

Antti Alaräisänen

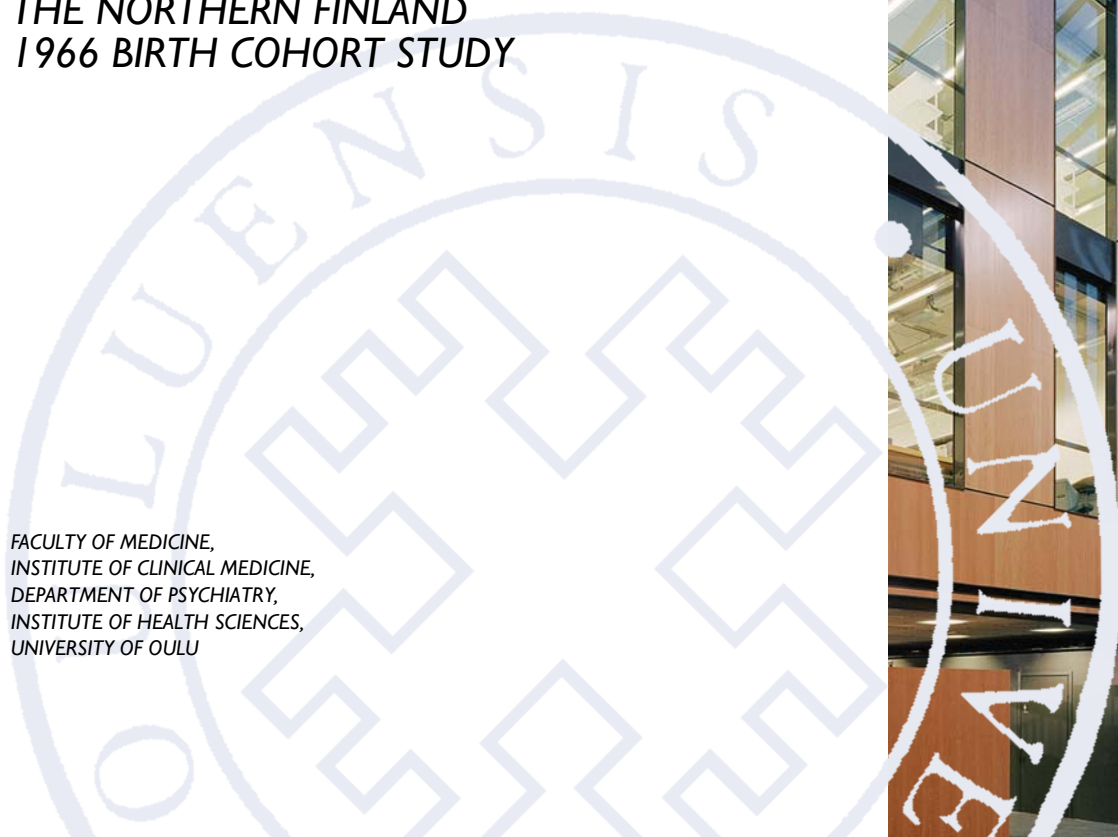
RISK FACTORS AND
PATHWAYS LEADING TO
SUICIDE WITH SPECIAL
FOCUS IN SCHIZOPHRENIA

THE NORTHERN FINLAND
1966 BIRTH COHORT STUDY

FACULTY OF MEDICINE,
INSTITUTE OF CLINICAL MEDICINE,
DEPARTMENT OF PSYCHIATRY,
INSTITUTE OF HEALTH SCIENCES,
UNIVERSITY OF OULU

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ANTTI ALARÄISÄNEN

**RISK FACTORS AND PATHWAYS
LEADING TO SUICIDE WITH
SPECIAL FOCUS IN SCHIZOPHRENIA**

The Northern Finland 1966 Birth Cohort Study

Academic Dissertation to be presented with the assent of the Faculty of Medicine of the University of Oulu for public defence in Auditorium I, Building PTI of the Department of Psychiatry (Peltolantie 17), on 3 September 2010, at 12 noon

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Abstract

The aim of this study was to investigate risk factors, developmental pathways and the rate of attempted or accomplished suicide in a longitudinal population-based prospective birth cohort.

The Northern Finland 1966 Birth Cohort (NFBC 1966) consists of 12,068 pregnant women with expected dates of delivery in 1966, and their 12,058 live-born children. The data used here was collected prospectively for 10,934 individuals who were alive and resident in Finland at the age of 16. This study utilized an extensive data set collected in antenatal clinics at mid-pregnancy, by postal questionnaire at the age of 14 years and through national registers.

A total of 121 suicide attempts (57 males) and 69 suicides (56 males) had occurred by the end of 2005. A single-parent family was a risk factor for attempted suicides and grand multiparity for suicides in male offspring. Adolescent regular smoking was associated with an increased risk of suicide attempts in both genders and for suicide among males. Good school performance at age 16 years was associated with an increased risk of suicide in psychosis cases, whereas in persons who did not develop psychosis it was associated with a lower suicide risk. The suicide rate in new-onset schizophrenia followed until the age of 39 was 7%. Over two thirds of the suicides took place during the first 3 years of the illness.

