PARENTAL SEPARATION AT BIRTH AND MATERNAL DEPRESSED MOOD IN PREGNANCY: ASSOCIATIONS WITH SCHIZOPHRENIA AND CRIMINALITY IN THE OFFSPRING

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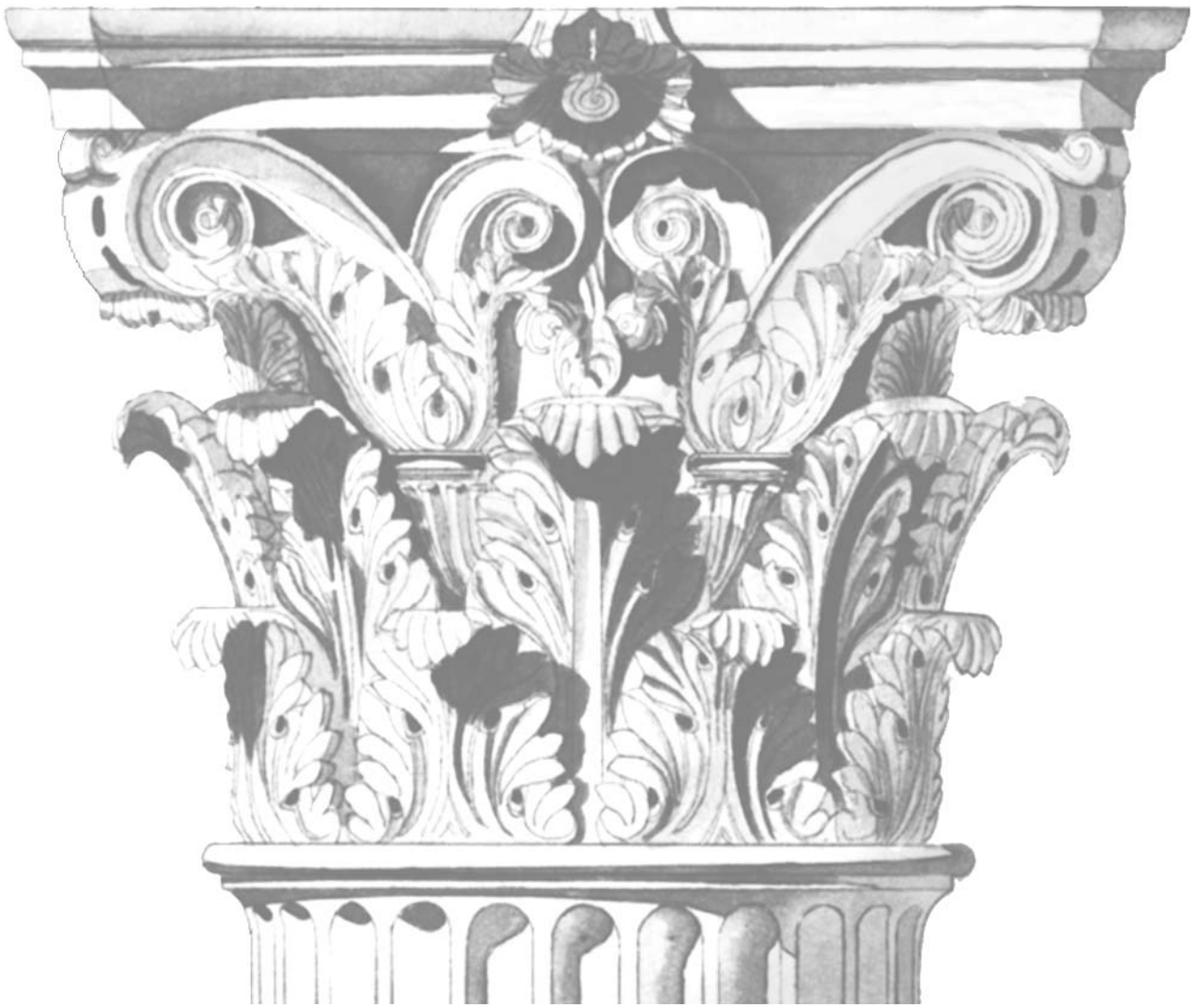
Abstract in Finnish



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Academic Dissertation to be presented with the assent of the Faculty of Medicine, University of Oulu, for public discussion in the Väinö Pääkkönen Hall of the Department of Psychiatry, Peltolantie 5, on September 26th, 2003, at 12 noon.

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Oulu, Finland
2003

Abstract

Early risk factors of the antenatal period and infancy have been increasingly linked to psychiatric disorders. The aim of this thesis was to study the associations between very early parental separation and maternal depressed mood in pregnancy on the other hand, and schizophrenia and criminality in the offspring in adolescence and adulthood, on the other, in two data sets.

In the Christmas Seal Home Children Study the index cohort consisted of 3 020 subjects born in Finland in 1945–65 who were temporarily isolated from their family immediately after birth to nursing homes, the Christmas Seal Homes, due to tuberculosis in the family. The average separation time was seven months. For every index subject, two reference subjects were matched for sex, year of birth and place of birth. Data were obtained on schizophrenia from the Finnish Hospital Discharge Register (FHDR) in 1971–98 and on criminal offences from Statistics Finland in 1977–98. The 28-year cumulative incidence of schizophrenia was 1.6% both in the index cohort and in the reference cohort (RR 1.0; 95% CI 0.8–1.4). Both male and female index subjects had committed crimes more commonly than the reference subjects (in men RR 1.3; 95% CI 1.2–1.4; in women RR 1.5; 1.2–2.0). Of the male index subjects 12.1% as compared with only 7.1% of the reference cohort had committed violent offences (RR 1.7; 1.4–2.1).

In the Northern Finland 1966 Birth Cohort mothers of 12 058 babies were asked at mid-gestation at the antenatal clinic if they felt depressed. This general population birth cohort of the children was followed up for 31 years being record-linked with the FHDR covering the years 1982–97 and with the criminal register of the Ministry of Justice up to 1998. We divided the schizophrenia patients into those having a psychotic first-degree relative (schizophrenia patients with familial risk for psychosis FR) and those without one. The cumulative incidence of hospital-treated schizophrenia was 1.3% among the offspring of depressed mothers and 0.9% among the descendants of non-depressed mothers (RR 1.5; 95% CI 0.9–2.4). The prevalence of antenatal depression was 35% in mothers of schizophrenia patients with FR. The respective prevalence was 14% both in the mothers of schizophrenia patients without FR and in the mothers of other cohort members. Both male and female offspring of antenatally depressed mothers were more commonly criminal offenders than offspring of non-depressed mothers (in men adjusted OR 1.5; 95% CI 1.2–1.9; in women OR 1.5; 0.8–3.0). In males, 6.5% with depressed mothers and 3.2% with non-depressed mothers had committed violent offences (adjusted OR 1.6; 1.1–2.4).

Very early separation and mothers' depressed mood in pregnancy are per se unlikely to increase the risk for schizophrenia in the offspring, but seem to be connected to criminal behaviour, especially violent criminality in men.

Keywords: antenatal depression, Christmas Seal Home, crime, early separation, follow-up studies, maternal depression, maternal deprivation, mother-child relations, Northern Finland 1966 Birth Cohort, pregnancy, schizophrenia

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2003
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Tiivistelmä

Raskaus- ja imeväisajan varhaiset tekijät on lisääntyvästi yhdistetty lapsen tuleviin mielenterveyshäiriöihin. Tarkoituksena oli tutkia hyvin varhaisen eron (separaation) ja äidin raskaudenaikaisen masentuneen mielialan yhteyttä lasten skitsofreniaan ja rikollisuuteen nuoruudessa ja aikuisuudessa kahdessa eri aineistossa.

Joulumerkkikoti-lasten tutkimuksessa indeksikohortti koostui 1945–65 syntyneistä 3 020 tutkittavasta, jotka erotettiin väliaikaisesti perheistään heti syntymän jälkeen hoitokoteihin, Joulumerkkikoteihin, perheen tuberkuloosin takia. Ero vanhemmista kesti keskimäärin seitsemän kuukautta. Jokaiselle indeksitutkittavalle valittiin kaksi sukupuolen, syntymävuoden ja -paikan mukaan kaltaistettua verrokkitutkittavaa. Tieto skitsofreniaan sairastumisesta hankittiin sairaaloiden poistoilmoitusrekisteristä vv. 1971–98 ja rikoksista Tilastokeskuksesta 1977–98. 28 vuoden kumulatiivinen sairastuvuus skitsofreniaan oli 1,6 % sekä indeksi- että verrokkikohortilla (riskisuhde RR 1.0; 95 %:n luottamusväli CI 0,8–1,4). Sekä miehistä että naisista indeksitutkittavat olivat tehneet useammin rikoksia kuin vertailuryhmä (miehillä RR 1,3; 1,2–1,4; naisilla RR 1,5; 1,2–2,0). Miehistä 12,1 % indeksitutkittavista ja vain 7,1 % vertailuryhmästä oli tehnyt väkivaltarikoksen (RR 1,7; 1,4–2,1).

Pohjois-Suomen 1966 syntymäkohortin 12 058 lapsen äideiltä kysyttiin keskiraskauden aikana äitiysneuvolassa, kokivatko he mielialansa masentuneeksi. Tämän väestötason syntymäkohortin (siis lasten) tietoja hankittiin 31-vuotisseurannassa sairaaloiden poistoilmoitusrekisteristä vuosilta 1982–97 ja oikeusministeriön rikosrekisteristä vuoteen 1998. Skitsofreniaan sairastuneet jaettiin niihin, joiden 1. asteen sukulainen oli ollut / ei ollut ollut psykoottinen. Sairaalahoitoa vaatineen skitsofrenian kumulatiivinen sairastuvuus oli 1,3 % masentuneiden ja 0,9 % masentumattomien äitien lapsilla (RR 1,5; 0,9–2,4). Raskaudenaikaisen masentuneen mielialan esiintyvyys oli 35 % niiden skitsofreniapotilaiden äideillä, joilla oli ollut lähisuvussa psykoosia. Vastaavasti masentunutta mielialaa esiintyi 14 %:lla sekä niiden skitsofrenia-potilaiden äideistä, joilla ei ollut sukurasitusta, että muiden kohorttitutkittavien äideistä. Sekä masentuneiden äitien pojista että tyttäristä useampi oli tehnyt rikoksen kuin masentumattomien äitien lapset (miehillä vakioitu vedonlyöntisuhde OR 1,5; 1,2–1,9; naisilla OR 1,5; 0,8–3,0). Masentuneiden äitien pojista 6,5 % ja masentumattomien äitien pojista 3,2 % oli tehnyt väkivaltarikoksen (vakioitu OR 1,6; 1,1–2,4).

Hyvin varhainen ero ja äidin masentunut mieliala raskauden aikana eivät todennäköisesti sinänsä lisää skitsofrenian vaaraa lapsilla, mutta näyttävät olevan yhteydessä lasten rikolliseen käyttäytymiseen, erityisesti väkivaltarikoksiin miehillä.

Asiasanat: Joulumerkkikoti, Pohjois-Suomen 1966 syntymäkohortti, raskaudenaikainen masennus, raskaus, rikollisuus, seurantatutkimus, skitsofrenia, varhainen ero, varhainen separaatio, äidin masentuneisuus, äiti-lapsi suhde

Children in a Finnish Christmas Seal Home. (The photograph is from the book edited by Tamminen (1982) with permission maintained from the Finnish Lung Health Association.)

Pium, paum, kehto heilahtaa
Lapsi viatonna nukahtaa.
Pium, paum, onni häilyvää,
se suopi iloa ja ikävää.
(Finnish lullaby)

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This study was carried out jointly at the Department of Psychiatry, University of Oulu, and as part of the Northern Finland 1966 Birth Cohort Study at the Department of Public Health Science and General Practice, University of Oulu.

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Oulu, 19 August 2003 Pirjo Mäki

Abbreviations

BCG	Bacille Calmette-Guérin
BDI	Beck Depression Inventory Scale
DACL	Depression Adjective Checklist
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised
EPDS	Edinburgh Postnatal Depression Scale
FHDR	Finnish Hospital Discharge Register
FIGS	Family Interview for Genetic Studies
FR	Familial risk
GHQ	The General Health Questionnaire
HDRS	Hamilton Depression Rating Scale
HPA	Hypothalamic-pituitary-adrenal
ICD-8	Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death, Eighth Revision
ICD-9	Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death, Ninth Revision
ICD-10	Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death, Tenth Revision
MMPI	Minnesota Multiphasic Personality Inventory
McLean-Hakstian	McLean-Hakstian Depression Scale
OR	Odds Ratio
PSS	Perceived Stress Scale
RDC	Research Diagnostic Criteria
RR	Rate Ratio (or estimated Relative Risk)
SADS	Schedule of Affective Disorders and Schizophrenia
SCL-90-R	Symptoms Checklist-90-Revised
SES	Socio-economic status
Zung's SDS	Zung's Self-Rating Depression Scale
95%CI	95-percentage Confidence Interval

List of original papers

The present thesis is based on the following original papers, which will be referred to in the text by the Roman numerals I-IV.

I 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(1): 13-19.

II Mäki P, Hakko H, Joukamaa M, Läärä E, Isohanni M & Veijola J (2003) Parental separation at birth and criminality in adulthood – the Finnish Christmas Seal Home Children Study. Social Psychiatry and Psychiatric Epidemiology, 38(7): 354-359.

III Mäki P, Veijola J, Rantakallio P, Jokelainen J, Jones P B & Isohanni M. Schizophrenia in the offspring of antenatally depressed mothers – a 31 year follow-up of the Northern Finland 1966 Birth Cohort. Schizophrenia Research, in press.

IV 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(3): 273-278.

In addition, some unpublished data have been included in this thesis. The originals papers (I-IV) are printed with the permission of the copyright holders.

Contents

1 Introduction

Early risk factors of the antenatal period and infancy have been linked to diseases and subsequently to psychiatric disorders. Problems in the early caretaker-infant relation pose a risk factor for disadvantages later on in life in the offspring (Bowlby 1981, Sameroff 1998, Belsky 1999, Nemeroff 1999, Rutter *et al.* 1999, Fonagy 2001). Deprivation of childhood family has been found to be associated with an increased risk for later criminality (McCord 1979, Kolvin *et al.* 1988a).

Bowlby (1978, 1981) emphasized the effects of loss on psychiatric disorders. Rutter (1973) has underlined the importance of the quality of deprivation and its consequences in child care, as well as the nature of separation and its effects on bonds with parents. There is also an extensive literature based on animal experiments that link early isolation to abnormal neurodevelopment (Kehoe *et al.* 1998, Williams *et al*. 1999, Barr *et al.* 2001).

The association between early separation and adult psychopathology has been investigated in a number of studies, especially concerning depression. There are fewer studies examining schizophrenia (Granville-Grossman 1966, Huttunen & Niskanen 1978, Watt & Nicholi 1979, Ingraham *et al.* 1995, Furukawa *et al.* 1998, Agid *et al.* 1999) and criminality (Weininger 1972, Huttunen & Niskanen 1978, Kolvin *et al.* 1988a, Virkkunen *et al.* 1996, Tardiff 2000) in the offspring with early separation. Studies of very early separation in the first year of life and its connection to adolescent and adult psychopathology are scarce.

In the past few years there has been growing interest towards maternal depression in pregnancy, which has been found to be common (Evans *et al.* 2001). There have been studies connecting early risk factors of antenatal period to diseases (Barker 1992 and 1994) and subsequently to psychiatric disorders (Cannon & Murray 1998). Studies based on animal experiments have connected antenatal stress to abnormal neurodevelopment (Schneider *et al.* 1998, Williams *et al.* 1999). Prenatal depression has been found to be a risk factor for postpartum depression (Wilson *et al.* 1996). Postpartum depression has been associated with mental distress of the offspring in childhood (Gizynski 1985, Murray *et al.* 1991, Philipps & O'Hara 1991, Mowbray *et al.* 1995, Murray & Cooper 1997a).

Still, studies investigating psychopathology of the offspring of antenatally depressed mothers are so far very limited. There have been two studies with follow-up to childhood and controversial results examining children of antenatally depressed mothers. Prenatal depressive symptoms screened with the Edinburgh Postnatal Depression Scale EPDS have been strongly linked to high externalizing problems and problems in general in the 8 and 9-year-old offspring (Luoma *et al.* 2001). On the other hand, in another study antenatal depression was not found to increase risk for behavioural and emotional problems of 4-year-old children (O'Connor *et al.* 2002).

Both schizophrenia (Räsänen *et al.* 1999b, Häfner 2003) and criminal behaviour (Rutter & Giller 1983, Pulkkinen 1988) usually begin to occur in adolescence and early adulthood. In this study schizophrenia and criminality were chosen to be the outcomes indicating if very early separation and maternal depressed mood in pregnancy might be acting as risk factors for problems in adolescence and adulthood in the offspring.

Two data sets were used in this study: The Finnish Christmas Seal Home Children Study concerning offspring with parental separation at birth and the Northern Finland 1966 Birth Cohort studying offspring of antenatally depressed mothers. The Finnish Christmas Seal Home Children were separated temporarily from their families at birth to remove them from the risk of tuberculosis during their first year of life. The Northern Finland 1966 Birth Cohort Study is a prospective project with mothers interviewed while pregnant in 1965-1966. In this thesis the associations of parental separation at birth (in the Finnish Christmas Seal Home Children Study) and maternal antenatal depressed mood (in the Northern Finland 1966 Birth Cohort) with risk of schizophrenia and criminal behaviour were explored in 30 and 40-year follow-ups.

2 Review of the literature

2.1 Separation in childhood

2.1.1 Different separations

Early separation can be defined as an emotional experience in which the child is physically separated from the most important object, i.e. mainly the mother (Mahler *et al.* 1975, Mangs & Martell 1995). The term separation has been used also to indicate separation from the parents due to the child's or parents' hospitalization or institutionalization, parental divorce or death (i.e. loss) or illness, child's adoption from the family, or a stressful family atmosphere with disagreement. In the past, separation has been also called maternal deprivation, a term that is too heterogeneous (Rutter 1973), both for the experiences and for the effects (Wolkind & Rutter 1985). Rutter (1973, 1989) has emphasized that the significant factor may not be the separation itself, but rather its consequences. The consequences depend on the quality of separation: the age of the child, the permanency of separation, and whether separation was due to parental divorce, parental death or other reasons.

The studies concerning childhood separation experiences have been rather varied and fragmentary (Räsänen 1988, Sauvola 2001). Generally in studies of the association between early separation and later psychiatric disorder, neither the child's age at the time of separation, nor the length of separation have been defined very strictly. In many studies, the child's age at the time of separation has varied, being defined as about age under 16 years: for example under 12 years, or between 12 to 18 years (in the study of Ragan & McGlashan 1986), under 15 years (Hopkinson & Reed 1966), between 1-15 years (Räsänen 1988), or under 16 years (Granville-Grossman 1966, Veijola 1996, Zahner & Murphy 1989), until the mean age of 15.9 years (Aro & Palosaari 1992), under 17 years (Kendler *et al.* 1992a, Harris *et al.* 1986, O'Neil *et al.* 1987) or under 18 years (Rodgers 1994), or between 2 to 17 years (Breier *et al.* 1988). On the other hand, Rutter (2003) has suggested that adverse psychological effects seem to be more infrequent in the

children with separations during the early infancy period and, again, during the school-age years, and maximal during the toddler period, maybe reflecting the role of selective social attachments.

There have been hardly any epidemiological studies concerning separation in the first year of life and its long-term consequences up to adolescence and adulthood. In a Finnish adoption study, infants adopted in their first year of life were followed up to adolescence and early adulthood (Lahti 1991). Heston *et al.* (1966) studied psychopathology in 47 adults separated after their birth until 24.7 months (mean age) in institutions.

Occurrence of separation In the last decades, due to divorce and single parenthood, the number of single-parent families has increased in most countries in Europe (Hess 1995, Targosz *et al.* 2003). Also in Finland the rates of single-mother or single-father families with 0-17 year-old children have increased: their respective proportions of the total number of families with children in 1985 were 9% and 1%, and in 2001 15% and 2% (Statistics Finland 2003). On the other hand, parental deaths have declined (Roos 1987). In two Finnish psychiatric studies childhood separations from parents were rather common (Aro & Palosaari 1992, Veijola 1998b), about one fifth to one fourth of the population studied. According to Statistics Finland (2003) in 2001, 10% of infants less than 1 year old lived in single-parent families, mainly with their mother, whereas about 20% of 17-year-old adolescents lived in families headed by a lone parent.

2.1.2 Mental health in the offspring with early parental separation

Early separation can be seen as an exposure, i.e. a risk factor for later life in the offspring (Kraemer *et al.* 1997). Quite a few studies have focused on the effects of childhood separation on later depression. The results of these studies have been somewhat variable. Some studies have shown that childhood separation is a risk for later depression (Sethi 1964, Brown & Harris 1978, Lloyd 1980, Bowlby 1981, Kennard & Birtchnell 1982, Roy 1985, O'Neil *et al.* 1987), while others have reported an unclear connection between childhood separation and depression in adulthood (Abrahams & Whitlock 1969, Hällström 1986, Zahner & Murphy 1989, Kendler *et al.* 1992b). Depression in young adulthood (age 22 years) has been found to be slightly more common among children from divorced families (Aro & Palosaari 1992).

