, N. D. (2012). Orbitofrontal cortex and impulsivity in borderline personality disorder: an MRI study of baseline brain perfusion. *European Archives of Psychiatry and Clinical Neuroscience.* Advance Online Publication. doi: 10.1007/s00406-012-0303-1

Workel, J. O., Oitzl, M. S., Fluttert, M., Lesscher, H., Karssen, A., & de Kloet, E. R. (2001). Differential and age-dependent effects of maternal deprivation on the hypothalamic-pituitary-adrenal axis of brown norway rats from youth to senescence. *Journal of Neuroendocrinology, 13,* 569-580.

World Health Organization. (1992). *International classification of diseases (ICD-10).* Geneva: World Health Organization.

Woodward, L., Fergusson, D. M., & Belsky, J. (2000). Timing of Parental Separation and Attachment to Parents in Adolescence: Results of a Prospective Study from Birth to Age 16. *Journal of Marriage and Family, 62,* 162-174.

Wyrwoll, C. S., Holmes, M. C., & Seckl, J. R. (2011). 11β-hydroxysteroid dehydrogenases and the brain: from zero to hero, a decade of progress. *Frontiers in Neuroendocrinology, 32,* 265-286.

Xiong, X., Harville, E. W., Mattison, D. R., Elkind-Hirsch, K., Pridjian, G., & Buekens, P. (2008). Exposure to Hurricane Katrina, post-traumatic stress disorder and birth outcomes. *The American Journal of Medical Sciences, 336,* 111-115.

Yang, M., Coid, J., & Tyrer, P. (2010). Personality pathology recorded by severity: national survey. *British Journal of Psychiatry, 197,* 193-199.

Yehuda, R., Bierer, L. M., Andrew, R., Schmeidler, J., & Seckl, J. R. (2009). Enduring effects of severe developmental adversity, including nutritional deprivation, on cortisol metabolism in aging Holocaust survivors. *Journal of Psychiatric Research, 43,* 877-883.

Young, R., Riordan, V., & Stark, C. (2011). Perinatal and psychosocial circumstances associated with risk of attempted suicide, non-suicidal self-injury and psychiatric service use. A longitudinal study of young people. *BMC Public Health, 11,* 875.

Zaboli, G., Gizatullin, R., Nilsonne, A., Wilczek, A., Jönsson, E. G., Ahnemark, E., … Leopardi, R. (2006). Tryptophan hydroxylase-1 gene variants associate with a group of suicidal borderline women. *Neuropsychopharmacology, 31,* 1982-1990.

Zanarini, M. C., Frankenburg, F. R., Hennen, J., Reich, D. B., & Silk, K. R. (2006). Prediction of the 10-year course of borderline personality disorder. *American Journal of Psychiatry, 163,* 827-832.

Zhang, T. Y., Hellstrom, I. C., Bagot, R. C., Wen, X., Diorio, J., & Meaney, M. J. (2010). Maternal care and DNA methylation of a glutamic acid decarboxylase 1 promoter in rat hippocampus. *The Journal of Neuroscience, 30,* 13130-13137.

Zimmerman, D. J., & Choi-Kain, L. W. (2009). The hypothalamic-pituitary-adrenal axis in borderline personality disorder: a review. *Harvard Review of Psychiatry, 17,* 167-183.

Zimmerman, M., Chelminski, I., Young, D., Dalrymple, K., Martinez, J., & Morgan, T. A. (2012). Which DSM-IV personality disorders are most strongly associated with indices of psychosocial morbidity in psychiatric outpatients? *Comprehensive Psychiatry, 53,* 940-945.