This was the first study of suicide rates in a prospectively followed population-based birth cohort of individuals with schizophrenia. This study replicated association between some early family-related risk factors for attempted and accomplished suicide, and also presented data for previously unstudied early factors, namely maternal antenatal depression, smoking and unwanted pregnancy. This study has clarified the association between adolescent smoking and later suicide risk. It also revealed the association between good school performance and elevated risk of suicide in psychotic people, in contrast to its protective effect in the non-psychotic population.

However, even though there were significant antenatal and developmental risk factors, a later psychiatric disorder seems to be the major risk factor for both attempted and accomplished suicide. Nevertheless, suicide usually seems to be a long multifactorial process that begins in early life and has complex trajectories in adolescence or early midlife.

Keywords: antenatal, birth cohort, longitudinal, perinatal, schizophrenia, school performance, smoking, suicide

Alaräisänen, Antti, Itsemurhan riskitekijät ja siihen johtavat kehityspolut erityisesti skitsofreniassa. Pohjois-Suomen vuoden 1966 syntymäkohorttitutkimus

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Tiivistelmä

Tämän tutkimuksen tarkoitus oli tutkia itsemurhien esiintyvyyttä, riskitekijöitä, siihen johtavia kehityspolkuja yleisväestöön perustuvassa prospektiivisessä pitkittäistutkimuksessa.

Pohjois-Suomen vuoden 1966 syntymäkohorttiin kuului alun perin 12,068 raskaana olevaa naista joiden laskettu aika oli vuonna 1966, ja heidän 12,058 elävänä syntynyttä lastaan, kohortin jäsenet. Tässä tutkimuksessa käytetty aineisto on kerätty 11,017 kohortin jäsenestä, jotka olivat elossa ja asuivat Suomessa 16-vuotiaana. Käytetty aineisto on kerätty äitiysneuvoloissa, 14-vuotiaana tehdystä postikyselyssä ja kansallisista rekistereistä.

Kaikkiaan 121 itsemurhayritystä (joista 57 miehillä) ja 69 itsemurhaa (56 miehillä) tapahtui vuoden 2005 loppuun mennessä. Yhden vanhemman perhe syntymän aikaan oli riski myöhemmälle itsemurhayritykselle ja syntyminen monilapsiseen perheeseen (yli viisi lasta) oli riski itsemurhalle. Tupakointi 14-vuotiaana ennusti itsemurhayrityksiä kummallakin sukupuolella sekä itsemurhia miehillä. Hyvä koulumenestys 16-vuotiaana liittyi kohonneeseen itsemurhavaaraan niillä jotka myöhemmin sairastuivat psykoosiin, kun muilla se liittyi alentuneeseen vaaraan. Skitsofreniaan sairastuneista 7 % teki itsemurhan ja yli kaksi kolmannesta skitsofreniaan sairastuneiden itsemurhista tapahtui kolmen vuoden kuluessa sairastumisesta.

Tämä tutkimus vahvisti aikaisempia havaintoja varhaisista riskitekijöistä itsemurhayrityksiin ja itsemurhiin. Tässä tutkimuksessa tutkittiin myös kokonaan uusia varhaisia riskitekijöitä, joita ei ole ennen tutkittu suhteessa itsemurhaan tai itsemurhayrityksiin, kuten äidin raskaudenaikainen masennus ja tupakointi sekä ei-toivottu raskaus. Tämän tutkimuksen avulla saatiin myös uutta tietoa teini-iässä aloitetun tupakoinnin suhteesta itsemurhiin ja -yrityksiin. Tutkimus paljasti hyvän koulumenestyksen lisäävän riskiä itsemurhaan henkilöillä jotka sairastuvat myöhemmin psykoosiin. Tämä oli ensimmäinen tutkimus, jossa skitsofreniaa sairastavien henkilöiden itsemurhakuolleisuutta selvitettiin yleisväestöön pohjautuvassa syntymäkohortissa.

Vaikka tutkimuksessa tuli ilmi sekä syntymän, että nuoruuden aikaisia varhaisia riskitekijöitä, myöhempi psykiatrinen sairaus on merkittävin itsemurhan ja -yritysten riskitekijä. Siitä huolimatta itsemurha on aina monitekijäinen prosessi, joka voi alkaa jo ennen syntymää ja johon myöhemmät elämänvaiheet vaikuttavat.

Asiasanat: itsemurha, koulumenestys, pitkittäistutkimus, raskauden aikainen, skitsofrenia, syntymäkohortti, tupakointi

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This work is dedicated to families of all suicide victims, and to you my dear friend who almost killed yourself but then luckily decided to carry on. Thank you for being still here.