In some studies early separation has not been found to be connected to adult psychopathology (Heston *et al.* 1966, Ragan & McGlashan 1986). Also Breier *et al.* (1988) found no association between type of early separation and psychopathology, but they did observe an important connection between poorer home conditions after the loss and mental disorders. Rushton and Minnis (2003) concluded in their review that even though levels of emotional and behavioural problems are increased in children in foster care, many ex-foster care adults do not have psychological or social problems. Quinton *et al.* (1984) found women reared in institutions having an increased rate of poor psychosocial functioning and of severe parenting difficulties in adult life. Nevertheless, the support of a spouse and of good living conditions in adult life was found to provide a powerful protective effect (Quinton *et al.* 1984). In other studies early separation has

been associated with anxiety disorders (Faravelli *et al.* 1985, Zahner & Murphy 1989, Kendler *et al.* 1992a), and with alcoholism (Cederblad *et al.* 1988, Mäkikyrö *et al.* 1998) and (mainly antisocial) personality disorders (Cederblad *et al.* 1988, Gelder *et al.* 1989).

Among children who were adopted into families in the United Kingdom from Romania, with former institutionalization and severe deprivation, a close association was found between duration of deprivation and severity of attachment disorder behaviours in longitudinal data at ages 4 (O'Connor *et al.* 1999) and 6 years (O'Connor *et al.* 2000). Those children from Romania with autistic features tended to differ from the other Romanian adoptees with respect to a greater degree of cognitive impairment and a longer duration of severe psychological privation (Rutter *et al.* 1999).

In a longitudinal study of Romanian adoptees in Canada improvements were noted in growth and development once the children were placed in a nurturing environment (Benoit et al. 1996). The majority of those Romanian children who had been 6 months or younger at adoption, and who had been likely to have been adopted from their birth home, demonstrated normal growth, development, and behaviour initially and at follow-up. However, those children adopted at older ages were more likely to demonstrate continuing growth, developmental, and/or behavioural deficits (Benoit et al. 1996).

In Finland, 379 war children sent to Sweden at the age of 1-15 years, were not found to have a significant excess of hospital-treated psychiatric disorders, but had more self-reported psychological symptoms than their comparison group (Räsänen 1988). In another Finnish study, children adopted at the age of 3-8 months were reported to have more mental disturbances and schizoid, schizotypal and borderline features in adolescence than the children adopted before the age of 2 months and also after 8 months (Lahti 1991).

Crittenden (1992) observed that in a so-called Strange Situation (with short-term separation and reunion), neglected children were cooperative in play with the mother, but anxious under stress and aggressive with siblings, whereas adequately reared children were cooperative with both their mothers and siblings and secure under stress. Early, extensive, and continuous nonmaternal care has been associated with less harmonious parent-child relations and elevated levels of aggression and non-compliance (Belsky 2001).

Infants and also toddlers respond to separation with vigorous protest. If by crying they cannot restore the adult, the protest eventually changes to despair and eventually possibly to pathological states of detachment and indifference (Black 1998).

In the study by Weyerer *et al.* (1987), the relative risk of a mental disorder in adulthood for those not raised by their biological parents was 1.5 in those offspring who had the loss at the age of less than 1 year, and 1.1 in the offspring having lost their parent at the age of 11-15 years.

According to Kendler *et al.* (2002), several studies have suggested that the association between parental separation and mental disorder might occur because parental loss may be a marker of other factors, such as genetic liability or family discord, which could actually represent the true risk factors.

2.1.3 Animal studies of early separation

Research based on animal experiments links postnatal stress and early isolation to abnormal neurodevelopment (Kehoe *et al.* 1998, Barr *et al.* 2001). In animal studies disrupted parenting has been found to produce a persistent biobehavioural impact on the offspring (Newport *et al.* 2002). Stress in the offspring, including prenatal maternal challenges and maternal separation, have been connected to persistent hyperresponsiveness in the hypothalamic-pituitary-adrenal (HPA) axis activity secondary to hypersecretion of corticotropin-releasing hormone (Newport *et al.* 2002). Postnatal handling in rats dampens HPA responsiveness to stress, while prolonged periods of maternal separation have the opposite effect (Liu *et al.* 2000). Early life events may influence the differentiation of noradrenergic neurones and alter HPA responses to stress in adulthood (Liu *et al.* 2000).

2.2 Maternal depression in pregnancy

2.2.1 Antenatal depression

Maternal depression is common both during the antenatal and the postnatal period (O'Hara *et al*. 1982, Evans *et al*. 2001). Postpartum depression has been associated with mental distress of the offspring in childhood (Gizynski 1985, Murray *et al*. 1991, Philipps & O'Hara 1991, Mowbray *et al*. 1995, Murray & Cooper 1997a, b).

Occurrence of antenatal depression Maternal depression in pregnancy has been studied less than depression in the postpartum period. However, studies on prepartum mental health were made as early as in the 18th century, but at that time depression and psychosis were subsumed under the same label (Brockington 1998). Anyway, it has been realized fairly recently that depression during pregnancy seems to be as common as after delivery (O'Hara *et al*. 1982, Brockington 1998, Evans *et al*. 2001). It has also been argued that the prevalence of depression in pregnancy is about the same as in non-pregnant women (Campbell 1988, O'Hara *et al*. 1990) and may reflect the general prevalence of depression in women during childbearing years (Brockington 1998). Campbell (1988) in her review concluded that neurotic disorders in pregnancy are similar in symptoms to those occurring at other times.

The occurrence of antenatal depression has been found to be between 5-17% (Jarrahi-Zadeh *et al.* 1969, Ancill & Hilton 1984, Kumar & Robson 1984, Watson *et al*. 1984, O'Hara *et al.* 1990, Gotlib *et al.* 1991, Areias *et al*. 1996a, Kitamura *et al*. 1996, Johanson *et al.* 2000, Evans *et al*. 2001, Luoma *et al.* 2001, Pajulo *et al.* 2001). In studies on the prevalence and incidence of prenatal depression different methods have been used, including Minnesota Multiphasic Personality Inventory MMPI (in the study of Jarrahi-Zadeh *et al.* 1969), Beck Depression Inventory BDI (in the study of O'Hara *et al*. 1982), Hamilton Depression Rating Scale HDRS (in the study of Ancill & Hilton 1984),

Goldberg Standardized Psychiatric Interview (in the studies of Kumar & Robinson 1984 and Watson *et al*. 1984), Zungs's Self-rating Depression Scale SDS (in the study of Kitamura *et al*. 1996), Depression Scale of Schedule of Affective Disorders and Schizophrenia SADS (in the study of Areias *et al*. 1996a) and Edinburgh Postnatal Depression Scale EPDS (in the studies of Areias *et al*. 1996a, Evans *et al*. 2001, Luoma *et al.* 2001, Pajulo *et al.* 2001). The studies on the occurrence of maternal antenatal depression have been conducted at different periods during pregnancy (Table 1).

Associative factors of antenatal depression Lack of social support, former depression and negative life events have been regarded as risk factors for antenatal depression (Areias *et al.* 1996b). Other risk factors for prenatal depression include smoking, medication, nausea in pregnancy, non-desired or first pregnancy, early parental death of the woman, less maternal care and paternal overprotectiveness in the childhood of the woman, negative attitudes toward pregnancy in the woman and her spouse, less closeness of the husband and remarriage (Kitamura *et al.* 1996). Substance dependency and experienced difficulties in social environment have been linked to prenatal depression (Pajulo *et al.* 2001). Marital discord has been also connected to antenatal depression (Johanson *et al.* 2000).

On the other hand, depressed mood during pregnancy has been associated with poor attendance at antenatal clinics, low birth weight and preterm delivery (Pagel *et al.* 1990, Hedegaard *et al.* 1993). Antenatal depression has been considered to increase considerably the risk for postnatal depression (O'Hara *et al.* 1982, Ancill *et al.* 1986, Areias *et al.* 1996b, Johanson *et al.* 2000, Honey *et al.* in press, and the reviews by Mowbray *et al.* 1995 and Wilson *et al.* 1996), which has been found to predict maternal depression later on (Uddenberg & Englesson 1978, Philipps and O'Hara 1991). Both antenatal and postnatal depression has been found to be frequently missed during routine consultation by general practitioners (Johanson *et al.* 2000).

2.2.2 Association of antenatal depression with childhood problems

Prenatal depressive symptoms have been strongly connected to externalizing problems (odds ratio OR 3.1; 95%CI 1.1-8.9) and problems in general (OR 8.5; 95%CI 2.7-26.5) in the 8 and 9-year-old offspring (Luoma *et al.* 2001). In another study, antenatal depression was not found to increase the risk per se for behavioural and emotional problems of 4-year-old children when adjusted, even though the crude OR was about 3 when mother's mood was self-reported depressed versus non-depressed at 18 weeks (crude OR 3.22; 95%CI 2.36-4.38) and 32 weeks of pregnancy (crude OR 3.16; 95%CI 2.34-4.25) using the Edinburgh Postnatal Depression Scale (O'Connor *et al.* 2002). Sameroff *et al.* (1987) followed up pregnant women with mental illness for 4 years with their infants. The authors suggested maternal neurotic depression to have more adverse impact on the child's development than mother's schizophrenia or personality disorder (Sameroff *et al.* 1987). Newborns of antenatally depressed mothers have been found to be 2.6 times more likely to be unconsolable and to cry excessively than infants of non-depressed mothers, which association remained significant even after taking into account confounding factors

such as cigarette smoking, alcohol, drug use, income and birth weight (Zuckerman *et al.* 1990).

Table 1. Antenatal depression studies; number of study sample, methods and occurence.

Authors (year)	Number of women	Methods	Period during pregnancy	Occurence of depression or mood disorder
Jarrahi-Zadeh *et al.* (1969)	86 pregnant women with a high level of SES	A short form of MMPI[1] with 56 items and various psychological tests	Last trimester	High score of MMPI[1] (depression items) in 5.9% of the women, and MMPI[1] (total items) in 11.2%.
Dalton (1971)	189 married women	Symptoms of depression, anxiety, irritability	Throughout pregnancy	35% rated as depressed at some point in pregnancy.
Rees & Lutkins (1971)	47 pregnant women	BDI[2] (≥17 and 25)	During pregnancy	Incidence of moderately sever depression was 9% (BDI[2] ≥17) and incidence of severe depression 3% (BDI[2] ≥25).
Playfair & Gowers (1981)	618 pregnant women, 42% primiparous	Checklist of 13 depressive symptoms	In various occasions	8.9% had ≥6 symptoms, 28.3% had ≥3 symptoms.
Cox *et al.* (1982)	105 women having live babies	Clinical interview by Goldberg *et al.*[3]	First before 20th, second at least about 35th week	4% had depression during pregnancy.
Manly *et al.* (1982)	61 primiparous	BDI[2] (≥15), DACL[4](≥70), McLean-Hakstian[5](≥32)	33rd -44th week	2-5.4% scored above cut off on one of the three scales.
O'Hara *et al.* (1982)	170; 45% primiparous	BDI[2]	2nd trimester	18.9% had mild or moderate depression.
Cutrona *et al.* (1983)	85 primiparous women	BDI[2], HDRS[6]	Last trimester	3.6% Major Depression (DSM-III), 25% ≥9 on BDI[2]
Elliott *et al.* (1983)	128 pregnant women	Self-rating questionnaire with 19 items, one of them concerning about depressed mood	Early pregnancy, appr. 13nd week	9% of the women reported their mood to be depressed.
Ancill & Hilton (1984)	117 pregnant women at antenatal care practice	Questionnaire of HDRS[6] (scores >17)	8-12th , 25-28th and 37-38th week	During the 8-12th week 5.1%, at 25-28th weeks 6.1% and at 37-38th weeks 11.8% of the women had depression.
Kumar & Robson (1984)	119 first-time mothers	Clinical interview by Goldberg *et al.*[3], RDC[7], GHQ[8] etc.	1st trimester	Incidence of new cases of depressive neurosis was 10% in the first three months.

Table 1. continues.

Authors (year)	Number of women	Methods	Period during pregnancy	Occurence of depression or mood disorder
O'Hara *et al.* (1984)	99; 50% primiparous	BDI[2], RDC[7] / SADS[9]	2nd trimester	9% had major or minor depression on RDC[7].
Watson *et al.* (1984)	128 pregnant women	Clinical interview by Goldberg *et al.*[3] etc.	Appr.16th week, and also in the end	By the end of the first trimester 3.9% and by the end of pregnancy 10.7% had mood disorder.
Buesching *et al.* (1986)	57 pregnant women	Zung's SDS[10]	10-12nd, 20-24th and 36-40th week	5.3%, 7.0% and 7.0% had moderate to severe depression, 17.5%, 17.5 and 29.8% had mild to moderate depression.
Gotlib *et al.* (1989)	360 pregnant women	Diagnostic status, BDI[2] and RDC[7]	During pregnancy	25% had depression on BDI[2], 10% on RDC[7].
Murray & Cox (1990)	100 pregnant women	Clinical interview by Goldberg *et al.*[3], RDC[7], EPDS[11]	28th – 34th weeks	8% had RDC[7] minor depressive disorder, 6% had RDC[7] major depressive.
O'Hara *et al.* (1990)	182 pregnant women (at least 18 years of age)	BDI[2], RDC[7], interview adapted from SADS[9], Depression subscale of the SCL-90-R[12] etc.	2nd trimester	7.7% had major or minor depression (9 women had major depression, and 5 minor depression).
Troutman & Cutrona (1990)	128 primiparous adolescent (age 14-18 years)	BDI[2], RDC[7], SADS[9] etc.	Mean gestational age=28.1 weeks, SD=8.5 weeks	Point prevalence of major depression was 6%, of minor depression 10%, of total depression 16%.
Gotlib *et al.* (1991)	730 pregnant women	BDI[2], RDC[7], a short version of SADS[9], PSS[13] etc.	An average of 23.1 weeks	10.3% had major or minor depression.
Areias *et al.* (1996a)	54 primipara mothers	SADS[9], EPDS[11]	6th month	Period prevalence was 16.7%.
Kitamura *et al.* (1996)	1 289 pregnant women	Zung's SDS[10] (high scores over 49)	1st trimester	7.2% had high scores.
Da Costa *et al.* (2000)	80 (age 19-40 years), married or in stable relationship	DACL[4] (≥14), stuructured interviews, several questionnaires	DACL[4] monthly starting 3rd month	Prevalence: 31% obtained elevated depressed mood scores (DACL[4] ≥14) in at least one trimester.
Johanson *et al.* (2000)	417 women booked for confinement	EPDS[11] (high scores > 14)	During pregnancy	9.8% of the women were depressed.

Table 1. continues.

Authors (year)	Number of women	Methods	Period during pregnancy	Occurence of depression or mood disorder
Evans *et al.* (2001)	12 059 pregnant women	EPDS[11] (using a treshold of 12/13), etc.	18th and 32th week	11.8% were depressed at18th week, 13.6% at 32th week.
Luoma *et al.* (2001)	279 healthy first-time mothers	EPDS[11] (a cut-off point ≥13) etc.	Last trimester	11% were depressed at the last trimester of pregnancy.
Pajulo *et al.* (2001)	391 pregnant women	EPDS[11] etc. (a cut-off point 12/13)	In the 14-37th week	7.7% of the sample screened positive on the EPDS[11].

[1]MMPI=A Minnesota Multiphasic Personality Inventory (Hathaway & McKinley1942), [2]BDI=Beck Depression Inventory Scale (Beck 1967), [3]Clinical interview by Goldberg *et al.*= Goldberg Standardized Psychiatric Interview (Goldberg et al. 1970), [4]DACL= Depression Adjective Checklist (Lubin 1965), [5]McLean-Hakstian =McLean-Hakstian Depression Scale (McLean & Hakstian 1979), [6]HDRS=Hamilton Depression Rating Scale (Hamilton 1960), [7]RDC=Research Diagnostic Criteria (Spitzer et al. 1977), [8]GHQ=The General Health Questionnaire (Goldberg 1972), [9]SADS=Schedule of Affective Disorders and Schizophrenia (Spitzer & Endicott 1979), [10]Zung's SDS=Zung's Depression Scale (Zung 1965), [11]EPDS=Edinburgh Postnatal Depression Scale (Cox *et al.* 1987), [12]SCL-90-R=Symptoms Checklist-90-Revised (Derogatis et al. 1983), [13]PSS=Perceived Stress Scale (Cohen *et al.* 1983).

2.2.3 Antenatal stress and its effects on the offspring

In humans, antenatal stress has been found to increase arterial resistance in utero (Teixeira *et al.* 1999). Maternal antenatal stress has been considered to predict lower birth weight and preterm delivery (Pagel *et al.* 1990, Hedegaard *et al.* 1993).

Maternal antenatal stress - but not antenatal depression- has been found to be a risk factor for behavioural and emotional problems in 4-year-old children (O'Connor *et al.* 2002). Huttunen and Niskanen (1978) have suggested that mother's antenatal stress caused by death of her spouse in pregnancy may increase the risk for schizophrenia and criminality in the offspring. Prenatal severe stress caused by earthquake has been linked to an increase of unipolar depression in offspring (Watson *et al.* 1999). Even so, children of mothers who were pregnant at the time of a war lasting for six months had significantly less developmental delays and regressive, non-affiliative and dissocial behaviour than those who were in their first half year of life at the time of the war (Meijer 1985).

2.2.4 Offspring of postnatally depressed mothers and depressed parents

Maternal postnatal depression can begin already during pregnancy or even before pregnancy (Da Costa *et al.* 2000, Hostetter & Stowe 2002, Marks *et al.* 2003). Generally in the studies mothers suffering from postpartum disorders in particular have not been separated from mothers with earlier onset of psychiatric disorder (Mowbray *et al.* 1995).

In a review by Wilson *et al.* (1996) with 118 studies analysed, postpartum depression was very strongly connected to antenatal depression. Also in another review by Mowbray *et al.* (1995), postnatal depression was connected to antenatal depression and also low parental care experienced by the mother in her childhood.

Offspring of postnatally depressed mothers There have been various studies following the effects of mother's postpartum depression on her offspring in infancy and childhood, but to the author's knowledge there are no published follow-up studies in English about the mental health in adulthood of the offspring of postnatally depressed mothers.

Maternal postnatal depression has been connected to difficulties in the mother-child relationship (Field *et al.* 1985, Cogill *et al.* 1986, Murray *et al.* 1991), behavioural problems in the child (Ghodsian *et al.* 1984, Wrate *et al.* 1985, Gizynski 1985, Philipps & O'Hara 1991, Sinclair & Murray 1998, Murray *et al.* 1999) and to adversely affected emotional and cognitive development in the children (Cogill *et al.* 1986, Murray *et al.* 1991, Stein *et al.* 1991, Weinberg & Tronick 1998a). Maternal postnatal depressive symptoms have also been connected to low social competence in 8 and 9-year-olds (Luoma *et al.* 2001). One-month-old infants of depressed mothers have been found to have right frontal EEG asymmetry (due to reduced left frontal activation) and more indeterminate sleep compared to infants of non-depressed mothers (Jones *et al.* 1997b). The infants of depressed mothers have been found to be less active and to cry less than infants of non-depressed mothers (Jones *et al.* 1997b). Postnatally depressed mothers have been found to have less vocal and visual communications with their 3-month-old infants (Righetti-Veltema *et al.* 2002). Murray and Cooper (1997b) in their review concluded that postnatal depression poses a risk for the mother-infant relationship and infant developmental outcome.

Offspring of depressed parents Many studies have found connections between parental mental disorder and psychological problems of the offspring (for reviews Rutter & Cox 1985, Beardslee *et al.* 1998, Weinberg & Tronick 1998b). Rutter and Quinton (1984) concluded that the associations between psychiatric disorder in parents and children are clearly demonstrated in numerous studies. The parents of children with severe depression tend to have psychiatric disorders (Tamminen & Räsänen 1990). Rates of major depressive disorder have been observed to be higher in the adolescent offspring of parents with affective disorder (Beardslee *et al.* 1993). Adolescent offspring of depressed parents have an increased risk of a major depression (Weissman *et al.* 1992). Compared with the children with neither parent suffering from depression, the offspring with parental depression had increased rates of major depressive disorders particularly before puberty, and phobias (both at approximately a 3-fold risk), panic disorder and alcohol dependence (at a 5-fold risk, Weissman *et al.* 1997). Parental depression has been found to predict major depression, anxiety disorders and conduct disorder in the offspring (Fendrich *et al.* 1990). Major depression in parents has been connected to major depression, generalized

anxiety disorder, antisocial personality disorder, alcohol abuse/dependence and drug abuse/dependence in their adolescent and adult descendants (Kendler *et al.* 1997). The offspring of depressed parents are a high-risk group for onset of anxiety disorder and major depressive disorder in childhood, major depressive disorder in adolescence, and alcohol dependence in adolescence and early adulthood (Weissman *et al.* 1997). Maternal and parental depression has been linked to an increased risk of behavioural difficulties in the children (Cummings & Davies 1994, Downey & Coyne 1990).