Oulu, June 2010

Antti Alaräisänen

Main concepts of suicidology

Suicide—self-inflicted death with evidence (either explicit or implicit) that the person intended to die.

Suicide attempt—self-injurious behavior with a nonfatal outcome accompanied by evidence (either explicit or implicit) that the person intended to die.

Aborted suicide attempt—potentially self-injurious behavior with evidence (either explicit or implicit) that the person intended to die but stopped the attempt before physical damage occurred.

Suicidal ideation—thoughts of serving as the agent of one's own death. Suicidal ideation may vary in seriousness depending on the specificity of suicide plans and the degree of suicidal intent.

Suicidal intent—subjective expectation and desire for a self-destructive act to end in death.

Lethality of suicidal behavior—objective danger to life associated with a suicide method or action. Note that lethality is distinct from and may not always coincide with an individual's expectation of what is medically dangerous.

Deliberate self-harm—willful self-inflicting of painful, destructive, or injurious acts without intent to die.

Abbreviations

5-HIAA	5-Hydroxyindoleacetic acid
5-HT	Serotonin
5-HTTLPR	Serotonin-transporter-linked promoter region
95% CI	95% Confidence Interval
CSF	Cerebrospinal fluid
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders. 3rd edition, revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders. 4th edition
FHDR	Finnish Hospital Discharge Register
HR	Hazard Ratio
ICD-8	International Statistical Classification of Diseases, Injuries and Causes of Death, 8th edition
ICD-9	International Statistical Classification of Diseases, Injuries and Causes of Death, 9th edition
ICD-10	International Statistical Classification of Diseases, Injuries and Causes of Death, 10th edition
IQ	Intelligence quotient
MAOA	Monoamine oxidase A
MET	Methionine
NFBC 1966	Northern Finland 1966 Birth Cohort Study
OR	Odds Ratio
RR	Relative risk, risk ratio
TPH	Tryptophan hydroxylase
VAL	Valine
VNTR	Variable number tandem repeat
WHO	World Health Organisation

List of original publications

This thesis is based on the following original publications, which are referred to in the text by the Roman numerals I–IV.

- I Alaräisänen A, Miettunen J, Pouta A, Räsänen P, Isohanni M, Mäki P (2010) Ante- and perinatal circumstances and risk of attempted suicides or suicides in offspring. The Northern Finland 1966 Birth Cohort Study. Manuscript.
- II Riala K, Alaräisänen A, Hakko H, Taanila A, Timonen M, Räsänen P (2007) Regular daily smoking among 14-year-old adolescents increases the subsequent risk for suicide: The Northern Finland 1966 Birth Cohort Study. *J Clin Psychiatry* 68: 775–780.
- III Alaräisänen A, Miettunen J, Lauronen E, Räsänen P, Isohanni M (2006) Good school performance is a risk factor of suicide in psychoses. A 35-year Follow-up of the Northern Finland 1966 Birth Cohort. *Acta Psychiatr Scand* 114: 357–362.
- IV Alaräisänen A, Miettunen J, Räsänen P, Fenton W, Koivumaa-Honkanen H, Isohanni M (2009) Suicide rate in schizophrenia in the Northern Finland 1966 Birth Cohort. *Soc Psychiatry Psych Epidemiol* 44(12): 1107–1110

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1 Introduction

Suicide is a devastating act causing a great deal of suffering to survivors, relatives, friends and other people near to the victim of suicide. It is also a public health problem causing loss of life years, particularly in young people. In most countries suicide is condemned for cultural or religious reasons and surrounded by taboo (WHO 2002). Suicide rates are particularly high in Eastern Europe and the lowest rates are found in Latin America (Levi *et al.* 2003).

Suicide is a long and multifactorial process and is never a consequence of a single cause or stressor (Hawton & van Heeringen 2009). The major contributory factor for suicide is mental disorder; this is identifiable in approximately 90% of suicide victims (Henriksson *et al.* 1993, Cavanagh *et al.* 2003). Risk factors for suicide includes proximal stressors like psychiatric disorder or acute psychosocial crisis and predispositive factors like personality characteristics, eg pessimism, impulsivity and aggression (Alaräisänen *et al.* 2007, Hawton & van Heeringen 2009).

Schizophrenia is a severe, often chronic psychotic disorder which usually has an early onset and may lead to persistent symptomatology, a decrease in the quality of life and increased mortality (Isohanni *et al.* 2006). It is estimated that approximately 5% of schizophrenia patients die by suicide (Palmer *et al.* 2005). In Finland 7% of suicides are committed by people suffering from schizophrenia (Heilä *et al.* 1997).

The Northern Finland 1966 Birth Cohort Study (NFBC 1966) is an unselected population-based birth cohort followed from mid-pregnancy until the present. A huge amount of data has been collected over the years in antenatal clinics, by postal questionnaires, from registers, and by special examinations and field studies (Lauronen 2007). The present study addresses the longitudinal perspective of the suicide process with the possibility of studying distal and proximal risk factors for suicide in the same sample, namely the NFBC 1966.

The NFBC 1966 has a long research tradition of perinatal circumstances, especially antenatal depressed mood (Mäki *et al.* 2010), adolescent smoking (Riala *et al.* 2009) and school performance (Isohanni 2001) and their association with unfavourable outcomes in later life (Jääskeläinen *et al.* 2008). Also, schizophrenia research is one of the main focuses in this cohort (Isohanni *et al.* 1997, Isohanni *et al.* 2010). This study continues research into these issues which focus on suicide.

2 Suicide

2.1 Definition of suicide and suicide attempt

For the act of killing oneself to be classified as suicide, it must be deliberately initiated and performed by the person concerned in the full knowledge, or expectation, of its fatal outcome (WHO 1998). Suicide attempt includes those situations in which a suicidal act has led to a non-fatal outcome (WHO 1998). There are also broader definitions for suicide attempts or parasuicides that include deliberate acts of self-harm with varying degrees of suicidal intent and lethality of suicide method (Suominen 1998).

A history of suicide attempt or deliberate self-harm is a strong risk factor for completed suicide and previous suicide attempt is present in approximately 40% of suicides (Cavanagh *et al.* 2003). After attempted suicide the risk of repeated suicide attempt is 30% and risk of suicide is 10% (Haukka *et al.* 2008), and the risk for suicide stays elevated for decades (Suominen *et al.* 2004). Suicidal behavior can be seen as a continuum ranging from suicidal ideation to attempted suicide and ultimately to completed suicide (Suominen 1998).

There are many similarities between suicide attempters and completers. Study conducted in New Zealand revealed that main similarities were current mood disorder; previous suicide attempts; recent psychiatric treatment; low income; a lack of formal educational qualifications; exposure to recent stressful interpersonal, legal and work-related life events (Beautrais 2001). Same study showed that suicide completers were more likely to be male, older, and to have a current diagnosis of non-affective psychosis, while suicide attempters were socially isolated and had more anxiety disorders as a current diagnosis (Beautrais 2001). Some of the main differences in a recent study were that suicide completers are more likely to use alcohol or drugs prior to their suicidal act and they are more likely to leave a suicide note. Suicide completers are also more likely to have encountered significant job stress and financial problems. (DeJong *et al.* 2009)

Procedures for recording death as suicide are far from uniform in different countries. Certification of the cause of unexpected death is made by different bodies, including police, physicians, coroners and medical examiners. In some countries there is also a requirement of external evidence of intent, such as a

suicide note, while in others the intent can be evaluated by judgment as long as there is certainty that the death was self-inflicted. (Hawton & van Heeringen 2009)

Finnish law requires a medicolegal determination of cause and manner of death when it either is or is suspected to be unnatural, or when it has been natural but sudden and unexpected. Determination of cause of death in Finland is considered reliable (Lahti & Penttilä 2001), however, it is estimated that 10–19% of suicides could be classified as undetermined deaths or accidents (Huusko & Hirvonen 1988, Öhberg & Lönnqvist 1998). Finnish suicide certification procedures are comparable to other democratic higher-income countries and especially to European countries, although there is some variation between sensitivity of classification (Rockett & Thomas 1999, Chishti *et al.* 2003).

2.2 Suicide mortality

The World Health Organization estimated in 2002 that the global burden of suicide is 815,000 deaths per year, or one death every 40 seconds. Worldwide annual suicide mortality is 14.5 deaths per 100,000 people, making it the thirteenth leading cause of death (WHO 2002). Suicide mortality in Finland reached its peak in 1990, when it was 30/100,000: 50.1/100,000 for males and 12.1/100,000 for females. Since 1990 there has been a descending trend in suicide mortality and in 2008 it was 18.6/100,000: 29.3/100,000 for males and 8.3/100,000 for females (Statistics Finland 2010).

Although suicide mortality has decreased significantly in Finland during the last twenty years it is still quite high compared to other European countries. Male age-standardized suicide mortality in Finland is the sixth highest in Europe, with higher rates being found in Lithuania, Hungary, Latvia, Moldova and Estonia. Female suicide mortality in Finland is the fourth highest in Europe, with only Belgium, Lithuania and Hungary ahead. Both genders together make Finnish suicide mortality the third highest in Europe, only Lithuania (30.7/100,000) and Hungary (21.5/100,000) have higher rates. Compared to our closest neighbor Sweden (11.4/100,000 for both genders, 16.3 in males and 6.6 in females) suicide mortality in Finland is too high. The lowest suicide rates in Europe are found in Azerbaijan, Georgia, Cyprus, Malta, Israel, Italy, Uzbekistan, the UK and Spain with under age-standardized suicide mortality under 8/100,000. (European detailed mortality database 2010)

Suicide is an important public health problem; in Finland in 2008 suicide was, with 677 deaths, the fourth leading cause of death among 15–64 year old males

and, with 190 deaths, the fifth leading cause among 15–64 year old females (Statistics Finland 2010).