2.2.5 Animal studies of the consequences of antenatal stress

Studies based on animal experiments have linked prenatal stress to abnormal neurodevelopment (Schneider *et al.* 1998, Williams *et al.* 1999). In rats, stress during pregnancy has been found to alter the hypothalamic-pituitary-adrenal (HPA) axis and testicular response to isolation on the day of weaning in the offspring, suggesting that the HPA axis of the offspring is differentially affected by the gestational stress (Williams *et al.* 1999). It has been suggested that impaired coping in stressful situations and dysregulation of the HPA axis may result from the action of maternal hormones released during stress on the developing foetus (Weinstock 1997). In rhesus monkeys, chronic unpredictable psychological stress in pregnancy caused by social separation has been suggested to have long-lasting effects on noradrenergic and dopaminergic activity and behaviour in the offspring of antenatally stressed primate mothers (Schneider *et al.* 1998). Antenatal stress in animals may cause impairment of development of hippocampal function, which can last into adulthood (Fride *et al.* 1986). Prenatal stress may also modify neuroanatomy in rats (Jones *et al.* 1997a).

In the study of pre and postnatal stress in rats, genetic factors have been suggested to determine the vulnerability of the organism to negative environmental factors with respect to emotional and neuroendocrine maladaptations (Neumann *et al.* 2002). Istvan in his review (1986) suggested that the manner in which stressors affect gestation in animals may relate to factors such as the genetic strain, the quality and quantity of the stress (duration, intensity and nature of the stressor) or other risk factors such as nutritional deficiency.

2.3 Early risk factors of schizophrenia

2.3.1 Schizophrenia

Schizophrenia may be the most severe and devastating of the mental illnesses (Andreasen 2001). Symptoms of schizophrenia have been described in medicine for at least about one hundred years (for example Alanen 1997). Emil Kraepelin (1919/1987) used the term

"dementia praecox" at the turn of the last century to refer to apathy and dementia in younger age. He connected it with a poor prognosis and the especially nowadays so-called negative symptoms such as chronic deterioration, catatony, flattened affects, disorders of attention and thought, and also positive symptoms such as auditory hallucinations and experiences of influence. Eugen Bleuler (1911/1966) chose to use the term "schizophrenia" describing it to be a group of mental illnesses (in Greek "schizo" means split or fragmented and "phren" mind) with a splitting of associative processes of thinking. He noted that some patients showed substantial improvement afterwards. According to Bleuler (1911/1966), fundamental symptoms in schizophrenia are altered association, affectivity, ambivalence, autism and altered attention, and accessory symptoms are hallucinations, delusions and catatonic symptoms. He concluded that schizophrenia is not generally dementia, but can be dementia in certain periods of the illness.

Several definitions of schizophrenia exist also nowadays (van Os & Verdoux 2003). American Psychiatric Association's Diagnostic and Statistical Manual, third version revised (APA: DSM-III-R 1994) has somewhat more narrow definitions focused on more severe types of illness including more younger males, whereas the criteria of World Health Organization's International Classification of Diseases, 10th version (WHO: ICD-10 1992) are broader, including more variable courses of illness and more women with affective symptoms (van Os & Verdoux 2003). The most important of the differences between ICD-10 and DSM-III-R-criteria for schizophrenia may be the duration criterion (ICD-10: one month without including prodromal phase; DSM-III-R: overall six months with one week of florid psychotic symptoms; Andreasen & Flaum 1991, Keith & Matthews 1991, Amin *et al.* 1999). Even so, in the study by Amin *et al.* (1999) it was concluded that DSM-III-R schizophrenia had similar stability as ICD-10 schizophrenia.

Schizophrenia is an aetiologically heterogeneous syndrome with peak onset in late adolescence or early adulthood. In the Northern Finland 1966 Birth Cohort the peak of onset of schizophrenia, when first psychotic symptoms became evident, was between 16-24 years (Räsänen *et al.* 1999b). Häfner (2003) has regarded the mean age of the first sign of illness to be 24 years, where as the mean age of first admission has been found to be 30 years.

Nowadays schizophrenia is considered to be a neurodevelopmental disorder (Weinberger 1995) acting in utero and in early childhood (Cannon & Murray 1998) and suspected to be also a neurodegenerative disorder (Church *et al.* 2002) with high genetic vulnerability (Zerbin-Rüdin 1967, Gottesman 1991, Cannon & Jones 1996, Cardno *et al.* 1999, Kendler 2000). On the other hand, environmental factors have also been found to play a role in the aetiology of the disease (Wahlberg *et al.* 1997, Norquist & Narrow 2000). It has been proposed that between 13% and 17% (Cannon *et al.* 1998, Cardno *et al.* 1999) of the variance in liability to schizophrenia might be explained by unique environmental factors, both biological and psychosocial.

2.3.2 Different early risk factors of schizophrenia

Many pre and postnatal environmental risk factors may act additively with each other, or may indicate the existence of gene environment interactions (Kendler 1995). Adverse psychosocial circumstances in childhood or birth complications may interact with genetic vulnerability to increase the risk of psychosis (Cannon *et al.* 1993). The pathogenic effects of adverse social circumstances may increase risk of schizophrenia only in children who have some degree of genetic vulnerability (Cannon & Murray 1998). According to Cannon *et al.* (2003), among many pre and perinatal risk factors which are in some way involved in increasing the risk for schizophrenia, most evidence seems to concern antenatal exposure to influenza, especially during the 2nd trimester (approximate effect size 2.0) and other respiratory infections (approximate effect size 2.1), rubella during pregnancy (approximate effect size 5.2), hypoxia-related obstetric complications (approximate effect size 2.1-4.4) and low birth weight (approximate effect size 1.6) or prenatal growth retardation (in males only approximate effect size 1.9-3.2). So far, the evidence is less secure for antenatal stress (approximate effect size 1.8-6.2) or malnutrition in pregnancy (approximate effect size 2.0, Cannon *et al.* 2003). Also, some studies do not support the association between prenatal influenza and schizophrenia either (Selten *et al.* 1999a, Mino *et al.* 2000)

Prenatal infections Maternal influenza A in pregnancy has been suspected to have a connection with schizophrenia in the children (Cannon *et al.* 2003). Those offspring whose mothers had been in the 2nd trimester of pregnancy during the 1957-58 influenza pandemic in Helsinki were found to be twice as likely to have hospital-treated schizophrenia than those not exposed at all antenatally or exposed earlier or later in pregnancy (Mednick *et al.* 1988). Usually in the studies influenza A has been associated with a rather modest 1.5-to-2-fold increase in schizophrenia (Cannon & Jones 1996), mainly in the 5th and 6th months of pregnancy (Cannon *et al.* 2003). Timing of influenza epidemics and the birth dates of offspring with schizophrenia have been found to have positive connection in many, but not all studies (Cannon *et al.* 2003, Selten *et al.* 1999a, Mino *et al.* 2000). Also other antenatal infections have been associated with schizophrenia in the offspring. 2nd trimester exposure to respiratory infections including influenza, pneumonia, tuberculosis and acute bronchitis was associated with a significantly increased risk of schizophrenia spectrum disorders in young adulthood (RR 2.1) when adjusted for maternal smoking, education, and race (Brown *et al.* 2000b). Exposure to rubella mainly in the first trimester has been demonstrated to increase the risk substantially (RR 5.2, Brown *et al.* 2000a). Also late winter birth (in January-April) has been found to elevate the risk for schizophrenia (OR 1.4, Hultman *et al.* 1999), which may have various possible explanations, such as higher rates of pregnancy complications in winter (Boydell & Murray 2003).

Famine in pregnancy Nutritional deficiency in pregnancy may play a role in the origin of some cases of schizophrenia (Susser *et al.* 1995). The risk for schizophrenia in the offspring exposed to famine during early gestation and conceived at the height of the famine during the Dutch Hunger Winter of 1944/1945, increased twofold (RR 2, Susser *et al.* 1995). Anyway, the causality remains partly open while congenital central nervous

system defects have been associated with antenatal famine in the same population (Cannon *et al.* 2003).

Prenatal stress There are some studies suggesting an association between antenatal stress and schizophrenia. Children of mothers whose husband died while they were pregnant have been found to have a significantly increased rate of schizophrenia (OR 6.2) compared to children who have lost their father in infancy in the first year of life (Huttunen & Niskanen 1978). In the Northern Finland 1966 Birth Cohort unwanted pregnancy has been found to be associated with schizophrenia in the offspring (adjusted OR 2.4, Myhrman *et al.* 1996). Van Os & Selten (1998) considered cumulative incidence of schizophrenia to be slightly higher in those exposed in the first trimester during the five-day invasion and defeat of the Netherlands by the German army in 1940 (RR 1.3). The people exposed during gestation to the 1953 flood disaster in the Netherlands have not been found to have a statistically significantly increased risk of non-affective psychosis, even though the rate of schizophrenia was increased among them (Selten *et al.* 1999b).

Obstetric complications Obstetric complications have been linked to schizophrenia in the offspring in numerous studies (Geddes & Lawrie 1995, Geddes *et al.* 1999, Cannon *et al.* 2002). Geddes *et al.* (1999) concluded in a meta-analysis of 12 studies on 700 schizophrenia subjects and 835 controls that some abnormalities of pregnancy and delivery are associated with development of schizophrenia, maybe via hypoxia. There were significant associations between schizophrenia and premature rupture of membranes, gestational age shorter than 37 weeks, and use of resuscitation or incubator, whereas the associations between schizophrenia and birth weight lower than 2 500 g and forceps delivery were of borderline significance (Geddes *et al.* 1999). A review by Cannon *et al.* (2002) concluded that three groups of complications were significantly associated with schizophrenia: 1) complications of pregnancy (bleeding, diabetes, rhesus incompatibility, preeclampsia), 2) abnormal foetal growth and development: (low birth-weight, congenital malformations, reduced head circumference) and 3) complications of delivery (uterine atony, asphyxia, emergency Caesarean section). However, the pooled estimates of effect sizes were generally rather weak, less than 2 (Cannon *et al.* 2002).

In the Northern Finland 1966 Birth Cohort especially perinatal complications (1. neonatal convulsions and/or 2. low Apgar score (0 at 1 minute or <5 at 15 minutes) and/or 3. diagnosis of asphyxia and/or 4. intraventricular haemorrhage and/or 5. being detained in, or readmitted to, a neonatal unit in a children's hospital and/or 6. brain injury during the newborn period) have been connected to an increased risk for schizophrenia (crude OR 7.5; 95%CI 3.2-17.6), also after adjusting for sex, socioeconomic status at birth, maternal depressed mood and smoking during pregnancy (adjusted OR 6.9; 95%CI 2.9-16.3, Jones *et al.* 1998). Besides schizophrenia, other mental disorders may also have similar obstetric risk factors (Cannon *et al.* 2003).

Early childhood infections In the Northern Finland 1966 Birth Cohort central nervous system infections during childhood up until the age of 14 years have been found to carry an increased risk of schizophrenia or other psychoses in adolescents and young adults, viral infections being important for schizophrenia (OR 4.8; 95%CI 1.6-14.0 when adjusted for neurological abnormalities and father's social class), especially Coxsackie B5 during the newborn period (Rantakallio *et al.* 1997).

Socio-economic status in childhood Parental socioeconomic status (SES) has been found to have effects on adult psychological health (Huurre *et al.* 2003), but there are discrepant opinions concerning the role of the social environment in schizophrenia (van Os and McGuffin 2003). The connection between childhood SES and schizophrenia is still not entirely resolved (Bresnahan & Susser 2003). Low or high SES in the family of origin has been found to be at least a modest risk factor for schizophrenia in some studies, but other studies report no increased risk (Bresnahan & Susser 2003). In some studies, schizophrenia has been linked to low social status of parents (Turner & Wagenfeld 1967, Castle *et al.* 1993), whereas in others no link has been observed (Goldberg & Morrison 1963, Timms 1998). Mäkikyrö *et al.* (1997) have suggested that there would be an association between high social class of childhood family and early onset schizophrenia until 23 years in the Northern Finland 1966 Birth Cohort.

Urbanization According to Boydell and Murray (2003) there is substantial evidence at least in Western countries that urban birth and/or living in a town as a child are associated with increased (about 1.3-2.4-fold) risk of schizophrenia. For example, in a Swedish study the incidence of schizophrenia was 1.6 times higher among men brought up in cities than among those who had had a rural upbringing (Lewis *et al.* 1992). In Denmark, a 2.4-fold increase in the risk for schizophrenia has been found in the capital versus rural areas (Mortensen *et al.* 1999).

Migration Migration has been connected to increased risk of schizophrenia especially among the second generation born in the new homeland (Boydell & Murray 2003). People of African and Caribbean origin living in Britain have been reported to have 2.4-18-fold increased rates of schizophrenia (Hickling *et al.* 1999). Among many other possible explanations, there have been reports of social isolation connected to schizophrenia (Boydell & Murray 2003).

Family factors In the Northern Finland 1966 Birth Cohort, the size of the family of origin has not been found to be associated with risk of schizophrenia (Kemppainen *et al.* 2000).

Schizophrenia in offspring has been linked with problems in mothers' general understanding and management of their children (OR 5.8) in the British 1946 Birth Cohort (Jones *et al.* 1994). Even so, the same study by Jones *et al.* 1994 demonstrated that pre-psychotic children are developmentally distinct, so the direction of causality is uncertain. In a Finnish adoption study, a greater risk of schizophrenia was found among genetically vulnerable children who were placed in poorly functioning adoptive homes compared with those placed in well functioning homes (Tienari 1991). Communication deviance – language production that is ambiguous and hard to understand - in the family has been concluded to increase the risk for schizophrenia by Goldstein (1987), and among adoptees only in high-risk children by Wahlberg *et al.* (1997). Interaction of adoptive-parent communication deviance and adoptee's genetic risk has been found to increase the risk for schizophrenia (OR 1.7; 95%CI 1.1-2.8), the risk being higher compared to the risk each one of them is connected to alone (Wahlberg *et al.* 2000). Having a positive relationship with both the mother and father might be protective against schizophrenia among high-risk children (Schiffman *et al.* 2002).

2.3.3 Schizophrenia in the offspring with early parental separation

There have been discrepant findings about the association between childhood separation and schizophrenia in adulthood. In a Finnish population study by Veijola (1996), parental death was found to be a risk factor for schizophrenia (adjusted RR 2.4; 95%CI 1.0-5.8 when compared to the offspring without parental separation). In the review by Olin and Mednick (1996), separation was considered to be one of the risk factors for psychoses. Earlier studies did not find any association between parental separation and psychoses. In the work by Granville-Grossman (1966), parental death was not connected to schizophrenia. In some studies, parental loss in childhood has not been associated with psychoses (Ragan & McGlashan 1986) or manic-depressive psychoses in adulthood (Hopkinson & Reed 1966). Finnish war-children sent to Sweden at the age of 1-15 years have not been found to have an increased risk of hospital-treated psychoses (Räsänen 1988).

Child-rearing in the setting of a kibbutz has been linked to psychopathology in young adults compared to offspring raised by their own parents (Mirsky *et al.* 1995). Even so, schizophrenia was found exclusively among children of ill parents, and no effect of kibbutz rearing on risk for schizophrenia was observed (Ingraham *et al.* 1995). High-risk children reared in a kibbutz were not found to have more increased rates of schizophrenia compared with those high-risk offspring who were reared in family homes (Ingraham *et al.* 1995).

Living in a single-parent family in childhood was not predictive of schizophrenia in the Northern Finland 1966 Birth Cohort (Mäkikyrö *et al.* 1998). However, antenatal maternal stress with paternal loss has been connected to later schizophrenia in the offspring (Huttunen & Niskanen 1978).

Generally in studies of the association between early separation and later schizophrenia, neither the child's age at the time of separation, nor the length of separation have been defined very strictly (Granville-Grossman 1966, Watt & Nicholi 1979, Ingraham *et al.* 1995, Furukawa *et al.* 1998).

2.3.4 Schizophrenia in the offspring of antenatally depressed mothers

To the author's knowledge, there have been few previous studies of antenatally depressed mothers and schizophrenia in their offspring, except for three former reports on the Northern Finland 1966 Birth Cohort with a follow-up time shorter by a few years than in the present study (Myhrman *et al*. 1996, Jones *et al.* 1998, Veijola *et al.* 1998a). Jones *et al.* (1998) found maternal depressed mood in pregnancy to have been elevated in schizophrenia patients followed up until the age of 27-28 years (OR 1.8; 95%CI 1.1-3.1). In the same cohort study with one year longer follow-up to the end of 1994, the offspring of antenatally depressed mothers were found to have an increased risk for non-psychotic disorders in particular (Veijola *et al.* 1998a).

2.4 Early risk factors of criminality

2.4.1 Criminality

The term criminality has been used to describe criminal behaviour and also juvenile delinquency. It is a legal term referring to persons committing offences against law. Most of the offences are committed by men (Stevenson & Goodman 2001). In criminal behaviour the peak age of onset in males is during adolescence (Rutter & Giller 1983, Pulkkinen 1988). Criminal behaviour may be divided into non-violent and violent offending (Räsänen *et al.* 1999a).

Antisocial behaviour is defined as chronic violation of social rules and norms, and can have both violent and non-violent manifestations (Wakschlag *et al.* 2002). In the 19th century antisocial behaviours began to be described in medicine (Tardiff 2000). Afterwards the term "psychopath" was used to describe a person committing crimes and regarded to have a hereditary defect, whereas later on when social factors were suspected to cause criminality, the word "sociopath" began to be used (Tardiff 2000). In 1950 Glueck and Glueck concluded that both hereditary and social factors were related to antisocial behaviour.

When occurring as severe, chronic and pervasive, antisocial behaviour can be categorized as a mental disorder (Wakschlag *et al.* 2002). In adolescents, severe antisocial behaviour is diagnosed as a conduct disorder, while in adults the diagnosis is antisocial personality disorder (Wakschlag *et al.* 2002). Even though adult antisocial behaviour virtually requires childhood antisocial behaviour, most antisocial children do not become antisocial adults (Robins 1978).

Since the 1980s there have been a number of studies linking violence, crime and mental illness (Marzuk 1996). Physical violence is connected to a number of psychiatric disorders, such as antisocial personality disorder, borderline personality disorder and conduct disorder which have violent behaviour as part of the diagnostic criteria, and also to alcoholism and other substance-related disorders, mental retardation, schizophrenia, other psychoses and bipolar disorders (Tardiff 2000). Patients in psychiatric wards have been found to be more likely to have convictions of crimes than persons never having been in a psychiatric hospital (Hodgins *et al.* 1996). Schizophrenia and antisocial personality have been connected to an increased risk of violent homicide offences (Eronen *et al.* 1996). Among female jail detainees over 80% were found to have a lifetime psychiatric disorder, while having significantly higher rates of substance abuse or dependence, post-traumatic stress and to a lesser extent major depressive disorder, but no elevated risk of schizophrenia compared to general population rates (Teplin *et al.* 1996). In male subjects in the 1966 Northern Finland Birth Cohort with at least one registered crime, risks were increased for different mental disorders: for schizophrenia (OR 3.0; 95%CI 1.4-6.3), mood disorders with psychotic features (OR 6.8; 1.2-38.7) and paranoid and other psychoses (OR 5.5; 1.3-23.8) when adjusted for the father's socioeconomic class at the subject's birth, urban residence, and one-parent family background (Tiihonen *et al.* 1997).

Besides environmental risk factors, genetic factors have also been connected to criminality (Lyons *et al.* 1995). In adopted-away sons non-violent recidivist criminality has been significantly associated with mental disorder and criminality in the adoptees' biological families, where, as violence in adopted-away sons showed a similar, but nonsignificant, elevation (Moffitt 1987). Biological parental diagnostic types associated most strongly with adopted-away sons' later criminality were drug abuse, alcohol abuse, and personality disorders (Moffitt 1987).

2.4.2 Different early risk factors in criminality

A number of early bio-psycho-social risk factors have been observed to predispose to criminal behaviour (Tardiff 2000). McCord (1979) has found six variables describing family atmosphere during childhood - mother's self-confidence, father's deviance, parental aggressiveness, maternal affection, parental conflict, and supervision - to have an important impact on criminality in men. In the study by Kolvin *et al.* (1988a), different types of deprivation of childhood family – poor physical/domestic care, poor quality mothering, social dependency, overcrowding, marital disruption and parental illness – were all associated with an increased risk for later criminality. Childhood deprivation gives rise to a higher rate of offending (Kolvin *et al.* 1988b). Compared to schizophrenia, criminal behaviour is a much more extensive phenomenon. Many early exposures have been connected to criminality.

Studies of juvenile delinquency usually claim the family environment to be more important than genetic factors, whereas in adult antisocial behaviour or criminality genetic factors are suspected to be more important (Lyons *et al.* 1995).