2.3 Suicide research

Throughout recorded history there has been constant interest into human suffering and suicide. There have been extensive research efforts to study epidemiology, methods, contributory factors, pathophysiology and prevention strategies of suicide (Hawton & van Heeringen 2009). Heterogeneity and different perspectives in suicide studies are enormous. While Emile Durkheim (1897) in his classical monograph studied suicide from a sociological point of view, the ‘modern day Durkheim’ J. John Mann (2003) has reviewed the neurobiology of suicidal behavior. Suicide research also follows current trends in psychiatric research. For example, endophenotypes, measurable but usually unseen neurophysiological, endocrinological, neuroanatomical, observational, self-reported, or cognitive components or combination of these components, are nowadays researched beyond the psychiatric diseases (Gottesman & Gould 2003, Ivleva *et al.* 2009, Isohanni *et al.* 2009) and recently also in connection with suicides (McGirr *et al.* 2009, Mann 2009)

The main challenges in suicide research are the relative rarity of suicides in the general population level, the absence of the most reliable source of information (the suicide victim) and the complex nature of the suicide process itself. The most useful approaches to suicide research from a psychiatric perspective are prospective population-based studies (eg birth cohorts) or clinical patient cohorts and retrospective studies of suicide victims (WHO 1998). A psychological autopsy method was developed to study suicide victims’ recent psychological factors and life circumstances prior to death. In the psychological autopsy method the information is obtained by interviewing those important to the deceased and, additionally, hospital records for example can be utilized. (Shneidman 1981) Different study designs produce different kinds of results: ecologic studies reveals suicide rate variations in different populations, prospective longitudinal follow-up studies offers change to identify risk factors and lifetime suicide mortality in different mental disorders, and retrospective approaches like psychological autopsy reveals proximal risk factors (Heilä 1999, Pirkola 1999)

These large research efforts have shown that there is no single reason or answer as to why some people end up committing suicide. Suicide is a

multidetermined act which has numerous biological, psychosocial, social, cultural and situational contributory factors behind it (Henriksson 1996). A stress-diathesis model (Figure 1) is one way to try to explain the relation between risk factors for suicide (Mann 2003, Hawton & van Heeringen 2009). In a stress-diathesis model, stressors represents proximal risk factors that have triggered the act, eg psychosocial crisis and psychiatric disorder including depression, substance abuse, psychotic disorders and personality disorders (Lönnqvist *et al.* 1995, Henriksson 1996, Hawton & van Heeringen 2009). Diathesis includes predispositive factors like genetic loading, physical or sexual abuse during childhood, impulsive-, aggressive- and pessimistic personality traits and perinatal circumstances (Mann 2003, Hawton & van Heeringen 2009).

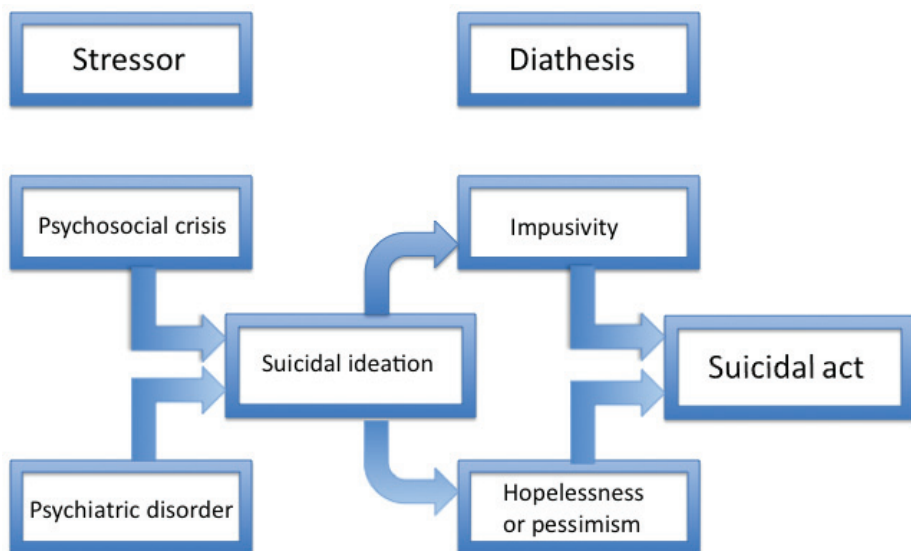


Fig. 1. Stress-diathesis model for suicide (Modified from Mann 2003).