In a Danish study with 423 men born between 1959-1961 and followed up to ages 17 to 19 years, Raine *et al.* (1996) identified three groups of males with criminality: 1. Group was characterized by neurological problems in the first week of life, slow motor development at age 1 year, early maternal rejection, family conflict, family instability, and criminal parent. 2. Obstetric group included relatively greater pregnancy complications, birth complications, prematurity, and slower motor development. 3. Group was characterized by social deficit of poverty and by having relatively more negative social, economic, educational, employment, and living status characteristics compared with those in the other 2 groups (Raine *et al.* 1996).

Obstetric and perinatal complications Obstetric and perinatal complications have been found to increase the risk for behavioural problems and violence (Kandel & Mednick 1991, Raine *et al.* 1996, Arseneault *et al.* 2002). In a cohort study of 15 117 persons born in Stockholm, Sweden in 1953, obstetric complications which were defined as deviations from normal development occurring at any point from conception through the neonatal period did not increase the risk of offending alone in the absence of family problems (Hodgins *et al.* 2001). Even so, pregnancy complications combined with inadequate parenting increased the risk of offending (in men OR 1.6 and in women OR 1.8) and violent offending (in men 2.9 and in women 1.8 Hodgins *et al.* 2001). In a sample of 849 boys from low socioeconomic areas of Montreal, Canada, obstetrical complications

(preeclampsia, umbilical cord prolapse, and induced labour) increased the risk of being violent at both 6 and 17 years of age (Arseneault *et al.* 2002).

However, in the Northern Finland 1966 Birth Cohort with 5 966 males, delinquency was not associated with a birth weight less than 2 500 g or greater than 4 000 g, preterm births < 37 weeks' gestation, or perinatal brain damage or having epileptic seizures before 14 years of age (Rantakallio *et al.* 1992a).

Substance use in pregnancy Mothers' smoking during pregnancy has been associated with criminality in their offspring (Wakschlag *et al.* 2002). It has been connected to delinquency even after controlling for a number of social and demographic variables (estimated OR of 1.7, Rantakallio *et al.* 1992b). The association between maternal smoking during pregnancy and risk for severe antisocial behaviour in youths is approximately 1.5 to 4 times greater in those exposed to maternal smoking during pregnancy than in the nonexposed (Wakschlag *et al.* 2002). Foetal alcohol syndrome has been connected to antisocial behaviour besides mental health problems, alcoholism and drug abuse in adulthood (Streissguth 1993). Rather little is known about children of heroin addicts, cocaine abusers, or polydrug abusers (Johnson & Leff 1999). Nonetheless, many researchers have suggested that the children of addicted parents and also those with maternal drug abuse in pregnancy are at greater risk for later dysfunctional behaviour (Johnson & Leff 1999). Prenatal exposure to alcohol or other drugs might not be the major influence on long-term effects for the offspring, but could be reinforced by years of deprivation, neglect, negative behavioural models, and other adverse conditions (Young 1997).

Central nervous system disorders In the Northern Finland 1966 Birth Cohort, in men a central nervous system trauma by the age of 14 years was connected to increased risk of criminality (adjusted OR 1.9) and violent offending (adjusted OR 3.2, Rantakallio *et al.* 1992a). Central nervous system disorders and some systemic disorders affecting the central nervous system have been connected to violent behaviour (Tardiff 2000). Brain abnormalities have been connected to homicides (Raine *et al.* 1997b). An intelligence quotient (IQ) of 50-84, but not below 50, has been associated with delinquency (Rantakallio *et al.* 1995).

Family factors Inadequate parenting indexed by social intervention has been shown to increase the risk of offending in a Swedish cohort study (in men OR 1.4; 95%CI 1.3-1.5, in women 2.1; 1.7-2.6) and of violent offending (in men OR 2.0; 1.7-2.4, in women 2.1; 1.7-2.6, Hodgins *et al.* 2001). Rutter and Giller (1983) reviewed that parental criminality, poor parental supervision, cruel, passive and neglecting attitudes, erratic or harsh discipline, marital conflict and large family size are among the important variables associated with both juvenile delinquency and adult criminality.

Child abuse and witnessing violence in the childhood family have been linked to violence committed by the victim afterwards (Tardiff 2000). Poor parental supervision, low parental reinforcement and low involvement of the boy in family activities have been connected to juvenile delinquency (Farrington *et al.* 2002). Offenders have been found to be highly concentrated in families (Farrington *et al.* 2001). Arrests of brothers, sisters, mothers, uncles, aunts, grandfathers and grandmothers have been reported to predict boys' delinquency, arrests of the father being the most important arrest of relatives (Farrington *et al.* 2001). Among other risk factors, Kolvin *et al.* (1988a) found parental illness to be connected to criminal behaviour.

Socio-economic status in childhood Low SES in childhood has been connected to offending and violence in various studies (Rutter and Giller 1983, Rantakallio *et al.* 1995, Tardiff 2000, Hodgins *et al.* 2001). In a Swedish cohort study among men, compared with nonoffenders (43.2%), a larger proportion of offenders (56.5%) and violent offenders (63.6%), and also early starters (68.0%) had been raised in families of low SES (Hodgins *et al.* 2001). Also among women, compared with nonoffenders (46.9%), a larger proportion of offenders (59.0%) and early-start offenders (67.9%) had had a low childhood SES (Hodgins *et al.* 2001).

Urban areas Crimes and violence offences are more concentrated in urban areas (Tardiff 2000). The rates of crime in big cities exceed those in rural areas (Rutter & Giller 1983).

Peer delinquency Peer context can be seen as an important influence on delinquency, but also acting in relation to family variables (Lerner & Galambos 1998). Peer delinquency has been found to be a strong correlate, but still not a cause of delinquency (Farrington *et al.* 2002).

2.4.3 Criminality in the offspring with early parental separation

Among other social determinants, pre and also postnatal paternal loss may be associated with criminality (Huttunen & Niskanen 1978). Weininger (1972) linked parental loss in childhood to juvenile delinquency and criminal behaviour in prisoners. Kolvin *et al.* (1988a) found parents' marital breakdown to be associated with criminality in their offspring.

Parental loss has been found to be a risk factor for violence as well (Tardiff 2000). Parental separation between 0-4 years of age has been found to predict robbery and assaults (Wadsworth 1979). Maternal rejection including institutionalization in the first year of life among other risk factors, combined with birth complications has been shown to predispose to violence in men (Raine *et al.* 1997a). In male alcoholic violent offenders and fire setters, recidivism was found to be associated with early paternal absence but presence of brothers compared to non-recidivists (Virkkunen *et al.* 1996).

In the Colorado Adoption Project with adopted children classified as being at genetic risk or not at genetic risk for antisocial behaviour based on their biological mothers' self-report history of antisocial behaviour collected prior to the birth of the child, children at risk were consistently more likely to receive negative parenting from their adoptive parents than children not at genetic risk, indicating an evocative genotype-environment correlation (O'Connor *et al.* 1998). Still, an additional environmentally mediated parental effect on children's behaviour was found to be plausible (O'Connor *et al.* 1998). The Finnish children with separation experience who were sent to safety in Sweden during the war were found to have committed more crimes in their youth than the controls, but not later on in life (Räsänen 1988).

In the Northern Finland 1966 Birth Cohort, parental death before age 14 of the child was connected to violent criminality in male offspring (OR 2.2) when adjusted for maternal age and smoking during pregnancy, psychiatric diagnosis, parental social class

and perinatal complications (Sauvola *et al.* 2002). Also parental divorce or separation by the child's age of 14 years (adjusted OR 2.5) doubled the risk for violence (Sauvola *et al.* 2002). Non-violent offences in the sons were associated with parental death (adjusted OR 1.5) and divorce (adjusted OR 2.0) as well (Sauvola *et al.* 2002). Single-parent family at birth (adjusted OR 3.6) and up to the age of 14 years (adjusted OR 5.2) were connected with an elevated risk for violent offences in an adult male offspring (Sauvola *et al.* 2002). Also risk for violent recidivism was significantly increased in sons with parental divorce (adjusted OR 2.0), single-parent family at birth (adjusted OR 5.0) and all time (adjusted OR 7.8), but not with parental death (Sauvola 2001). Being an only child combined with paternal absence increased the risk for violent criminality (OR 8.4) and for non-violent criminality in male offspring (OR 2.5, Kemppainen *et al.* 2001). In females in the Northern Finland 1966 Birth Cohort, paternal absence during childhood up to age 14 years was a risk factor for criminality (OR 2.5, Kemppainen *et al.* 2002).

2.4.4 Criminality in the offspring of antenatally depressed mothers

Problems in maternal affection (McCord 1979) seem to increase the risk of committing criminal offences in offspring. Huttunen and Niskanen (1978) have suggested that the mother's stress caused by her spouse's death, especially antenatally, might increase the risk for criminality among the offspring. Kolvin *et al.* (1988a) found poor quality of mothering to be connected to criminal behaviour.

2.5 Theories connecting adverse events in pregnancy and early childhood to mental disorders and behavioural problems

Human beings are by nature developing subjects both physically and mentally. Biological, psychological and social factors have effects on this development (Cicchetti & Cannon 1999, Epstein 2001). Environmental and genetic risk factors are acting in time on developing and senescent organisms (Kendler 1995). Adverse events during pregnancy and early childhood have been associated with later outcome of mental health and behavioural problems (e.g. Raine *et al.* 1994, Geddes & Lawrie 1995, Wahlberg *et al.* 1997). Because various factors influence the psychological development of human beings, a number of different approaches may be used when describing this phenomenon.

2.5.1 Biological aspects

Neurodevelopment Brain development starts antenatally and continues in childhood and adolescence, mainly stagewise (Epstein 2001). Postnatally the first rapid brain growth

including expansion of neural network arborisation has been found to occur between the ages of 3 and 10 months (Epstein 2001). Brain structures may depend on a combination of biological events and psychosocial factors (Epstein 2001). Early abnormalities may have adverse effects on neurodevelopment and aberrant neural circuitry, which can eventuate in psychopathology (Cicchetti & Cannon 1999).

Neurotransmitters which have been linked to the pathophysiology of schizophrenia (Lieberman & Koreen 1993, Sedvall & Farde 1995) and violence (Virkkunen *et al.* 1987, Virkkunen *et al.* 1994) may be acting in early development. Brain neuropeptide levels have been found to be decreased in rats' brains in a situation with early life maternal separation (Jimenez-Vasquez *et al.* 2001). Adverse early relational experiences may result in activation of the hypothalamic-pituitary-adrenal (HPA) axis, causing sensitization of some pathways in the brain (Beatson & Taryan 2003). The salivary cortisol level of children has been found to correlate significantly with the mother's extent of depressive symptomatology (Lupien *et al.* 2000). Glucocorticoids have been connected to neurotoxicity (Cotter & Pariante 2002). An association has been found between excess exposure to cortisone in early life and brain sensitivity, actions of cortisol possibly being modulated by dehydroepiandrosterone and gonadal steroids (Goodyer *et al.* 2001). Steroid hormones may participate in shaping behavioural function during early development and may be risk factors for psychopathology (Goodyer *et al.* 2001).

The origins of schizophrenia have been suspected to include a neurodevelopmental disorder (Weinberger 1995) acting in pregnancy and childhood (Cannon & Murray 1998). E.g. obstetric complications, which can cause defects in the central nervous system, have been connected to schizophrenia in the offspring (Geddes *et al.* 1999). Neurodevelopment could be related to criminal behaviour, too. Obstetric complications have also been connected to criminality (Raine *et al.* 1996). Minor physical anomalies, which can be considered indicators of foetal developmental disruption, have been found to be significantly associated with an increased risk of violent delinquency in adolescence (Arseneault *et al.* 2000) and with schizophrenia, too (Ismail *et al.* 1998).

Barker's hypothesis Barker (1992, 1994) has proposed that foetal and infant origins are linked with adult somatic diseases. There are regarded to be sensitive periods in the development. In the phenomenon known as programming early exposure, such as malnourishment in pregnancy and infancy, can have lifelong effect (Barker 1994). The dynamic interplay between genes and environment in utero may be linked to mental disorders and also schizophrenia (Kandel 1998, Cannon *et al.* 2003). Cannon *et al.* (2003) concluded that normal variation in the foetal environment might have an impact on the risk of schizophrenia later on in the offspring's life by modifying the developmental programme.

2.5.2 Psychological theories

Attachment theory Bowlby (1969) described in the first book of his trilogy Attachment and Loss the formation of the attachment between the mother and the infant that is a dynamic interaction between the mother-child pair. Apart from physical care and feeding,

it is essential for the child's psychological development for him/her to experience love, a warm, intimate and continuous relationship with the child's mother or her substitute, another permanent care-taker (Bowlby 1969).

Usually in a family setting, at the age of about four months an infant is already responding differently to its mother than to other people (Bowlby 1969). However, attachment behaviour not only contains the evidence that the infant recognizes the mother but also tends to behave in a special kind of manner to maintain its proximity to her (Bowlby 1969). Bowlby (1969) noted that during the first three-quarters of his/her first year, the infant does not make conscious plans to attachment behaviour, where as thenceforward he/she seems to begin to plan its behaviour and make decisions to try to control the environment. Attachment behaviour of the child usually grows in the first year of life and is maintained strong at least until almost the end of the third year. After that most children are increasingly able to feel secure in strange places with a subordinate attachment-figure, such as another relative or a school teacher. In adolescence, attachment of an offspring towards the parents usually becomes weaker (Bowlby 1969), but is however maintained (Rosenstein & Horowitz 1997). It has therefore been postulated that attachment behaviour does not vanish with childhood but persists throughout life by maintenance of proximity and communication with old or/and new figures (Bowlby 1969). The pattern of attachment between infant and parent is an important source of security throughout life (Black 1998).

Bowlby (1978, 1981) emphasized the effects of loss on anxiety and psychiatric disorders. He (1981) found that early separation from the mother led to disturbed attachment between the child and mother. Subjects with interrupted attachment had a high risk of developing various psychiatric disorders, especially depression (Bowlby 1981).

Ainsworth *et al.* (1978) described in a so-called Strange Situation with separation and reunion of the child and his mother, three patterns of attachment: one secure and two insecure (avoidant and ambivalent). Later disorganized/disoriented subtype was identified (Crockenberg & Leerkes 2000). In a Swedish study, index mothers and their babies had a 15-20 minutes' suckling and skin-to-skin contact during the first hour after the birth (De Chateau & Wiberg 1977). In a 3-month follow-up infants of those mothers who had had the extra contact were observed to smile more often and cry less frequently compared with the infants without extra contact with their mothers immediately after the birth.

Beatson and Taryan (2003) found in their review that adverse early relational experiences might result in activation of the hypothalamic-pituitary-adrenal (HPA) axis, causing sensitization of depression pathways in the brain. Secure attachment has been considered to act as a buffer against HPA activation in response to stress, whereas infants with insecure attachment lack this buffering effect and may be predisposed to depression and other psychiatric disorders (Beatson & Taryan 2003). Maunder and Hunter (2001) suggested in their review that there would be an association between attachment insecurity, physiological stress response and physical illness.

Antenatal attachment Research has recently been focused on prenatal attachment (Brockington 1998). It has been recognized that the mother bonds to her unborn baby in a way analogous to the formation of the mother-infant attachment after birth (Brockington 1998). Antenatal attachment, the relationship expectant parents develop during pregnancy with their unborn baby (Cranley 1981, Condon 1993) and its nature may be predictive for

future maternal-infant attachment (Condon & Corkindale 1997). In a study by Siddiqui & Hagglof (2000) maternal prenatal attachment towards the unborn baby has been found to be a good predictor of the early mother-infant relationship. Maternal representations of attachment (autonomous versus dismissing or preoccupied) in women expecting their first child have been found to predict subsequent infant-mother attachment patterns (secure versus insecure, Fonagy *et al.* 1991).

Maternal low attachment in pregnancy has been linked to high levels of depression and anxiety, low levels of social support (outside the partner relationship) and high levels of control, domination and criticism within the partner relationship (Condon & Corkindale 1997).

Father-infant attachment Apart from the mother-child bonding also paternal attachment and attachment to other possible principal caretaker occur (Brockington 1998). In infants reared in institutions attachment may develop between a staff member and the child. In a minority of families, father-child bonding is the principal attachment in infancy. Children have been found to engage differently with mothers and fathers in emotionally arousing situations already in the first year of life (Crockenberg & Leerkes 2000). Nowadays it is more usual for men to be more commonly and heavily involved in child-rearing (Brockington 1998). The role of the father is important in the family, and the importance increases if the mother is depressed (Stakes 1999). Fathers may have close involvement and identification with the pregnancy (Peterson et al. 1979, Condon 1985, Brockington 1998). After the birth they begin their own process of bonding with the infant (Brockington 1998). A father can be as competent as a mother in nurturing his infant (Brockington 1998).

In a Swedish study, index fathers were allowed to handle their new-born infant immediately after the Caesarean section delivery, while the control group was not permitted to do so. Three months later in a play situation, the index fathers showed more touching behaviour towards their infants than the control group (Rödholm 1981).

Psychodynamic theories In the psychoanalytic model, psychopathology is thought to be caused by active and sustained psychological conflict between drive-created wishful impulses and antithetical wishes, reality or conscience (McGlashan & Hoffman 2000). Freud (1917/1964, 1923/1964) emphasized that these structures develop during infancy and early childhood, and are stable by the end of the Oedipal period (ages 3 to 5). In psychoanalytic theories, infancy and early childhood are usually regarded to be very important for the personality and mental health (e.g. Erikson 1950/1982, Winnicott 1965/1981, Mahler *et al.* 1975). Stern (1985) considered that the beginning of sense of self is in the infant at least from birth, if not antenatally. The first separation-individuation process has been seen to occur in toddlerhood, while the second occurs in adolescence (Rosenstein & Horowitz 1997).

Erikson (1950/1982) elaborated the eight stages of ego development across the life cycle, where the first period from birth to about 18 months deals with trust versus mistrust. Stable identity could not be created without basic trust. A person without a basic sense of trust or hope may be predisposed to schizophrenia and depression (Erikson 1950/ 1982).

Spitz (1965/1975) considered that the newborn does not feel separated from the environment. In the first half of the first year the infant does not have other memories besides memories of some signals. Spitz (1965/1975) claimed that infants after age of 6

to 8 months and separated very early from their mothers for three months or more were at risk for so-called anaclitic depression. First symptoms after separation were crying, isolation, sleeplessness, weight decline, respiratory infections, and afterwards after the weeping solidified, stiffness, passivity and increased difficulties in making contact with the infant. After 5 months of separation and lack of proper mother substitute, the state was followed by so-called hospitalism, increase of symptoms and even death (Spitz 1965/1975).

Mahler *et al.* (1975) considered that there are three developmental phases in mother-infant object relations. During the first two months of life the infant spends most of the day in a half-sleeping, half-waking state, in the autistic phase. From 2 to 6 months of age, the infant enters a phase of symbiosis, an undifferentiated state of fusion between the baby and mother. The separation-individuation period with four subphases starts around 6 months and lasts until about 36 months (3 years). First in this period comes the differentiation subphase between 6 and 10 months of age, when the child is observed to become aware of the fact that the mother is a separate person. The second subphase, practicing, occurs between about 10 and 16 months of life, followed by rapprochement between 16 and 24 months, and the development of objects constancy between 24 and 36 months (Mahler *et al.* 1975).

Stern (1985) denied the autistic and symbiotic phases in the normal development of an infant. Stern considered that the beginning of sense of self has been in the infant at least from birth if not antenatally. The sense of self and interaction are constructed in five stages in the first 3 years of life. The emergent self from birth to 2 months is based on bodily self and physiological needs. The core sense of self appears between 2 and 6 months, and is associated with greater interpersonal relatedness. The sense of subjective self appears between 7 and 9 months, and is a major progress in the matching of intrapsychic states between the mother and the child. The verbal or categorical sense of self appears between 15 and 18 months, and the narrative sense of self between 3 and 5 years (Stern 1985).

In psychoanalytic theories schizophrenia is hypothesized to be associated with an early disharmony in the caregiver-child bond (Alanen 1997, Gabbard 2000, McGlashan & Hoffman 2000). Disruption of early bonding has been suggested to increase the risk of psychotic disorders (Olin & Mednick 1996). Even so, this traumatic-developmental perspective on the aetiology of schizophrenia has been generally discredited (McGlashan & Hoffman 2000). Criminal behaviour has been connected to the person's faulty development of the superego and lack of anxiety and guilt feelings about his behaviour (Tardiff 2000). Freud (1917/1957) and Winnicott (1964/1973, 1965/1981) have suggested that parental loss or separation is connected to psychopathology later on in offspring. According to Kandel (1998) insights from psychoanalytic works have usually been derived from clinical studies of individual cases.

2.5.3 Gene-environment interaction

In most major psychiatric disorders familial risk has been shown to predispose to the disorder (Kendler *et al.* 1995, Mathews & Freimer 2000). Risk for schizophrenia for a child with a parent with schizophrenia is thirteen times the risk of general population (Gottesman 1991). Genes have been postulated to be responsible for the high risk (Cardno *et al.* 1999). Behavioural problems and antisocial behaviour also have familial predisposition (Brennan & Mednick 1993, Szatmari *et al.* 1993). Even so, this familial pattern of aggressive behavioural problems especially in adolescents has not been associated with genetic risk to the same extent as in schizophrenia (Lyons *et al.* 1995, Mathews & Freimer 2000, Steiner & Feldman 2000).

Genotype – environment interaction may be described as a genetic control of sensitivity to environmental factors and on the other hand, environmental control of gene expression (Kendler & Eaves 1986, Wahlberg *et al.* 2000). Many pre and postnatal environmental risk factors may act additively with each other, or may indicate the existence of gene environment interactions (Kendler 1995). Genes control the way in which the development of the nervous system is modified by the environment (Cannon *et al.* 2003). Adverse psychosocial circumstances in childhood or birth complications may interact with genetic vulnerability to increase the risk of psychosis (Cannon *et al.* 1993). The effect of life events can vary according to genetic vulnerability. Individual differences in environmental risk exposure are influenced by genetic factors (Rutter & Silberg 2002). The interplay between nature and nurture has been emphasized (Rutter 2002), and their effects should not be considered separately (Rutter *et al.* 1997).

High-risk adoptees with genetic liability to schizophrenia seem to be more sensitive than control adoptees to environmental factors in the family (Tienari *et al.* (1994). In the Finnish Adoptive Family Study of Schizophrenia Tienari *et al.* (1994, 2002) found that adoptees at genetic risk were more vulnerable than control adoptees to family environmental adversities.

2.5.4 Biopsychosocial model

The biopsychosocial model has been created to integrate biological, psychological and social aspects of human beings. Engel (1980) has applied the biopsychosocial model in describing the genesis of diseases. Diseases are influenced by factors at different levels: from molecules and cells to individual psychology and to interpersonal and social context, culture and nation. Each level in the hierarchy represents a dynamic system (such as a person). Each system is at the same time a component of the higher system. So, nothing exists in isolation. A person cannot be fully characterized as a dynamic system without characterizing a larger system, e.g. the environment.

All mental processes can be seen as functions of the brain, too (Kandel 1998). Genes, their combinations and protein products are important for interconnections between neurons in the brain and the details of their functioning, so genes exert a significant control over behaviour (Kandel 1998). Even so, altered genes do not explain all of the

variance in mental disorders. Social or developmental factors also contribute to a significant degree. Just as genes contribute to behaviour, so do behaviour and social factors affect the brain by feedback, modifying the expression of genes and thus the function of nerve cells. Learning can induce alterations in gene expression, which give rise to changes in neuronal connections. For example, it is conceivable that effective psychotherapy or counselling may produce long-term changes in behaviour, presumably through learning, by changing gene expression that alter the strength of synaptic connections and by producing structural changes that alter the anatomical pattern of interconnections between nerve cells of the brain (Kandel 1998).

A child's development is connected to positive and negative feed back mechanisms in different levels of the biopsychosocial model (Wahlberg 1994). The development of the central nervous system, for example, provides the baby with tools with which to observe the environment more closely and be in psychological and social interaction with the parent, which can in turn promote more neural development (Wahlberg 1994).

Early emotional adaptational functions may differ from later functions (Emde 1998). The first 18 months of life are probably different in adaptive organization from the second and third years. Developmental psychobiology involves increasingly organized complexity. Genetic and environmental influences with respect to emotional processes are likely to change with development. Also, new configurations of emotions as well as new sets of genetic and environmental influences are likely to rise (Emde 1998).

The human life cycle involves changing systems, such as family life cycle (Gerson 1996). A person's life contains varying developmental stages with differing environmental contexts (Kendler 1995). In infancy and early childhood, social environment is practically almost the same as the family of origin. In adolescence, this environment begins to get larger towards friends and social activities. The school environment also remains often rather important. In early adult life, individuals usually leave their parental home, make decisions about an occupation and their couple, and concentrate on their own work, family, and social environments (Kendler 1995).

2.5.5 Longitudinal life-course model

Developmental epidemiology is interested in early-life risk factors for disease later on in life (Cannon *et al.* 2003). Causation of the outcome can be seen as a dynamic process involving time dimension, development over time and an interplay of causal interactions (Krieger 1994). Three former studies of the Northern Finland 1966 Birth Cohort have presented a life-span developmental model including schizophrenia (Isohanni 2000, Isohanni *et al.* 2000, Kemppainen 2001).

In spite of the fact that schizophrenia is regarded as a brain disease (Lieberman 1999), there is evidence that early family environment has an impact on the development of the disease. This is understandable, as interaction with the most important persons during the development of an individual plays a crucial role in the development of neural connections in the brain (Siegel 2001).

2.6 Summary of the literature

Early risk factors of the antenatal period and infancy have been increasingly linked to psychiatric disorders, besides genetic origins. One seventh part of the variance in liability to schizophrenia is estimated to be explained by unique environmental factors, both biological and psychosocial (Cannon *et al.* 1998, Cardno *et al.* 1999). Previous studies have suggested that a range of different biological factors and psychological stresses, mainly during gestation, may increase the risk of later schizophrenia in the offspring (Cannon *et al.* 2003). Various early bio-psycho-social risk factors have been observed to predispose to criminal behaviour, too (Tardiff 2000). Studies on juvenile delinquency usually consider the family environment to be more important than genetic factors (Lyons *et al.* 1995).

In earlier studies, the child's age at the time of separation has varied, and the separation type has not been defined clearly (as was also discussed by Räsänen 1988, Sauvola 2001). A number of studies have examined the question of whether parental separation increases the later risk of depression (Sethi 1964, Abrahams & Whitlock 1969, Brown & Harris 1978, Lloyd 1980, Bowlby 1981, Kennard & Birtchnell 1982, Roy 1985, Hällström 1986, O'Neil *et al.* 1987, Zahner & Murphy 1989, Kendler *et al.* 1992b), but there have been fewer to examine its role in relation to schizophrenia (Granville-Grossman 1966, Veijola 1996). There have been some studies of criminality in the offspring with parental separation (Wadsworth 1979, Räsänen 1988, Virkkunen *et al.* 1996, Raine *et al.* 1997a, Kemppainen *et al.* 2002, Sauvola *et al.* 2002). However, to the author's knowledge, no epidemiological studies have been published in English or Finnish about the association between separation in the first year of life and later schizophrenia in the offspring, except for preliminary results from a Danish project reported in a review where reference was made to an unpublished manuscript (Schiffman *et al.* 2001). Also, as far as the author knows, no previous studies have been published before in English on the association between separation in the first year of life and later criminality, except for the Danish study of male criminality by Raine and colleagues (1997a), where institutionalization in the first year of life was included in mother's early rejection of the child among other risk factors.

Even though maternal depression is common both during the antenatal and the postnatal period (O'Hara *et al*. 1982, Evans *et al*. 2001), studies following the mental health in the offspring of antenatally depressed mothers are far fewer than in the case of offspring of postnatally depressed mothers. In the studies of offspring with maternal postpartum depression the focus has been on problems in childhood and not in adolescence and adulthood in the offspring. As far as the author knows, there have been reports concerning schizophrenia in the offspring of antenatally depressed mothers only in the Northern Finland 1966 Birth Cohort (Myhrman *et al*. 1996, Jones *et al.* 1998, Veijola *et al.* 1998a). To the author's knowledge, no report has been published before in English of schizophrenia in the offspring of antenatally depressed mothers where familial vulnerability is taken into account among the subjects with schizophrenia. Also, as far as the author knows, no follow-up studies on the association between maternal antenatal depressed mood and criminality of the offspring in adolescence and adulthood have been reported in English before.

3 Aims of the present study

The aims of the present study were to investigate in two data sets whether very early separation in the first year of life and maternal antenatal depressed mood in pregnancy are risk factors for schizophrenia and criminality in the offspring later on in adolescence and adulthood.

The detailed aims of the study were:

1. To investigate if separation at birth is associated with schizophrenia in the offspring in the Christmas Seal Home Children Study (I).
2. To investigate if separation at birth is associated with criminality in the offspring in the Christmas Seal Home Children Study (II).
3. To investigate if maternal depressed mood in pregnancy is associated with schizophrenia in the offspring in the Northern Finland 1966 Birth Cohort Study (III).
4. To investigate if maternal depressed mood in pregnancy is associated with criminality in the offspring in the Northern Finland 1966 Birth Cohort Study (IV).

4 Subjects and study design

In this thesis, two data sets were used: the Christmas Seal Home Children Study (in originals papers I and II) and the Northern Finland 1966 Birth Cohort Study (in originals papers III and IV).

4.1 Subjects and study design of the offspring with separation at birth in the Finnish Christmas Seal Home Children Study (I, II)

4.1.1 Finnish Christmas Seal Homes (I, II)

In 1936 the Finnish Anti-Tuberculosis Association founded the first institution, Joulumerkkikoti (the "Christmas Seal Home"), into which the children born into tuberculous families were gathered. Between 1936 and 1973, infants born into families with acute tuberculosis were admitted to three special nurseries in Tampere, Oulu and Kuopio (Anttolainen 1972). The institutions were funded by selling special Christmas Seals or stamps for Christmas cards, also used in the campaign against tuberculosis in other Nordic countries and the United States (Doyle 1989, Härö 1992). Apart from these three nurseries, there was the Pitäjänmäki Children's Home maintained by the Deaconess Institute of Helsinki, which looked after children born into tuberculous households in Helsinki (Anttolainen 1972). The Pitäjänmäki Children's Home does not belong to the study design.

The newborn infants were isolated directly at the maternity hospital before any contact with the tuberculous mother or other close relative. This was done with maternal consent and became an accepted aspect of public health policy and practice. Children in tuberculous households had a high risk of morbidity and mortality due to tuberculosis (Anttolainen 1972). In former reports from 1925-1964, infants and small children living in a tuberculous environment were estimated to have a mortality rate between 6.1 – 81.8% in other countries, and 35.0% in Finland, reported in 1964 (Anttolainen 1972). So,

the isolation was aimed to save the infant from a life-threatening disease. Care in the Christmas Seal Homes was provided by specialized doctors and nurses, according to prevailing standards. During the isolation all infants were given milk obtained from other mothers. Efforts were made by the staff in the Christmas Seal Homes to foster contact with the children's families, by sending them letters describing the development of the infant with attached photographs of him/her. An attempt was made to ensure that every child had his/her own nurse as a substitute for their mother, even though each nursery nurse had more than one infant to care for (Tamminen 1982).

Protection against tuberculosis The principles of infant isolation due to tuberculosis in the family as a prophylactic method were introduced at the beginning of the 20th century. Studies conducted on the effectiveness of isolation showed that the earlier an infant was removed from the source of exposure, the better its chances of avoiding infection (Bernard *et al.* 1925). Later, BCG (Bacille Calmette-Guérin) vaccination proved to be a good method of protecting children of tuberculous families against infection (Rosenthal *et al.* 1961). The results obtained by BCG vaccination were considered superior to those obtained by isolation alone (Kendig 1969). BCG vaccination became an integral part of this prophylactic procedure in Finland from 1941 onwards (Anttolainen 1972). In the general population in Finland, one third of infants were BCG vaccinated during the 1940s, and the percentage increased so that in the 1960s almost every infant was BCG vaccinated (Härö 1977).

The tuberculous member of the family was in most cases (75.5%) the mother (Anttolainen 1972). The newborns were first isolated and then given BCG vaccination to reduce the risk for tuberculosis. Usually, the newborn entered the Christmas Seal Homes within the first 24 hours of their life. When the tuberculin test had become positive, at the age of about two months, the infants were allowed to return home, provided there was no longer any apparent risk of infection. Frequently, however, particularly during the first years of the study period, the mother was unable to assume responsibility for her infant after the two months owing to inadequate nursing facilities. Hence, most of the children had to be kept in the Christmas Seal Home longer than would have been necessary for medical reasons. The average separation time was 218 days. The mean separation time was 288 days in 1945, but was reduced to 180 days in 1964. Until 1953, mortality in the nurseries was noticeably high, but after that the mortality was even lower than the infant mortality in the general population in Finland (Anttolainen 1972).

This policy employed for children born into tuberculous families was effective in reducing early mortality and morbidity of tuberculosis (Anttolainen 1972). In general, the deaths caused by tuberculosis per year diminished from 1.46‰ between 1941-1950, to 0.39‰ in 1951-1960 and to 0.13‰ in 1965 in Finland (Central Statistical Office 1969).

4.1.2 Study sample and referee subjects in the Finnish Christmas Seal Home Children Study (I, II)

Study sample The original index cohort consisted of 3 918 subjects born between 1945 and 1965 and isolated in three Christmas Seal Homes in Finland, located in the towns of

Kuopio, Oulu and Tampere (Figure 1). Of the original index cohort, 2 017 (51.6%) were males and 1 892 (48.4%) were females. The sex was unknown for nine subjects as no first name was mentioned in the original files.

Name, date of birth, place of birth, mother's name and father's name of each index subject were obtained from the archives of the Christmas Seal Homes. These data were given to the Population Register Centre of Finland for identification and to obtain the personal identification numbers used in Finland since the late 1960s. Of the original cohort the Population Register Centre was able to identify 3 069 index subjects. As the follow-up period was decided to start from 1 January 1971, the 14 identified individuals who had died and the 35 subjects who had emigrated from Finland before that date were excluded. Of the original cohort 77% (3,020, 1 617 males and 1 403 females) were included as index subjects. Of the final index subjects, 53.3% were males and 46.5% females. With regard to the remaining 849 subjects the authors were unable to establish whether they had died, emigrated or could not be identified for any other reason.

Reference subjects For every identified index subject two matched reference subjects were randomly chosen from the files of the Population Register out of those population members with the same sex, year of birth and municipality at birth as the index subjects. Six reference subjects died and 40 emigrated from Finland before 1 January 1971. In addition, 24 index subjects were accidentally assigned by the Population Register Centre to be reference subjects. Hence, 70 subjects were excluded from the reference group, leaving 70 (2.3%) index subjects with only one comparator. Altogether we obtained 5 970 reference subjects (3 197 males and 2 773 females; Figure 1).

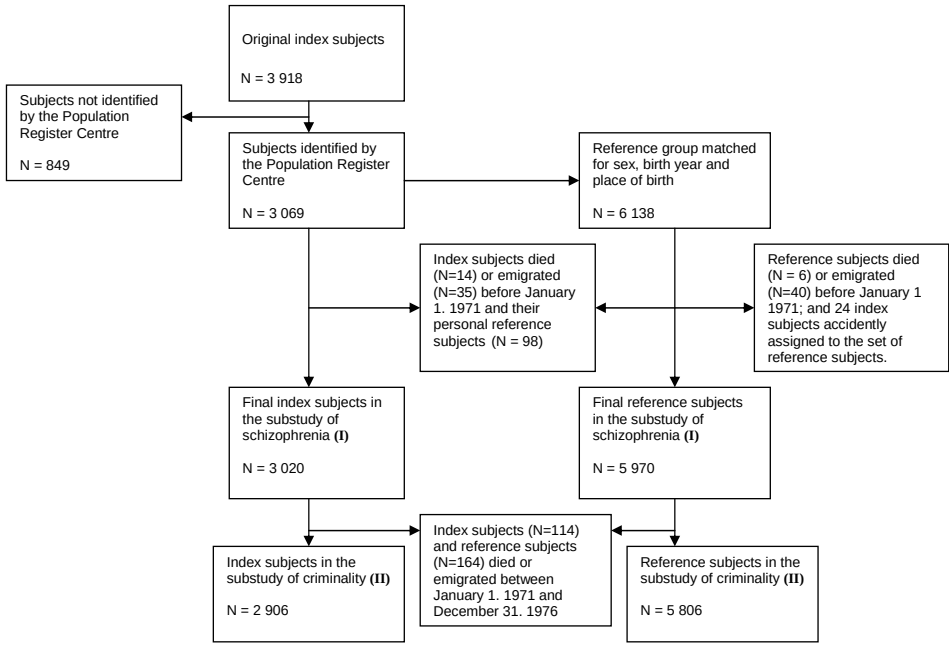

Fig. 1. Flow-chart of the Christmas Seal Home Children Study with the numbers (N) of the index and reference groups.

4.1.3 Additional data and socio-economic status in the Finnish Christmas Seal Home Children Study (I, II)

The original index cohort represents 0.2% of all children born during 1945-1965 in Finland. In 59% of the subjects the mother alone, in 24% the father alone, in 16% both mother and father and in 1% other family members had tuberculosis. 5% of the infants had birth weights lower than 2 500 grams (Anttolainen 1972). At an individual level the authors were not able to identify those subjects whose mother had tuberculosis or those who weighed less than 2 500 grams at birth. Nor was the length of stay in the nurseries available at an individual level for the index children. From the final index subjects of the substudy of schizophrenia, 92% of the children were returned to their homes after the separation period.

Socio-economic status The socio-economic status (SES) of the family of origin was not available for the reference group. Therefore, it was compared to the SES of the index group with the SES of the general working population in 1960 in Finland (Rauhala 1981). The SES was defined by the occupation of the father or if there was no father mentioned, by the occupation of the mother. Information on parental occupation was lacking for 335 index subjects. An originally 9-level classification (Rauhala 1966) was grouped into three broad SES categories: high, middle and low classes, each of the three comprising three original levels (highest, middle and lowest three levels), respectively. The same evaluation of SES was used in the population sample. In the index group 1.3% belonged to the high social class compared with 1.7% in the general population. 47.7% of the index group and 51.5% of the population belonged to the low class.

4.1.4 Drop-out group in the Finnish Christmas Seal Home Children Study (I, II)

There were 898 drop-out subjects in the original index cohort (including the 849 the Population Register Centre could not identify and the 14 who had died as well as the 35 who had emigrated before 1 January 1971). There were 400 males (45.0%) and 489 females (55.0%) in the drop-out group. The sex was unknown for nine drop-out subjects as no first name was mentioned in the original files. Of the original Christmas Seal Home Children sample, 20% (N = 400) of the males and 26% (N = 489) of the females were drop-outs. 29% (N = 443) of those born in 1945-1954 and 19% (N = 450) of those born 1955-1965 were drop-outs. For five drop-outs no birthday was available. After the isolation period 15% of the drop-outs (N=131) and 7% of the index subjects (N=201) did not return home from the Christmas Seal Home, but were instead most commonly replaced in children's' homes, nursing homes and adopted away. The place of return was unknown for six subjects (three drop-outs and three index subjects).

In a comparison of the drop-out group (N=898) with the final index group (N=3 020), there were no apparent differences in the SES. Of the index subjects 1.4% belonged to the high class and 47.9% to the low class, whereas the respective figures in the drop-out

group were 1.8% and 50.8%. Information on parental occupation was lacking in the case of 133 drop-out subjects and 335 index subjects.

4.1.5 Subjects and study design in the substudy of schizophrenia in the Finnish Christmas Seal Home Children (I)

Study sample The index cohort for schizophrenia substudy consisted of all 3 020 subjects (1 617 males and 1 403 females, Figure 1) born between 1945 and 1965 and isolated in three Christmas Seal Homes in Finland due to tuberculosis in the family, and 5 970 reference subjects (3 197 males and 2 773 females). After the separation 93% of the index subjects (N=2 819) went home from the Christmas Seal Home, whereas 7% of the index subjects (N=201) did not. The most common places for replacement instead of homes were children's' homes, nursing homes and adoption away. The place of return was unknown in three cases in index subjects.

Follow-up A 28-year follow-up for the cumulative incidence of schizophrenia and other psychotic disorders started on 1 January 1971 and ended on 31 December 1998. The subjects initially aged 6 to 26 were followed up until the ages of 33 to 53 years. The starting date for the follow-up was taken to be 1 January 1971, because from that year onwards the data in the computerized files were considered to be reliable. The Population Register Centre provided the information on date of death and emigration from Finland. The discharge date of the first hospitalization due to schizophrenia and other psychoses was obtained from the Finnish Hospital Discharge Register (FHDR). All Finnish citizens have virtually free access to inpatient and outpatient health care. The FHDR contains all diagnoses, admission and discharge dates for inpatient stays at public and private facilities. During the 28-year follow-up period, three different diagnostic classification systems were used on the FHDR, namely ICD-8 until the end of 1986, ICD-9 in 1987-1995 and ICD-10 from January 1, 1996. Individual follow-up was stopped at the date of death, emigration, the date of first admission due to schizophrenia, or on December 31, 1998, whichever came first.

Outcome variables During the 28-year follow-up period, three different classification systems for diagnosis were used on the FHDR, namely ICD-8 until the end of 1986, ICD-9 in 1987-1995 and ICD-10 from January 1, 1996. Schizophrenia cases were those individuals who had ICD code 295 (ICD-8 and ICD-9) or F20 (ICD-10). The specificity of the FHDR has been found to be good regarding schizophrenia (Isohanni *et al.* 1997), but its sensitivity is low. Many patients reaching DSM-III-R criteria for schizophrenia at a research assessment are diagnosed clinically (and so on the FHDR) as having other psychoses than schizophrenia (Isohanni *et al.* 1997). Hence, we also included other, non-organic psychotic disorders in the analyses. The codes for other psychotic disorders were 296-299 (ICD-8 and ICD-9) or F22-33 (ICD-10), except non-psychotic mood disorders.