2.3.1 Suicide research in Finland

There is a long (Achté *et al.* 1966) and internationally acknowledged tradition of suicide research in Finland (Wilson 2004). The National Suicide Prevention Project in Finland (Lönnqvist 1988), in which all suicides in Finland (n=1397) over a 12-month period between April 1, 1987 and March 31, 1988 were carefully analyzed using the psychological autopsy method (Shneidman 1981, Isometsä

2001) and produced a huge amount of data and publications concerning Finnish suicide (for example academic dissertations by Sorri 1993, Heikkinen 1994, Isometsä 1994, Marttunen 1994, Henriksson 1996, Heilä 1999, and Pirkola 1999). Finnish registers have also been utilized to serve suicide research (Lindeman 1997, Hakko 2001, Räsänen *et al.* 2002, Miettunen *et al.* 2010)

2.4 Suicide prevention

Suicide is a multidetermined and complex process and suicide prevention strategies are also multifaceted in nature and have been discussed in detail in a recent expert review (Mann *et al.* 2005). The main approaches involve increasing awareness and education of suicides in the general population level, in primary care physicians and especially in gatekeepers (those who are in contact with high-risk groups); better screening of suicidality; enhanced treatment of mental disorders; means restriction; and media control (Mann *et al.* 2005).

Since over 90% of suicide victims receive diagnosis of some psychiatric disorder in psychological autopsy studies (Henriksson *et al.* 1993, Cavanagh *et al.* 2003), recognizing and adequate treatment of mental disorders is a cornerstone of suicide prevention strategies (WHO 1998). Every depressed patient should be screened for suicide risk by specifically asking about suicidal thoughts and plans. If there is suicidal ideation then the risk factors for suicide should be correspondingly assessed. If suicide risk is present the further assessment should be the imminence of suicidal behavior. Lots of different instruments have also been developed to help suicide risk assessment (Brown 2002). If there is imminent risk of suicide then immediate action for prevention is needed including supervision of the patient and initiation of vigorous treatment of the underlying psychiatric disorder. (Hawton & van Heeringen 2009) In recent Finnish study well-developed community mental-health outpatient services were better in terms of of suicide prevention than services oriented towards inpatient treatment provision (Pirkola *et al.* 2009)

In addition, the restriction of the means used for suicide, like guns and poisons, is recommended and effective at the general population level (Mann *et al.* 2005). In Northern Finland there is reported to be a peak of shooting suicides among adolescents in autumn during the hunting season (August to October). The proportion of shootings in all suicides was 59.5%, and 80% of shooting suicides were committed with licensed hunting guns (rifles and shotguns). (Lahti *et al.* 2006) Restrictions on the availability of guns prevent the shooting suicides and

substitution with other methods of suicide is not very common (Brent & Bridge 2003). However, in Finland between 1947–1990 it was noted that even though restriction of some methods, eg parathion (highly lethal pesticide), decreased suicides by this method, other methods tended to replace it (Öhberg *et al.* 1995).

Based on the findings from The National Suicide Prevention Project in Finland a program to reduce suicides was introduced. The main suggestions were: to develop support and treatment models of suicide attempters; to enhance treatment of major depression; to reduce alcohol consumption and enhance treatment of people with substance use problems; to give more social and psychological support in somatic illnesses; and to increase optimism, courage, self-esteem among Finns and to help them in supporting each other (Upanne *et al.* 1991). To achieve these goals action is needed at all levels of society and throughout the healthcare system.

2.5 Risk factors for suicide

Suicide is a long, multifactorial process starting from genes and ending in a sometimes highly impulsive suicidal act (Alaräisänen *et al.* 2007, Hawton & van Heeringen 2009). Distal or trait-dependent risk factors for suicide include genetic loading, personal characteristics (eg impulsivity, aggression, pessimism), restricted foetal growth and perinatal circumstances, early traumatic life events and neurobiological disturbances. Proximal or state-dependent risk factors are psychiatric disorder, physical disorder, psychosocial crisis, availability of means and exposure to models. (Hawton & van Heeringen 2009)

2.5.1 Mental disorders and suicide

The main risk factor for both attempted and completed suicide is psychiatric disorder (Henriksson *et al.* 1993, Suominen 1998, Agerbo *et al.* 2002, Cavanagh *et al.* 2003, Mann *et al.* 2005). The most common mental disorders among suicide completers are depressive disorders, which are present in approximately 60% of suicides (Henriksson *et al.* 1993, Cavanagh *et al.* 2003). Substance use disorder, mainly alcohol, is present in 15–56% of suicides, being a major contributory factor for suicide (Pirkola 1999). In Finland alcohol dependence was found in 34% and alcohol abuse in an additional 9% of suicides (Henriksson *et al.* 1993). Psychotic disorders are present in 25% and personality disorders in 31% of suicides in Finland (Henriksson *et al.* 1993). Comorbidity of mental disorders

among suicide completers is common (Henriksson *et al.* 1993, Cavanagh *et al.* 2003). Suicide rates in different mental disorders vary: 4% of depressed patients (Coryell & Young 2005), 10–15% of bipolar of patients (Goodwin & Jamison 2007) and 5% of patients with schizophrenia (Palmer *et al.* 2005) die by suicide.

2.5.2 Sociodemographic risk factors for suicide

Males commit two to four times more suicides than females worldwide (WHO 2002), but for example in China females commit more suicides than males (Phillips *et al.* 2002). Suicide rates increase with age, however, the absolute numbers are highest among those below the age of 45 years (WHO 2002). Those with Caucasian ethnicity commit more suicides than other ethnic groups (Hawton & van Heeringen 2009). Also in immigrants suicide rates are similar to those in the country of birth (Voracek & Loibl 2008). Unemployment is a risk factor for suicide (Platt & Hawton 2000), but this association might be biased because mental illnesses and psychosocial problems are contributing to both suicides and employment status (Blakely *et al.* 2003). Some occupational groups are also at higher risk of suicide. High- risk professions are physicians, especially anesthesiologists and female physicians, nurses, dentists, pharmacists, veterinary surgeons and farmers (Lindeman *et al.* 1997, Hawton *et al.* 2001, Schernhammer & Colditz 2004, Agerbo *et al.* 2007). All of these professions have in common easy access to highly lethal poisons or drugs (Kelly & Bunting 1998).

Low income as a marker of low socioeconomic status (SES) is a risk factor for suicide especially in males (Qin *et al.* 2003). Low childhood SES has been found to be a risk factor for suicides or suicide attempts in England, Scotland and New Zealand (Fergusson *et al.* 1995, Neeleman *et al.* 1998, Riordan *et al.* 2006). Meanwhile, in Norway and Denmark high SES in childhood has been connected with elevated suicide mortality in adulthood register studies, especially in females (Strand & Kunst 2006, Silverton *et al.* 2008). These observations suggest that the effect of childhood SES on suicides might be culturally determined.

2.5.3 Genetic risk factors

In recent years there has been rising research interest towards the genetic basis of suicidal behaviour. This research was reviewed by Bondy and co-workers (2006). Most of the research has concentrated on the serotonergic system. The most plausible evidence is on the tryptophan hydroxylase 1 (TPH1) gene and its

association with suicide (Li & He 2006). There have been controversial results about the association between serotonin transporter gene promoter (5-HTTLPR) polymorphism and suicide. The 5-HTT gene promoter region is known to play a major role in the pathogenesis of depression (Pezawas *et al.* 2005). It has been linked to violent suicidal behaviour and more suicide attempts (Bayle *et al.* 2003, Campi-Azevedo *et al.* 2003). De Luca *et al.* (2006) also showed that intron 2 VNTR polymorphism in the serotonin transporter gene may influence suicidal behaviour in schizophrenia. However, Helbecque (2006) found no association between suicide and 5-HTTLPR. No association between different serotonin receptors and suicides has been found (Bondy *et al.* 2006).

It is probable that the monoamine oxidase A (MAOA) gene does not influence suicidality, although there is some evidence for this in schizophrenia (De Luca *et al.* 2006). It might however affect the choice of more lethal methods of suicide (Bondy *et al.* 2006). Catechol-O-methyltransferase (COMT) gene 158 VAL/MET polymorphism is associated with suicide in that VAL/VAL genotype is a protective factor from suicide (De Luca *et al.* 2006, Ono *et al.* 2004). The 14-3-3 epsilon gene, which is related to neurogenesis, has also been found to be associated with suicide (Yanagi *et al.* 2005).

2.5.4 Ante- and perinatal circumstances and risk of attempted suicides or suicides

A family history of mental disorder can increase the risk of suicide among adolescents and young adults (Brent *et al.* 1994, Brent *et al.* 1996, Gould *et al.* 1996, Agerbo *et al.* 2002, Qin *et al.* 2002 & 2003, Christoffersen *et al.* 2003, Mittendorfer-Rutz *et al.* 2008).

A mother's high parity and young age have been connected with suicide attempts or suicides in the offspring in large register studies in Sweden and Scotland (Mittendorfer-Rutz *et al.* 2004, Riordan *et al.* 2006), and a single-parent family has been found to be a risk factor for suicides in males (Sauvola *et al.* 2001a). These studies did not take into account psychiatric disorders in the parents or offspring, however. Gender differences in these early factors have not been studied.