Statistical analyses The cumulative incidence proportions of any outcome were calculated by the Kaplan-Meier method for the index group and the reference group. We also stratified by sex, and by birth cohort to those born in 1945-1954 and those born 1955-1965, respectively. The statistical analyses of the relative morbidity rate for

schizophrenia or, separately, other psychotic disorders between the index and reference groups were performed using the summary Mantel-Haenszel estimator of the rate ratio (RR), together with the 95% confidence interval (obtained from the standard error of the logarithm of RR), in which the age, sex, and municipality-matched sets formed the strata over which the estimator was calculated (Rothman & Greenland 1998).

4.1.6 Subjects and study design in the substudy of criminality in the Finnish Christmas Seal Home Children (II)

Study sample The study sample in the substudy of criminality in the Finnish Christmas Seal Home Children comprised those index and reference cohort members who were alive and living in Finland on 1 January 1977, which was the starting date for the follow-up of criminal offences. Due to deaths and emigration before 1977, the final index cohort consisted of 2 906 subjects: 1 570 males and 1 336 females (Figure 1). Of the index subjects, 1 048 belonged to the older birth cohort born 1945-54, and 1 858 index subjects to the younger birth cohort born 1955-65. Altogether, we obtained 5 806 reference subjects: 3 113 males and 2 693 females.

Follow-up Data on criminal offences were obtained from the registers of the computerized files of Statistics Finland (Statistics Finland 1999), from adolescence to middle age, for a 22-year follow-up period between 1 January 1977 and 31 December 1998. The subjects, initially aged 12-32, were followed up until the age of 34-54 years. 1 January 1977 was chosen as the date for starting the follow-up, because from that year onwards data on crimes were available in computerized files. The national register includes criminal records for the population over 15 years of age (Statistics Finland 1999), so for the youngest subjects follow-up started on their 15th birthday. Only aggregated numbers of criminal and non-criminal index and reference subjects according to subgroups (sex, age cohort) were given by Statistics Finland. Criminal records of individual subjects were not obtained because of privacy protection. For this reason, the date of crime was not available at individual level. Possible death or immigration was taken into account and person years at risk were calculated during the follow-up time 1977-1998**,** so that follow-up ended on the date of death or date of emigration.

Outcome variables The recorded and collected data on criminal offences obtained from the registers of computerized files of Statistics Finland (Statistics Finland 1999) covered all crimes by persons sentenced in courts of first instance (Kinnunen 2002). The data did not include persons sentenced to petty fines or summary penal orders (Kinnunen 2002). The crimes were classified into violent and non-violent crimes. The category of violent crimes included homicide, assault, robbery, arson, sexual crime and violation of domestic peace (Räsänen *et al.* 1999a). All other crimes were defined as non-violent. Subjects who had committed at least two violent crimes were defined as violent recidivists as suggested by Tengström *et al.* (2000).

Statistical analyses Cumulative incidences or incidence proportions of subjects with any crimes, non-violent or violent crimes and violent recidivism during the period 1977-98 were calculated in the index and in the reference cohorts, separately for males and

females and also in the two 10-year birth cohorts. The relative risk (RR) between index and reference cohorts was estimated by the ratio of corresponding proportions. As individual matching was dissolved in record linkage, it could not be taken into account in the analysis either. Hence, the approximate confidence intervals for the RRs were calculated using standard formulas for independent groups (Rothman & Greenland 1998).

4.2 Subjects and study design of the offspring of antenatally depressed mothers in the Northern Finland 1966 Birth Cohort (III, IV)

4.2.1 Subjects and data collection in the Northern Finland 1966 Birth Cohort (III, IV)

This prospective study is based on unselected, population-based, geographically defined material of the Northern Finland 1966 Birth Cohort with 12 058 live-born babies. Inclusion in the survey was determined by the calculated term, which fell between 1 January - 31 December 1966. The cohort covered 96.3 % of all the births over a period of one year in the two northernmost provinces of Oulu and Lapland in Finland (Rantakallio 1969, Rantakallio 1988).

Of all cohort members living in Finland at the age of 16, information as to the mothers' antenatal mood was available for 10 705 offspring. Data concerning the mother and offspring were gathered antenatally and at birth in 1965-1966. As part of the antenatal data collection, the mothers were asked by the interviewing nurse at the antenatal clinic during midgestation (mainly between the 24th and 28th gestational week) whether they felt that their mood had been normal, depressed or very depressed during pregnancy.

4.2.2 Study design in the substudy of schizophrenia in the Northern Finland 1966 Birth Cohort (III)

Follow-up Cohort members who appeared in the Finnish Hospital Discharge Register FHDR between the years 1982-1997 for any psychiatric disorder treated in inpatient ward were identified by record linkage using personal identification codes. Hospital-treated schizophrenia and psychosis in the cohort members were followed up to 31 years.

Outcome variables All psychiatric diagnoses of the cohort members in the FHDR were re-checked against DSM-III-R criteria (Isohanni *et al.* 1997, Moilanen *et al.* 2003). By the end of the 31st year, 100 cases (65 men) of DSM-III-R schizophrenia were identified and 55 cases (26 men) of other psychoses (Isohanni *et al.* 2001). Of the cohort

members (N=11 017), 0.9 % had hospital-treated schizophrenia (1.2 % in men, and 0.7 % in women). Data on maternal mood in pregnancy were missing in one case of schizophrenia and two cases of other psychoses.

Confounding variables We divided the group of schizophrenia patients into those having a psychotic first-degree relative and those without a known psychotic first-degree relative. In the case of the cohort members with schizophrenia, all hospital notes and available outpatient notes were checked to find out whether or not a first-degree relative had had a psychotic episode. According to the notes, 19 schizophrenia patients had a psychotic first-degree relative. Additionally in a field survey during 1999-2001, all of the 45 participating schizophrenia patients underwent Family Interview for Genetic Studies (FIGS; Maxwell 1992). In the FIGS procedure the patient and the mother, or if the mother was not willing or able to participate, the father or one of the siblings were asked whether any of the first-degree relatives had had psychotic symptoms. The FIGS found five additional cases. Of the 24 schizophrenia patients with a first-degree relative having a psychotic disorder (the familial risk FR group), the mother was psychotic in eight cases. Information on the mother's mood was lacking in one case with familial risk. The offspring with schizophrenia but without a known psychotic disorder in the close family (N = 76), were classified as having no familial risk for vulnerability for psychosis (no familial risk known group). In the familial risk group of schizophrenia cases, subgroups with and without a known maternal psychotic disorder were formed (e.g. schizophrenia patients with the mother having been psychotic; or with the father or the sibling having had psychosis). In the cohort members without schizophrenia, data on familial risk were not available.

Statistical analyses Cross-tabulations were used to assess the relation between maternal depression and schizophrenia and other psychoses of the offspring. The significance of the differences in frequency tables was tested using the Pearson Chi-Square test. In schizophrenia, all other cohort members were used as a reference group, whereas in other and all psychoses the reference group was all other cohort members except schizophrenia patients. Crude risk ratios (RR) with 95% confidence intervals (95%CI) were calculated for males and females in the association between mothers' depression and schizophrenia and other psychotic disorders in the offspring.

Also the association between very depressed maternal mood (versus non-depressed maternal mood) and schizophrenia in the offspring was analysed. In the subgroup of schizophrenia cases we compared the familial risk and no known familial risk groups of children of depressed and non-depressed mothers using the Chi-Square test. Because of the small number of cases with mothers feeling very depressed, we used Fisher's exact test when comparing the cohort groups of no schizophrenia, and schizophrenia with and without familial risk, with mothers' non-depressed versus very depressed mood in pregnancy. The computation was performed using SAS statistical software version 8 (SAS Institute Inc. 1999).

4.2.3 Study design in the substudy of criminality in the Northern Finland 1966 Birth Cohort (IV)

Follow-up Data on all crimes committed by cohort members until the end of 1998 resulting in a criminal record were collected from the files maintained by the Ministry of Justice in Finland. This national register includes criminal records for the population over 15 years of age as described in detail by Rantakallio *et al.* (1995). The criminal record is wiped clean after every 10 years (Sauvola 2001). The original data set included the years 1981-1992 and it was updated during the year 1999, covering the years 1993-1998 (Sauvola 2001). Hence, complete criminal records of the cohort members were followed up to age 33.

Outcome variables Data on crimes committed by cohort members is described in detail in the previous study of Rantakallio *et al.* (1995). Unconditional fines without imprisonment did not lead to a criminal record. In the present study the crimes were classified into violent and non-violent crimes. The category of violent crimes included homicide, assault, robbery, arson, sexual crime and violation of domestic peace (Räsänen *et al.* 1999a). All other crimes were defined as non-violent. The most common non-violent crimes among males were traffic offences and among females theft (Rantakallio *et al.* 1995). Subjects who had committed at least two violent crimes were defined as violent recidivists as suggested by Tengström *et al.* (2000). All other offenders were considered non-recidivists.

Confounding variables In the sub-study of criminality the logistic regression analysis was based on those risk factors which were significantly associated with either antenatal depression or with criminality from variables mainly presented in the earlier study of the cohort with a shorter follow-up (Rantakallio *et al.* 1995). The variables were parental socioeconomic status (high: I, II/low: III, IV/farmers), mother's marital status (married/not married), maternal age during delivery (age 20 years or more/age less than 20 years), place of residence at the time of the child's birth (rural/urban) and maternal smoking during pregnancy (none or the mother stopped before pregnancy/smoked daily more than one cigarette during the entire duration of pregnancy). Also wantedness of pregnancy (wanted or preferred later/unwanted; as described by Rantakallio and Myhrman 1990) and perinatal complications (no complications/yes, if low birth weight <2 500 g or short gestation time <37 weeks or perinatal brain damage; as described by Rantakallio *et al.* 1987) were taken into consideration as potential risk factors.

Statistical analyses Cross-tabulations were used to assess the relation between maternal depression and criminality of the offspring. The significance of the differences was tested using the Pearson Chi-Square test. Crude and adjusted odds ratios (OR) with 95 % confidence intervals (95%CI) were calculated for males and females in the association between maternal depression and criminality. Estimates were calculated for violent and non-violent criminals, violent recidivists and non-recidivists, and these were all compared with the category of non-criminals. Logistic regression analyses (McCullag & Nelder 1989) were conducted to examine the association between maternal antenatal mood and criminality as well as pre and perinatal biopsychosocial factors. SPSS for Windows statistical software was used (Norusis 1994).

4.3 Ethical considerations

4.3.1 Ethical considerations in the Finnish Christmas Seal Home Children Study (I, II)

Permission for gathering data for the Finnish Christmas Seal Home Children Study was obtained from the Data Protection Board in Ministry of Justice on 19 May 1997. The Data Protection ombudsman gave her permission to use the FHDR data on 1 October 1997. Different register institutions gave permits to gather their register data between the years 1998-2000: Population Register Centre on 4 December 1998, Statistics Finland on 18 December 2000, and the National Research and Development Centre for Welfare and Health (Stakes) in the Ministry of Social Affairs and Health on 23 October 1997.

This study has been approved by the Postgraduate Research Committee of the Faculty of Medicine, University of Oulu on 10 June 1997. The research plan was under review by the Ethics Committee of the Faculty of Medicine, University of Oulu on 15 August 1997.

4.3.2 Ethical considerations in the Northern Finland 1966 Birth Cohort Study (III, IV)

Permission for gathering data for the whole Northern Finland 1966 Birth Cohort Study was obtained from the Ministry of Social Welfare and Health Affairs in 1993 (Kemppainen 2001). The research plan for the 31-year follow-up study design of the Northern Finland 1966 Birth Cohort entitled the Northern Finland Health and Well-being Study (Sorri & Järvelin 1998) was reviewed by the Ethics Committee of the Faculty of Medicine, University of Oulu on 17 June 1996.

This present study has been approved by the Postgraduate Research Committee of the Faculty of Medicine, University of Oulu on 10 June 1997.

4.4 Personal involvement

Since 1996, the author has participated as a researcher in the Finnish Christmas Seal Home Children Study and since 1997 in the Northern Finland 1966 Birth Cohort Project. In the Finnish Christmas Seal Home Children Study the author has taken part from the beginning in the psychiatric study, including study design, applying for permissions to perform the study and to gather register data, gathering data and participating in the data analysis and reporting. In the Northern Finland 1966 Birth Cohort Project the author has been accorded permission to use the data and to report in psychiatric and criminality substudies and has participated in substudies' design, data analysis and reporting.

5 Results

5.1 Results in the Finnish Christmas Seal Home Children Study of the offspring with separation at birth (I, II)

5.1.1 Schizophrenia in the Finnish Christmas Seal Home Children with separation at birth (I)

During the 28-year follow-up, 46 (1.6%) subjects developed schizophrenia in the index group and 89 (1.6%) in the reference group (RR 1.01; 95%CI 0.75-1.37). The numbers of other psychoses were 43 (1.6%) and 75 (1.3%) respectively, implying 89 (3.2%) and 164 (2.9%) cases, respectively, for all psychotic disorders. In the original publication **I**, Table 1, the cumulative incidences and estimated rate ratios (RR) of schizophrenia and other psychotic disorders between the index and the reference subjects are presented. No evidence for an elevated morbidity in the index subjects was found in any of the subgroups (by gender or by birth cohort) of hospital-treated schizophrenia or of any other psychoses except very mildly in the younger female birth cohort for combined psychotic disorders (**I**: Table 1) .

5.1.2 Criminality in the Finnish Christmas Seal Home Children with separation at birth (II)

During the 22-year follow-up, 38.4% (N=603) of the male index subjects had committed at least one crime in 32 922 person-years (mean 21.0 y), whereas the corresponding figure among reference subjects was 30.5% (N=949) in 66 319 person-years (mean 21.3 y) (**II**: Table 1). Among females the cumulative incidences of any offences were 9.1%

(N=121) in 28 589 person-years (mean 21.4 y) in the index cohort and 5.9% (N=158) in 57 515 person-years (mean 21.4 y) in the reference cohort (**II**: Table 2).

Of the male index subjects 12.1% (N=190) and 7.1% (N=221) of the reference cohort had committed violent offences. Corresponding proportions for violent recidivism in males were 5.2% (N=82) and 3.6% (N=112), respectively. 26.3% (N=413) of the male index subjects and 23.4% (N=728) of the reference cohort had committed non-violent crimes. The corresponding proportions for non-violent crimes in females were 7.9% (N=105) and 5.0% (N=137), respectively. Violent crimes were rare among female subjects.

In male index subjects, the risk for violent crimes was 1.7-fold, for violent recidivism 1.5-fold and for non-violent crimes 1.1-fold when compared with the controls (**II**: Table 1). The estimated relative risks for different crime categories were above 1.0 for both the older and younger birth cohort in men, although the relative risks were slightly higher among the younger birth cohort (**II**: Table 1). In female index subjects, a 1.5-fold increase was seen in the risk for non-violent crimes (**II**: Table 2).

5.2 Results in the Northern Finland 1966 Birth Cohort Study of the offspring of antenatally depressed mothers (III, IV)

5.2.1 Maternal depressed mood in pregnancy in the Northern Finland 1966 Birth Cohort Study (III, IV)

Altogether 14.4% (N=1 704) of the mothers (N=11 804) felt themselves depressed (depressed or very depressed) during pregnancy when asked at mid-gestation in 1965-1966. Of these mothers, 12.1% (N=1 432) had a depressed mood and 2.3% (N=272) a very depressed mood. Of the mothers of the offspring living in Finland at the age of 16, 11.8% felt depressed and 2.1% very depressed during pregnancy, covering altogether 13.9% of the mothers.

Of those cohort members who were alive and living in Finland at the age of 16 (N=11 017), information was available as to the maternal mood for 10 705 offspring, 14.0% (N=1 493) of whom had a mother with antenatal depression.

5.2.2 Schizophrenia in the offspring of antenatally depressed mothers in the Northern Finland 1966 Birth Cohort (III)

The cumulative incidence of schizophrenia was constantly higher in the offspring of depressed mothers than in the offspring of non-depressed mothers (Figure 2). Of the offspring of mothers without maternal depressed mood, 0.9% (N=80) had schizophrenia, whereas 1.1% (N=14) of the children of somewhat depressed mothers and 2.2% (N=5) of the offspring of very depressed mothers had schizophrenia. When comparing schizophrenia in the offspring of very depressed to the children of non-depressed mothers, the difference was statistically significant (RR 2.61; 95%CI 1.07-6.38).

In Table 2 the offspring of depressed and very depressed mothers are combined. The cumulative incidence of hospital-treated schizophrenia was 1.3% among the offspring of depressed mothers and 0.9% among the descendants of non-depressed mothers (RR 1.46; 0.89-2.40). The cumulative incidence of schizophrenia was higher among both male and female offspring of depressed mothers than among the descendants of non-depressed mothers, but the associations were statistically non-significant.

In Figure 3 there are columns presenting prevalences (%) of mothers' antenatal depressed mood among the non-schizophrenic and schizophrenic offspring with and without familial risk for psychosis. The prevalence of antenatal depression was 34.8% in mothers of schizophrenia patients with familial risk for psychosis, and 14.5% in the mothers of schizophrenia patients without familial risk (p=0.023, RR 2.25; 95%CI 1.12-4.51, Table 3). The corresponding rate was 13.8% in the mothers of other cohort members. In a subgroup of offspring with schizophrenia and a psychotic mother, the prevalence of depression among mothers was 50% (three depressed mothers and one very depressed mother out of 8 psychotic mothers).

Fig. 2 Cumulative incidence (%) of schizophrenia by the age (years) of onset (the first hospitalization) in the offspring of antenatally depressed and non-depressed mothers in the Northern Finland 1966 Birth Cohort.

Table 2. Cumulative incidence (%) and number (N) of schizophrenia and other psychotic disorders (from 1 January 1983 up to 31 December 1997) in the offspring of antenatally depressed and non-depressed mothers in the Northern Finland 1966 Birth Cohort.

	Maternal depression		
	Yes	No	Risk ratio
	% (N)	% (N)	(95% Confidence Interval)
Males	(N=755)	(N=4 727)	
Schizophrenia [a]	1.5 (11)	1.1 (53)	1.29 (0.68-2.47)
Other psychoses [b]	0.1 (1)	0.5 (25)	0.25 (0.03-1.85)
All psychotic disorders [b]	1.6 (12)	1.7 (78)	0.96 (0.53-1.76)
Females	(N=738)	(N =4 485)	
Schizophrenia [a]	1.1 (8)	0.6 (27)	1.78 (0.81-3.92)
Other psychoses [b]	0.8 (6)	0.5 (21)	1.73 (0.70-4.28)
All psychotic disorders [b]	1.9 (14)	1.1 (48)	1.76 (0.79-3.18)
All	(N=1 493)	(N =9 212)	
Schizophrenia [a]	1.3 (19)	0.9 (80)	1.46 (0.89-2.40)
Other psychoses [b]	0.5 (7)	0.5 (46)	0.94 (0.42-2.08)
All psychotic disorders [b]	1.7 (26)	1.4 (126)	1.27 (0.83-1.93)

[a] Reference group: all other cohort members [b] Reference group: all other cohort members except schizophrenia patients

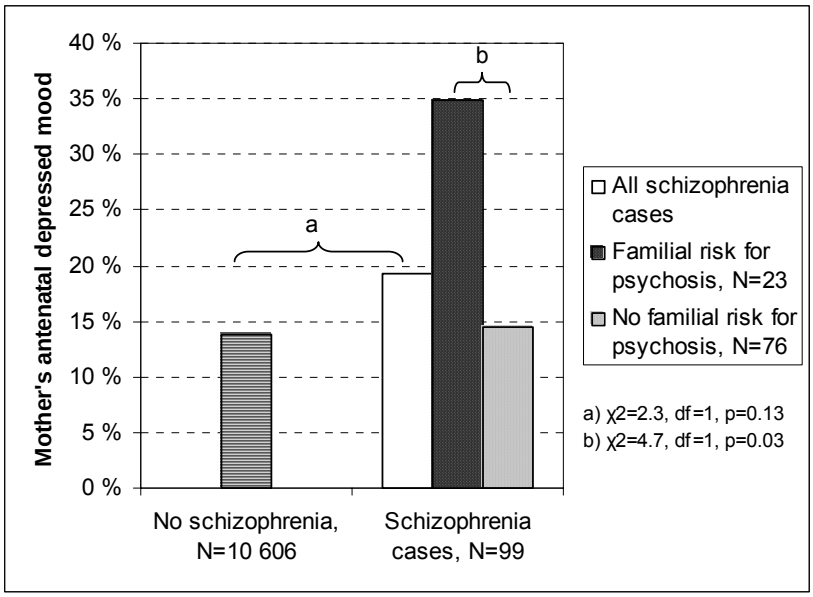

Fig. 3. Prevalence (%) of mothers' antenatal depressed mood in their non-schizophrenic and schizophrenic offspring with and without familial risk for psychosis in the Northern Finland 1966 Birth Cohort.

Table 3. Prevalences (%) and numbers of mothers' self-reported depressed mood during pregnancy in the nonschizophrenic and schizophrenic offspring (with and without known familial risk FR for psychosis) in the Northern Finland 1966 Birth Cohort.

Maternal antenatal mood	No schizophrenia (N=10 606)	Schizophrenia cases (N=99)	Risk Ratio (95%CI)[a]	Schizophrenia without FR (N=76)	Schizophrenia with FR (N=23)	Risk Ratio (95%CI)[b]	Schizophrenia with FR, mother not psychotic[c] (N=15)	Schizophrenia with FR, mother psychotic[d] (N=8)
Depressed	13.9% (1474)	19.2% (19)	1.46 (0.89-2.40)	14.5% (11)	34.8%(8)	2.25 (1.12-4.51)	26.7% (4)	50.0% (4)

[a] Risk ratio and 95% confidence interval; the cohort group of no schizophrenia compared with all schizophrenia patients. [b] Risk ratio and 95% confidence interval; the cohort group of schizophrenia patients with familial risk compared to those without familial risk for psychosis. [c] Schizophrenia patients having had a psychotic father or sibling, but mother not known to have been psychotic. [d] Of the offspring with schizophrenia and familial risk, six mothers were known to have had schizophrenia and two mothers had other psychoses

5.2.3 Criminality in the offspring of antenatally depressed mothers in the Northern Finland 1966 Birth Cohort (IV)

In the cohort, there were altogether 679 criminal offenders (6.2 %) at the age of thirty-two years. Of these, 607 (10.9%) were male and 72 (1.3%) female criminal offenders. Of the males, 7.1% were non-violent offenders (N=395), 3.8% violent offenders (N=212) and 1.8% violent recidivists (N=98). The corresponding proportions in female subjects were 1.2% (N=63), 0.2% (N=9) and 0.1% (N=4), respectively.

Of all the offspring whose mothers reported a depressed mood, 136 (9.1%) had committed a crime versus 525 (5.7%) descendants of non-depressed mothers (Pearson Chi-Square test, value 25.8, df 1, $p<0.001$). The proportions of different kinds of crimes in male and female offspring are shown in article **III**: Tables 1 and 2 according to the mothers' antenatal depression. In men, 15.6% (N=118) with depressed mothers had criminal records versus 10.0% (N=472) of those with non-depressed mothers ($p<0.001$, adjusted OR 1.5; 95%CI 1.2-1.9). The corresponding figures among women were 2.4% (N=18) versus 1.2% (N=53, $p<0.01$, adjusted OR 1.5; 95%CI 0.8-3.0).

Compared to the sons of mothers not suffering from depression during pregnancy, the sons of antenatally depressed mothers demonstrated a twofold risk of having committed a violent crime or of being violent recidivists. Similarly, maternal antenatal depression increased two-fold the risks of non-violent crimes and criminality in general in daughters, but the association diminished when other risk factors were controlled. In the association between maternal depression and criminality, the adjusted odds ratios in the male offspring were 1.6 (95%CI 1.1-2.4) for violent offenders and 1.4 (1.0-1.9) for non-violent offenders, 1.7 (1.0-3.0) for violent recidivists and 1.5 (1.1-1.9) for non-recidivists.

6 Discussion

6.1 Main findings (I-IV)

Separation at birth and maternal antenatal depressed mood were not found to be statistically significantly associated with schizophrenia per se (**I**, **III**), but they were linked to criminal behaviour in the offspring (**II**, **IV**). The findings support socio-environmental aetiology of criminal behaviour. Such support was not found in the case of schizophrenia. The findings are in line with the idea that genetic and biological factors are more important in the aetiology of schizophrenia.

6.2 Schizophrenia

6.2.1 Schizophrenia in the Finnish Christmas Seal Home Children with separation at birth (I)

Very early separation from the mother was not observed to increase the risk for schizophrenia. The cumulative incidences of schizophrenia and other psychotic disorders in the Christmas Seal Home Children did not differ from those in the reference group. Studies of groups from a similar background have not been published earlier.

In the sub-groups, the analysis of the differences between the index cohort and the reference cohort revealed that there was a somewhat elevated risk for all psychotic disorders in the younger female birth cohort, which might well be a chance finding, as over 20 associations were examined (Sterne & Smith 2001).

The separation was mainly temporary, more than 90% of the infants were sent home from the Christmas Seal Homes. The separation between the mother and the child occurred immediately after the birth. The infant experienced a new separation when

leaving the familiar Christmas Seal Home environment at an average age of 7 months. It may well be that the overall separation affected attachment (Bowlby 1978) between the mother (or other principal caregiver) and the child. Even so, no separation was connected to schizophrenia in the Finnish Christmas Seal Home Children Study.

The quality of the nursing in the Christmas Seal Homes was probably better than in some other institutions, such as the Foundling Home that Spitz (1965/1975) described or in the case of Romanian adoptees with severe early privation (O'Connor *et al.* 2000). Lack of breast-feeding has been put forward as a risk for schizophrenia by some (McCreadie 1997) but refuted by others (Leask *et al.* 2000, Sasaki *et al.* 2000). In the present study all index subjects received human milk, but were not breast-fed (Tamminen 1982).

The cumulative incidence of schizophrenia was slightly higher, 1.6%, compared to estimated lifetime prevalence of 0.4% to 1.4% as reported from certain study populations in the United Kingdom and the United States (Cannon & Jones 1996). It is still in line with earlier findings of schizophrenia in Finland, 1.2% (Hovatta *et al.* 1997) and 1.3% (Lehtinen *et al.* 1990) being quoted. The definition of schizophrenia also included schizoaffective and schizophreniform psychoses (ICD-8 and ICD–9). This may have raised somewhat the cumulative incidence of schizophrenia in the study. In the present study 2.9% of the index cohort and 2.8% of the reference cohort had a hospital treated psychotic episode, where as the prevalence of all psychoses has been found to be 2.2% in the Finnish adult population (Lehtinen *et al.* 1990). In our study, schizophrenia was equally prevalent among men and women. In a recent review by Räsänen *et al.* (2000), the lifetime risk for schizophrenia has been found to be equally common in both sexes in most studies. No differences were found in the cumulative incidence of schizophrenia between the two birth cohorts.

Temporary placement from tuberculosis-affected family to an adequate nursing home in the first year of life was not found to be associated with schizophrenia in the offspring later on in adolescence and adulthood. Even though there was no excess of schizophrenia or psychosis in the Christmas Seal Home Children, they have had a somewhat increased risk for depression (Veijola *et al.* in press) and mortality (Veijola *et al.* 2003).

6.2.2 Schizophrenia in the offspring of antenatally depressed mothers in the Northern Finland 1966 Birth Cohort (III)

In an earlier study of the same birth cohort with some years' shorter follow-up, Jones *et al.* (1998) found maternal depressed mood in pregnancy to have been elevated in schizophrenia patients. In the present study we found that the association could be explained by familial risk, as the mothers of schizophrenia patients with familial risk for psychosis had an excess of both depressed and very depressed mood during pregnancy. So, our study provides no evidence per se for an association between mothers' self-reported depressed mood during pregnancy and the subsequent risk of schizophrenia in their offspring.

Very depressed maternal mood during pregnancy was associated with an almost 3-fold risk for schizophrenia. Mothers' very depressed mood was elevated in the schizophrenia patients with familial risk, especially with the mother herself having had psychosis, but also to a lower extent in the cases without known familial risk. However, the number of schizophrenia cases among the children of very depressed mothers was limited.

The mothers of schizophrenia cases with familial risk had suffered from depressed mood during pregnancy two times more often than others. This could be explained by familial risk including genetic risk for psychosis. Mothers with schizophrenia and mothers with a close relative having schizophrenia tend to be more commonly depressive. Also, mothers with schizophrenia could have depressed mood. Depressive symptoms occur frequently in schizophrenia patients (Chintalapudi *et al.* 1993, Subotnik *et al.* 1997, Sands and Harrow 1999, Bottlender *et al.* 2000). Women married to husbands with schizophrenia may feel depressed. Spouses of psychiatric patients - also of schizophrenia patients - have an elevated risk for depressive disorders (Wittmund *et al.* 2002). Furthermore, mothers whose offspring - in this case an older sibling - has become schizophrenic, may tend to get depressed (Natale & Barron 1994).

Maier *et al.* (1993) suggested that there might be a familial relationship between predisposition to schizophrenia and to major depression. Schizophrenia in a family member has been connected to increased risk for affective disorder and vice versa (van Os & Verdoux 2003). Depression in a relative raised the risk for schizophrenia 1.9-fold (while almost the same, i.e. a 2.0-fold increase, was seen in unipolar depression; Maier *et al.* 1993). Parental affective disorder has been associated with a 8.6-fold risk for schizophrenia-related psychoses (Erlenmeyer-Kimling *et al.* 1997). In some families, the same genes could contribute to susceptibility to both schizophrenia and affective disorder (Henn *et al.* 1995). In some cases there could be genetic transmission, i.e. antenatal depressed mood and schizophrenia might be different expressions of phenotypes of the same susceptibility genes (Kelsoe 2000). Erlenmeyer-Kimling *et al.* (1997) concluded that familial liabilities to schizophrenia and affective disorders show both specificities and commonalities.

The cumulative incidence of schizophrenia was 0.9%, which is in line with earlier findings of schizophrenia in Finland, 1.2% (Hovatta *et al.* 1997) and 1.3% (Lehtinen *et al.* 1990) being quoted; and also when compared to the estimated lifetime risk of about 1% in European populations (Gottesman 1991). In men the rate of schizophrenia was somewhat higher, 1.2%, compared to 0.7% in women, which may be due to some women getting schizophrenia later in life than men.

In this study the prevalence of antenatal maternal depressed mood was 13.9%. The prevalence is in the same range as in the few previous studies dealing with the rates of antenatal depression (Watson *et al.* 1984, O'Hara *et al.* 1990, Kitamura *et al.* 1993, Areias *et al.* 1996a, Kitamura *et al.* 1996). In fact, it was almost the same as in the British study reported by Evans *et al.* (2001), where 13.5% of the women had probable depression at 32 weeks of pregnancy scored by the Edinburgh postnatal depression scale.

6.3 Criminality

6.3.1 Criminality in the Finnish Christmas Seal Home Children with separation at birth (II)

First, we found that temporary separation at birth from a tuberculous family was associated with criminal behaviour in general, both in the male and female offspring. Second, in male indexes, the risk was especially elevated for violent crimes and violent recidivism. Third, in both sexes, the index subjects had committed non-violent offences more commonly.

The index subjects had a somewhat elevated risk for overall offending, which is in line with former findings of the early risk factors of criminality (Weininger 1972, Kolvin *et al.* 1988a). In the review by Weininger (1972), parental loss in childhood was connected to juvenile delinquency and criminality in prisoners. Kolvin *et al.* (1988a) found poor quality of mothering, parents' marital breakdown and parental illness to be connected to criminal behaviour. Childhood deprivation gives rise to a higher rate of offending (Kolvin *et al.* 1988b). Also, antenatal maternal stress together with paternal loss has been connected to later criminality in the offspring (Huttunen & Niskanen 1978).

Very early parental separation in tuberculous families was especially associated with violent crimes and violent recidivism in sons. The result linking very early separation and severe violent criminality in men is in line with the former finding of paternal absence in recidivist violent male offenders and male arsonists (Virkkunen *et al.* 1996). Early maternal rejection together with birth complications (Raine *et al.* 1994) as well as an unstable family environment combined with early neuromotor deficits (Raine *et al.* 1996) have been shown to predispose men to violent crime in adolescence in a Danish 1959-1961 birth cohort. Maternal rejection, mainly institutionalization in the first year of life and attempted abortion, interacting with birth complications was found to predispose specifically to violence in men (Raine *et al.* 1997a).

In the present study, mainly the mothers of the index subjects had tuberculosis, also when expecting the baby (Anttolainen 1972). We do not know about their mood during pregnancy. In another substudy of this thesis, mothers' depressed mood in pregnancy has been connected to criminality in their offspring, especially to severe violent criminality in sons (**IV**).

Among girls separated from home, the risk for non-violent crimes was somewhat elevated. In the Northern Finland 1966 Birth Cohort Study, criminality was increased in girls born to single mothers (Rantakallio *et al.* 1995). The proportions of crimes, especially violent and violent recidivist ones, were rare among women. It has been a common finding that crimes and especially violent crimes in women are rare (Smith 1995). It is thus impossible to say whether or not very early separation increases the risk for violent and violent recidivist offending in women.

In male index subjects, the risk for non-violent offending was slightly elevated. Raine *et al.* (1997a) found maternal rejection with birth complications to be specifically associated with violent crimes in men, but not with non-violent criminality. In the present

study, the estimated risk ratio for violent crimes in males was higher than for non-violent crimes, which is in line with the findings of Raine and colleagues (1997a).

In the present study, the cumulative criminality rate was rather high in both male cohorts. About a third of all the men (male index and reference subjects) had a criminal record in Statistics Finland. This is due to the fact that rather minor offences are included in the register (Statistics Finland 1999) and to the rather long follow-up time. In the national register on persons sentenced in courts of first instance in 1996, the most prevalent groups of principal offences were traffic infractions and traffic offences (including drunken driving), the third largest group, e.g. petty theft, trailing far behind (Statistics Finland 2002). In an earlier report of criminal statistics in a Finnish sample born in the late 1950s, 47% of males (and 16% of females) had been convicted at least once by the age of 27 when taking into account all convictions, including drunkenness and traffic offences (Pulkkinen 1988). In British, Danish and North-American samples, one quarter to one third of males had been convicted for crimes in early adulthood (McCord 1979, Farrington 1988, Kolvin *et al.* 1988a, Raine *et al.* 1997a), whereas only about 6% of the females had offended (Kolvin *et al.* 1988a). In a Danish study, almost 11% of the young adult men were classified as violent and 20% as non-violent offenders (Raine *et al.* 1997a). On the whole, in the present study the proportions of crimes committed by males and females, and also violent and non-violent offences in men, are in line with previous findings.

In the younger birth cohorts among males, the number of offences in different criminal categories was slightly elevated compared to the elder cohorts, which is in line with the findings that the peak age of onset and incidence of convictions in males is during adolescence (Pulkkinen 1988). Adult convictions are usually preceded by juvenile convictions (Pulkkinen 1988).

Several bio-psycho-social risk factors are associated with criminal behaviour (Tardiff 2000). In the attachment theory, Bowlby (1978) suggested anger and aggressive behaviour of a child as being a response to separation. Interrupted bonding between the child and the caregiver may increase the risk for later criminality (Bowlby 1955). The separation between the mother and the child occurred immediately after the birth, but the infant also experienced a new separation when leaving the familiar Christmas Seal Home environment at an average age of 7 months. It may well be that the overall separation affected the attachment (Bowlby 1978) between the mother (or other principal caregiver) and the child. Bowlby (1955) linked prolonged separation of a child from its mother during the first 5 years of life to lack of affection and persistent delinquency. The quality of the nursing in the Christmas Seal Homes was probably better than in institutions such as the Foundling Home Spitz (1965/1975) described, or in case of Romanian adoptees with severe early privation (O'Connor *et al.* 2000).

Separation from both parents has been linked to an elevated rate of antisocial behaviour in boys, but only in homes with very poor marriage relationship between parents (Rutter 1971). Parental absence has been considered to be a major contributing factor to delinquency, but by no means the only factor (Marino & McCowan 1976). Rising levels of parental divorce and more frequent hospital admission with temporary separation have been considered to play a minor role in the rise in delinquency (Rutter & Giller 1983). Rutter (1973) has stressed the importance of the nature of separation and its effects on bonds with parents. Also in this study, very early separation per se may have

been connected to other forms of stress, e.g. chronic serious disease in a family member. It was mainly the mothers of the index subjects who had tuberculosis. In any case, when studying the association between offending and different areas of deprivation in the families, parental illness appeared to carry the lowest risk (Kolvin *et al.* 1988b).

Besides criminal behaviour, the Christmas Seal Home Children have been found to have a somewhat increased risk for depression (Veijola *et al.* in press) and mortality (Veijola *et al.* 2003), but not for schizophrenia or psychosis. Very early separation may act as an indicator of problems in the wellbeing of the offspring and the family. Many mechanisms are involved in the different separation experiences of children, the separation itself probably being the main stress in only a few (Rutter 1979). A solitary traumatic early experience may not usually totally disturb one´s life; rather an accumulation of adverse events may be necessary (Vaillant, 1977).

6.3.2 Criminality in the offspring of antenatally depressed mothers in the Northern Finland 1966 Birth Cohort (IV)

Our main finding was that the emotional state of a pregnant mother might have some, although slight, influence on later criminality in the offspring. This finding supports the former finding of Huttunen and Niskanen (1978) on the effects of antenatal stress. For male offspring of antenatally depressed mothers there was a statistically significant but slight increase in criminality in the boys' adult lives.

When adjusted for other biopsychosocial risk factors, maternal depression increased the risk for both non-violent, violent, non-recidivist and violent recidivist crimes as well as for criminality in general approximately 1.5-fold in male offspring. The risk for violent and violent recidivist criminality diminished more when adjusted than the risk for non-violent crimes. This indicates that one or more risk factors other than maternal depression could explain more severe violent and violent recidivist criminality.

We also demonstrated that maternal depression in pregnancy was associated with non-violent crimes in their daughters. As the proportions of violent and violent recidivist crimes in particular were low among women, it is difficult to say whether or not maternal depression could increase the risk for violent and violent recidivist offences in female offspring. Crimes, especially violent crimes have commonly been rare among women (Smith 1995). For daughters of depressed mothers, there were no statistically significant associations with criminality after adjustment for confounding factors, even though a tendency may be seen parallel to the findings in the male offspring with a greater number of criminal offenders. In the present study, the connection between maternal antenatal depression and the offspring's criminality was not strong, being statistically significant in males, but not in females, after adjustment.

If the association we found is not spurious but clinically relevant, there are some theoretical explanations. Maternal antenatal depression may be connected to severe personality disorders, especially antisocial personality disorders, in the offspring. Antisocial personality disorder has been connected to criminal behaviour in earlier reports (Lyons 1995). The association between the mothers' antenatal depression and

criminality of the offspring may be due to the previous finding that antenatal depression increases the risk for postnatal depression (Mowbray *et al.* 1995, Wilson *et al.* 1996), which increases the risk for difficulties in the mother-infant relationship (Cogill *et al.* 1986, Murray *et al.* 1991) and for behavioural problems in the child (Gizynski 1985, Philipps & O'Hara 1991). The latter in turn forms a risk for later antisocial and other personality disorders (Hellgren *et al.* 1994). Many biopsychosocial risk factors are associated with maternal depression, which may also increase the risk for personality disorders in the offspring. Taken separately, both parental depression and family risk factors are significant predictors of conduct disorder among children (Fendrich *et al.* 1990).

Another explanation for our finding may also be the biological effects of maternal depression on the infant, perhaps through the hormonal systems (Steer *et al.* 1992, Rosenblum & Andrews 1994). The correlation between maternal and foetal cortisol might help to explain the effects of antenatal maternal stress on the foetus (Gitau *et al.* 1998). One explanation that has been put forward is genetic transmission (Merikangas & Weissman 1986, Kringlen 1993, Langbehn *et al.* 1998), i.e. offspring of depressed mothers may have a genetic risk for criminal tendency. Antenatal depression may also be connected to other risk factors of criminality not yet studied. Mothers' antenatal depressed mood may be part of general difficulties in life, such as biopsychosocial problems, which may increase the risk for criminal behaviour in the offspring. Maternal depressed mood may act as an indicator of problems in the wellbeing of the offspring and the family.

In this study, the prevalence of antenatal maternal depressed mood was 14%. This is in the same range (8-17 %) as in the few previous studies dealing with the rates of antenatal depression (Watson *et al.* 1984, O'Hara *et al.* 1990, Kitamura *et al.* 1993, Areias *et al.* 1996a, Kitamura *et al.* 1996).

6.4 Limitations and strengths of the study

6.4.1 Limitations in the Finnish Christmas Seal Home Children Study of the offspring with separation at birth (I, II)

The Finnish Christmas Seal Home Children study with substudies of schizophrenia and criminality was strictly a register study. Even though the exposed cohort was relatively large, the numbers of outcome cases in the substudy of schizophrenia were quite small as can be expected for such a relatively rare disease as schizophrenia. However, the specificity of the FHDR has been found to be high regarding schizophrenia (Isohanni *et al.* 1997).

We were not able to match the controls with childhood socioeconomic status. However, when we compared the childhood socioeconomic status of the indexes with the socioeconomic status of the general working population in 1960, there were no

significant differences. In addition, in several other studies childhood social class has not been associated with later schizophrenia (Done *et al.* 1994, Jones *et al.* 1994, Aro *et al.* 1995, Cannon & Jones 1996). Criminality, on the other hand, has been associated with low paternal socio-economic status (Rantakallio *et al.* 1995). Even though tuberculosis in general has been strongly associated with poverty (Spence *et al.* 1993, Davies 1999), it may not be the case in Finland (Wasz-Höckert & Donner 1962). Still, we did not have access to data on how much poverty was increased due to the tuberculosis in the families of the index subjects.

Because of the design of our study, with a register-based approach, many potential risk factors for later schizophrenia or criminality (perinatal complications, nutritional deficiency, other maternal prenatal infections than tuberculosis, parental death, parental chronic somatic illness) were beyond the scope of the design, as were also possible protective factors (for example, Kolvin *et al.* 1988b in the case of criminality).

It is unknown how many of the controls or later on of the indexes had separation experiences. In two Finnish studies, childhood separations (mainly parental death and parental divorce) from parents were rather common (Aro & Palosaari 1992, Veijola *et al.* 1998b), about one fifth to one fourth of the population studied. However, we can presume that very early separation did not happen systematically in the controls.

Another risk factor that could not be taken into account was birth weight lower than 2 500 g in about 5 % of the original material (Anttolainen 1972). Nor could we control obstetric complications (Rifkin *et al.* 1994, Kendell *et al.* 1996, Jones *et al.* 1998), nutritional deficiency in pregnancy (Jones 1994, Hulshoff Pol *et al.* 2000) or other prenatal infections than tuberculosis, e.g. viral infections in pregnancy (Mednick *et al.* 1994). We were not able to investigate the quality of attachment between the infant, the mother and father, and the caregivers in the Christmas Seal Home. In this setting it was not possible to study how a longer separation or less adequate care would affect the risk for future schizophrenia or criminal behaviour. Even so, the finding that indexes did not have higher rates of schizophrenia or other psychoses than the reference group remains the principal finding of the study.

There was a rather high drop-out (N=898, 23%) rate among the original material of all the Christmas Seal Home Children born 1945-1965. It is possible that those indexes who died before the follow-up period would have had higher risk for developing schizophrenia. In the drop-out group the proportion of female subjects (55%) was somewhat increased compared with the original index sample (48%), which may be due to the tracking problems caused by the change of surname of women when getting married. From the Christmas Seal Homes the drop-out subjects were about twice as commonly as final index subjects replaced to children's' homes, nursing homes or adopted away. The change of surname due to adoption may partly explain the rate of the drop-out group. In the older cohort in the original sample there were more drop-out subjects than in the younger cohort, which might be due to higher rates of change of surname, mortality and immigration among the older subjects.

There was a slight increased proportion of males in the final study sample when compared with the original sample. In the final index subjects 54% were males and 46% females, whereas in the original study sample 52% were male and 48% were female subjects. However, the final index subjects had reference subjects matched for gender, age and municipality of birth.

Due to privacy protection, the data on crimes were not available to us at individual level. Therefore, we could not calculate exact individual person times until the occurrence of the events of interest, so no lifetable method was used to correct the incidence proportions for variable follow-up times. The relative comparisons between the index and reference cohorts were not materially affected as the mean follow-up times in the groups were very similar. Because of lack of detailed individual data on dates of crimes, the cumulative incidences of criminality are probably slightly underestimated. The confidence intervals of the relative risks may be somewhat wider than they would be if individual matching could have been taken into account.

6.4.2 Strengths in the Finnish Christmas Seal Home Children Study of the offspring with separation at birth (I, II)

Every index subject had a separation experience in his or her first year of life, which lasted for approximately the first 7 months. In other studies of the association between early separation and later schizophrenia or criminal behaviour, neither the child's age at the time of separation nor the length of separation had been so strictly defined (Granville-Grossman 1966, Weininger 1972, Watt and Nicholi 1979, Ingraham *et al.* 1995, Furukawa *et al.* 1998, Agid *et al.* 1999).

The material was also rather extensive, about 3 000 indexes with very early separation and 6 000 matched reference subjects chosen by the population-based register. The follow-up time was fairly long, up to the ages of 33-53 years, covering 28 years in the substudy of schizophrenia and 22 years in the substudy of criminality. It may be that some older cohort members who had had their first admission to hospital due to schizophrenia before 1971 were still taken into account as cases while having later admissions. By virtue of individual matching, the index and reference groups were comparable with respect to age and place of birth.

There are different kinds of separation, such as parental divorce and parental death. When investigating the effects of parents' divorce on the child, it is difficult to separate the separation itself and parents' marital discord. In case of parental death, it may not be possible to look for the effects of parental death itself on the psychological development of the offspring without it being associated with the subsequent consequences of parental loss, such as economical decline or fall in social status. In the Christmas Seal Home Children Study it was possible to study rather implicitly how temporary separation at birth from the family may be associated with mental health problems and criminal behaviour later on in adolescence and adulthood in the offspring, even though the impact of parents' chronic somatic illness cannot be excluded.

The topic of the substudies of schizophrenia and criminal behaviour in the Finnish Christmas Seal Home Children with separation at birth was new.

6.4.3 Limitations in the Northern Finland 1966 Birth Cohort Study of the offspring of antenatally depressed mothers (III, IV)

There are some limitations inherent to the substudies of schizophrenia and criminality in the offspring of antenatally depressed mothers in the Northern Finland 1966 Birth Cohort Study. First, it is notable that maternal depression did not signify a clinical condition, but was the mothers' self-reported depressed mood, and can therefore be considered to be a limitation of this study. However, the prevalence of antenatally depressed mood was in the same range as in earlier reports. Also, mothers reported their mood to the nurse who had met with them on their earlier visits to the antenatal clinic, i.e. who had known them earlier. It might also be that a simple question as to the depressed mood is useful for detecting antenatal depression, the same way as a single-item interview "Are you depressed ?" was determined to be valid when screening for depression in terminally ill cancer patients (Chochinov *et al.* 1997). Whooley *et al.* (1997) found that two questions were as good as more questions for detecting depression. Their other question concerned feeling down, depressed or hopeless.

Second, even though the birth cohort was big, more than 10 000 cohort members, the number of cases of schizophrenia was relatively small (N=100) because the disease is rather rare. Third, because of the study design, we were unable to study the attachment between the infant and the mother and also father.

Fourth, the schizophrenia groups with and without familial risk were divided according to the known existence of a psychotic first-degree relative. Hospital case notes and available outpatient notes of all subjects were used, and less than half of the subjects were additionally interviewed with the Family Interview for Genetic Studies (FIGS; Maxwell 1992), that is all subjects who were willing to participate. The FIGS procedure uncovered additional cases. The author presumes that there were probably some more familial risk cases in the subjects who did not participate in the FIGS. The validity of the hospital notes may also be questionable. However, the variable of the familial risk for schizophrenia was the best that could be got out of the material. Gottesman (1991) presumed that about 63% of schizophrenics are estimated to have negative family histories, without any first or second degree relatives having schizophrenia, which means that about one third of schizophrenics have affected relatives. In our study about one fourth of the schizophrenia patients had a first-degree relative with a psychotic episode. Data on familial risk were not available for other cohort members without schizophrenia.

6.4.4 Strengths in the Northern Finland 1966 Birth Cohort Study of the offspring of antenatally depressed mothers (III, IV)

The strength of the substudies of schizophrenia and criminality in the offspring of antenatally depressed mothers was that this was a prospective project with a long follow-up time started antenatally. The material was representative with all cohort members born in the same year and in a geographically defined area. There were no age, period or

cohort effects because of the birth cohort design (Zahner *et al.* 1995). Also the topic of the study was rather new. There have been reports of the same cohort study concerning schizophrenia with follow-up times shorter by a few years (Myhrman *et al*. 1996, Jones *et al.* 1998, Veijola *et al.* 1998a). To the author's knowledge, this was the first report of schizophrenia in the offspring of antenatally depressed mothers where familial vulnerability was taken into account among the subjects with schizophrenia. Also, as far as the author knows, no follow-up studies on the association between maternal depressed mood during pregnancy and criminality of the offspring in adolescence and adulthood have been reported in English before.

7 Conclusions

7.1 Main conclusion (I - IV)

In conclusion, mother's depressed mood in pregnancy or separation at birth per se is unlikely to increase the risk for schizophrenia, but seems to be connected to criminal behaviour, especially violent criminality in men.

7.2 Schizophrenia in the offspring with parental separation at birth or maternal depressed mood in pregnancy (I and III)

Separation at birth and maternal antenatal depressed mood were not found to be statistically significantly associated with schizophrenia. Even though the risk for schizophrenia was not statistically significant, the offspring of antenatally depressed mothers had somewhat elevated levels of schizophrenia. The familial risk for psychosis explained the elevated prevalence of depressed mood during pregnancy among the mothers of the offspring with schizophrenia. So, very early separation and maternal depressed mood during pregnancy per se are unlikely to raise the risk for schizophrenia in the offspring.

7.3 Criminality in the offspring with parental separation at birth or maternal depressed mood in pregnancy (II and IV)

Parental separation at birth or mother's depressed mood in pregnancy seems to be connected to criminality in adolescence and adulthood, especially violent criminality in men. However, the effect of both exposures on criminal behaviour was not very strong.

Criminal behaviour was more prevalent among subjects separated at birth temporarily from their families due to tuberculosis in the family than in the reference cohort. Especially violent crimes were prevalent in the male the Christmas Seal Home Children cohort. Very early separation may have some influence on later criminality in the offspring. This may be explained by a variety of risks experienced during pregnancy, delivery and childhood. One explanation may be that the very early temporal separation from the parents at birth may have unfavourable effects on later psychological development, especially in some of the male subjects.

There was a significant but slight increase in criminality among male offspring of antenatally depressed mothers. The emotional state of a pregnant mother may have some, albeit limited influence on later criminality in the offspring. It may be that mothers' depression during pregnancy is part of general difficulties in life, e.g. biopsychosocial problems, which may increase later criminality in their children.

7.4 Practical implications

Children with very early separation should receive adequate care from caretakers after the separation. It seems that in the Christmas Seal Homes this was done in a proper way. In the case of a child being separated from its parents due to severe illness, war or other traumatic experiences which may lead to separation from the family, efforts should be taken to protect the development of the child adequately. In case of parental loss, children need a warm, secure and continuous experience of care from a few caretakers as suggested by Black (1998).

In the maternity clinics questions should be asked about the mothers' frame of mind. A simple inventory might be the best way to screen possible depressive mothers. Actually, in recent years more effort has been focused on the psychological and social wellbeing of the mother and the family in the antenatal clinics in Finland. In the recommendations issued by Stakes, the National Research and Development Centre for Welfare and Health in Finland, maternal clinic workers in the primary health care system, mainly mid-wives and nurses, are recommended to talk with the mother and also the father, among other things, also about their frame of mind and postnatal depression and also to make a house call fairly immediately after the delivery (Stakes 1999).

In case of a depressive mother, the background factors including familial risk for psychosis should be explored thoroughly. An intervention to help the mother should be used. This can be conducted by the maternity clinic staff, or in severe cases, by specialized psychiatric services staff. Mothers with antenatal depression should be followed after delivery. Nowadays in Finland it is recommended that a good contact is maintained in the primary health care maternal care system, even if the mother is also sent to maternity policlinic in the hospital or to psychiatric outdoor department, with special emphasis on adequate collaboration between the health care instances (Stakes 1999). In the case of maternal depression, concrete practical help for the daily home work and child care could be offered to the mother and her family, in addition to conversations or therapy with a specialized health care worker, group sessions and support with other

mothers, and sometimes an antidepressant or other medication (Stakes 1999). There has been a project aimed at educating primary health care workers to put more emphasis on observing the early interaction between the mother and her child (Stakes 1999, Kurki *et al.* 2000). However, so far there has been limited evidence from randomized controlled trials to support the implementation of antenatal group interventions to reduce postnatal depression in women at risk (Austin 2003).

Special care should be taken if the mother has psychosis or if the mother's depression is combined with psychotic disorder in another close family member of her child.

7.5 Implications for further study

The Finnish Christmas Seal Homes Children present a unique data set to study the effect of very early separation on the offspring. In this study two outcomes were explored later in adolescence and early adulthood of the separated children: schizophrenia and criminal behaviour. Also other outcomes in the Christmas Seal Home Children have been and will be studied, e.g. depression and social attainment. At individual level the separated children could be interviewed in the frame of the attachment theory. One future topic in the Christmas Seal Home Children Study would be to study whether the attachment of the child and the mother might have been permanently affected even though the children are relatively well in adulthood.

In the present study schizophrenia and criminal behaviour were studied in the offspring of antenatally depressed mothers. Also other aspects of wellbeing should be explored in these children. Antenatal depression has not been studied as much as maternal postnatal depression, even though both are relatively common. The consequences of antenatal depression for the wellbeing of the offspring are still mostly unexplored both in childhood, adolescence and adulthood. In order to be reliable, the setting of such studies should be prospective with proper samples. The Northern Finland 1966 Birth Cohort is the only study so far to follow adult mental health fulfilling these criteria. Further studies are needed to replicate the results obtained from our study.

Maternal depression may be considered as psychological separation for the offspring. Also in the Northern Finland 1966 Birth Cohort study – as in the Christmas Seal Home Children study – the attachment theory might be a suitable theoretical frame to explore the relation of the child and the mother, and consequently the later attachment style/type and also mental health of the offspring. For this purpose, individual approaches are needed.

The interaction between early environmental and genetic factors and its effects on mental health would be an interesting topic for further studies. When possible early environmental risk factors for schizophrenia are explored, familial risk should be taken account.

8 Summary

8.1 Background and aims of the study

Early risk factors of the antenatal period and infancy have been increasingly linked to diseases and subsequently to psychiatric disorders. Problems in the early mother-infant relation pose a hypothetical risk of disadvantages later on in life in the offspring. The objective of this thesis was on the one hand to study the associations between parental separation at birth and maternal depressed mood in pregnancy, and on the other hand, the development of schizophrenia and criminality in the male and female offspring in adolescence and adulthood in two data sets: the Finnish Christmas Seal Home Children Study (in the originals papers I-II) and the Northern Finland 1966 Birth Cohort (III-IV).

8.2 Material and methods

8.2.1 The Finnish Christmas Seal Home Children Study (I, II)

I Schizophrenia in the offspring with parental separation at birth. In the Christmas Seal Home Children Study the index cohort consisted of 3 020 subjects born in 1945-1965 in Finland who were temporarily isolated from their family immediately after birth to nursing homes due to tuberculosis in the family. The average separation time was seven months. For every index subject, two reference subjects were matched for sex, year of birth and place of birth. Data were obtained on diagnoses of schizophrenia and other psychoses from the Finnish Hospital Discharge Register arising from adolescence to middle age, between 1 January 1971 and 31 December 1998.

II Criminality in the offspring with parental separation at birth. The criminality substudy of the Christmas Seal Home Children Study consisted of 2 906 index subjects. Also for

these subjects two matched reference subjects were randomly selected. Data on criminal offences were obtained from Statistics Finland between 1 January 1977 and 31 December 1998. The association between parental separation and subcategories of non-violent and violent criminality and violent recidivism in male and female offspring, respectively, was analysed. Subjects who had committed at least two violent crimes were defined as violent recidivists.

8.2.2 The Northern Finland 1966 Birth Cohort Study (III, IV)

III Schizophrenia in the offspring of antenatally depressed mothers. At mid-gestation mothers of 12 058 babies in the Northern Finland 1966 Birth Cohort were asked by a nurse at the antenatal clinic if they felt depressed. This general population birth cohort (i.e. offspring) was followed up for 31 years being record-linked with the Finnish Hospital Discharge Register covering the years 1982-1997. All psychiatric diagnoses were re-checked against DSM-III-R criteria. 100 cases of schizophrenia were identified. We divided the schizophrenia patients into those having a psychotic first-degree relative (schizophrenia patients with familial risk for psychosis) and those without a known psychotic first-degree relative.

IV Criminality in the offspring of antenatally depressed mothers. The Finnish Ministry of Justice provided information on the criminal offences of all descendants up until the end of 1998. The associations between maternal depression and subgroups of violent and non-violent, violent recidivist and non-recidivist criminality in male and female offspring were analysed.

8.3 Results

8.3.1 The Finnish Christmas Seal Home Children Study (I, II)

I Schizophrenia in the offspring with parental separation at birth. In the Finnish Christmas Seal Home Study the 28-year cumulative incidence of schizophrenia was 1.6% both in the index cohort and in the reference cohort (rate ratio RR 1.0; 95%CI 0.8-1.4).

II Criminality in the offspring with parental separation at birth. Of the male index subjects 12.1%, as compared with only 7.1% of the reference cohort (RR 1.7; 95%CI 1.4-2.1), had committed violent offences. 5.2% of the male index subjects and 3.6% of the male reference subjects were violent recidivists (RR 1.5; 1.1-2.0). 26.3% of the male index subjects and 23.4% of the reference cohort had committed non-violent crimes (RR 1.1; 1.0-1.3). Among females non-violent crimes had been committed by 7.9% of the

index subjects and by 5.0% of the reference subjects (RR 1.5; 1.2-2.0). Violent crimes were rare among female subjects.

8.3.2 The Northern Finland 1966 Birth Cohort Study (III, IV)

III Schizophrenia in the offspring of antenatally depressed mothers. In the Northern Finland 1966 Birth Cohort Study 14 % of the mothers had depressed mood during pregnancy. The cumulative incidence of hospital-treated schizophrenia was 1.3% among the offspring of depressed mothers and 0.9% among the descendants of non-depressed mothers (RR 1.5; 95%CI 0.9-2.4). The prevalence of antenatal depression was 35% in mothers of schizophrenia patients with familial risk for psychosis. The respective prevalence was 14% both in the mothers of schizophrenia patients without familial risk and in the mothers of other cohort members.

IV Criminality in the offspring of antenatally depressed mothers. In men, 9.1% with depressed mothers and 6.8% with non-depressed mothers had committed non-violent offences (crude OR 1.4; 95%CI 1.1-1.9, when adjusted for mother's marital status, smoking, wantedness of the pregnancy, place of residence, socioeconomic status and perinatal complications, OR 1.4; 1.0-1.9). The proportions of violent offences were 6.5% versus 3.2% (crude OR 2.2; 1.5-3.0, adjusted OR 1.6; 1.1-2.4) and of recidivist violent offences 3.2% versus 1.4% (crude OR 2.4; 1.5-3.8, adjusted OR 1.7; 1.0-3.0) in men. The corresponding figures among women were for non-violent offences 2.0% versus 1.0% (crude OR 2.0; 1.1-3.5, adjusted OR 1.7; 0.9-3.3) and for violent offences 0.4% versus 0.1% (crude OR 3.1; 0.8-12.3, adjusted OR 0.6; 0.1-6.0).

8.4 Discussion

I and III Schizophrenia in the offspring with parental separation at birth and in the offspring of antenatally depressed mothers. In conclusion, separation at birth and maternal antenatal depressed mood were not found to be significantly associated with schizophrenia. Even though the risk for schizophrenia was not statistically significant, the offspring of antenatally depressed mothers had somewhat elevated levels of schizophrenia. The familial risk for psychosis explained the elevated prevalence of depressed mood among the mothers during pregnancy. Maternal depressed mood during pregnancy and very early separation per se are thus unlikely to raise the risk for schizophrenia in the offspring. Support was not found for socio-environmental aetiology of schizophrenia.

II and IV Criminality in the offspring with parental separation at birth and in the offspring of antenatally depressed mothers. Temporary placement from a tuberculosis-affected family to adequate nursing homes in the first year of life and mothers' depressed mood in pregnancy seem to be connected to criminality (especially violent criminality in

men) in adolescence and adulthood. Criminal behaviour was more prevalent among subjects separated at birth from their families because of tuberculosis in the family than in the reference cohort. Especially violent crimes were more prevalent in the male Christmas Seal Home Children cohort. Among male offspring of antenatally depressed mothers there was a significant but slight increase in criminality, especially in severe violent criminality. The emotional state of a pregnant mother and very early separation may have some influence on later criminality in the offspring. This may be explained by a variety of risks experienced during pregnancy, delivery and childhood. One explanation may be that the very early temporal separation from the parents at birth and maternal depressed mood may have unfavourable effects on later psychological development, especially in some of the male subjects. The findings support socio-environmental aetiology of criminal behaviour.

8.5 Conclusions

Separation at birth or mother's depressed mood in pregnancy per se is unlikely to increase the risk for schizophrenia, but seems to be connected to criminal behaviour in adolescence and adulthood, especially violent criminality in men. Very early separation and maternal depressed mood may act as indicators of problems in the wellbeing of the family. Family problems may affect the child. In case of adverse events in the family, special attention may be needed to protect the normal development of the child. In case of a depressive mother, the background factors including familial risk for psychosis should be explored thoroughly. Special care should be taken if the mother has psychosis or if the mother's depression is combined with psychotic disorder in another close family member of her child.

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