There are no studies of associations between maternal antenatal depression, smoking or unwanted pregnancy and suicides in the offspring. However, those have previously been linked to other unfavourable outcomes. Maternal depression is common during both the antenatal and postnatal periods, affecting 10–15% of

mothers (Evans *et al.* 2001), and the mother's depression during pregnancy has been connected with an increased risk of violent criminality and psychiatric disorders in the offspring (Veijola *et al.* 1998, Mäki *et al.* 2003, Mäki *et al.* 2010). Maternal smoking during pregnancy is associated with an elevated rate of criminality, psychiatric hospitalisations, substance abuse and other psychological problems in the offspring (Räsänen *et al.* 1999, Brennan *et al.* 1999 & 2002, Button *et al.* 2007), and unwanted pregnancy with an increased risk of schizophrenia in the children (Myhrman *et al.* 1996) as well as other long-term negative consequences for the offspring (Myhrman 1992).

2.5.5 Smoking and suicide

Several earlier epidemiologic (Miller *et al.* 2000, Breslau *et al.* 2005) and clinical (Tanskanen *et al.* 1998, Mann *et al.* 1999) studies have revealed the positive relationship between smoking and suicidality. This relationship seems to be dose-related (Miller *et al.* 2000, Iwasaki *et al.* 2005) and independent of major depression and alcohol or drug disorders (Breslau *et al.* 2005). Also, when suicides were studied by using a psychiatric autopsy method, Schneider *et al.* (2005) found that among males, current nicotine consumption independently predicted suicides (OR 2.6, 95% CI 1.3–5.2). Furthermore, Moriya and Hashimoto (2005) found high post-mortem levels of blood nicotine among smoking suicide victims compared to smokers who did not commit suicide.

Interestingly, only a few earlier studies have focused on early onset adolescent smoking and its putative association with suicide attempts or committed suicides. In a systematic review of population-based studies Evans *et al.* (2004) found eight studies investigating the association between adolescent smoking and suicidal phenomena, and the results strongly indicated a positive association. However, Hemmingsson & Kriebel (2003) were able to study suicides and smoking among more than 49,000 male military conscripts aged 18–20 years, and they were also able to investigate the confounding effect of psychiatric diagnoses in adolescence and alcohol use diagnoses during the 26-year follow-up period. In their study, the risk of suicide among those smoking >20 cigarettes/day was strongly increased (OR 3.03, 95% CI 1.72–5.34) during the first 13 years of follow-up. However, the association in their study was almost entirely explained by an increased prevalence of heavy alcohol consumption and low mental well-being among smokers. This might suggest that smoking is also an indicator of other risk factors for suicide.

2.5.6 School performance and suicide

Only a little is known of how suicidal behavior is affected by educational achievements or intellectual functioning in general. At the general population level, low IQ is associated with an increased risk of suicide (Gunnell *et al.* 2005).

In the case of people suffering from serious mental diseases the association may be different; high IQ or good school performance seems to be a risk factor for suicide (Hawton *et al.* 2005). The first finding on the topic was made in a sample of 438 patients at a Veterans Administration neuropsychiatric hospital in the USA (Farberow *et al.* 1966). That study consisted of 218 patients who had committed suicide during the hospitalization and 220 control patients who had not committed suicide. Compared to the controls, the patients who had committed suicide had more frequently gone further in school, had more often finished college, and were more than twice as often considered to be above average in intellectual functioning. Suicidal patients also more often had diagnoses of psychosis (schizophrenia and manic-depression) while the controls had less severe diagnoses. Similar findings have been reported from Missouri by Sletten *et al.* (1972). In a sample of 97 psychiatric patients (over half of whom were psychotic) there seemed to be more college-educated individuals among the suicides than in the reference group without suicidal tendencies.

In a study of Drake *et al.* (1984), the subjects were 15 schizophrenia patients who had committed suicide, and 160 living controls also suffering from schizophrenia. All patients had been treated in the public sector mental health system. In the suicide group 73% had college education, compared to only 29% in the control group ($p < 0.01$). Similar findings have also been made by Dingman & McGlashan (1986) in a private hospital serving patients from higher social classes. In a sample of 460 mostly psychotic patients, 10 inpatients and 28 discharged patients committed suicide. Patients in the suicide group were more likely to be intelligent and to have achieved higher occupational and socioeconomic levels prior to admission.

Examining intelligence ratings from draft military records in relation to subsequent suicide in Israeli men revealed higher than average ratings in 43 who committed suicide (Apter *et al.* 1993). The subjects' overall functioning was also very high. In a psychological autopsy 53.5% of them received a diagnosis of major depressive disorder, while 7% were diagnosed as having schizophrenia, which are usual percentages of these mental disorders among suicide completers (Marttunen *et al.* 1991, Henriksson *et al.* 1993). High premorbid IQ has also been

found to be a risk factor for suicide with OR 4.3 in a sample of 63 schizophrenia patients who committed suicide compared with 63 patients in Belgium who did not commit suicide (De Hert *et al.* 2001).

3 Schizophrenia

Schizophrenic psychoses are a major public health problem and among the leading unsolved diseases, afflicting about 1% of humans. Schizophrenia usually begins early in adult life and the prognosis is often poor (Lauronen 2007). Schizophrenia causes excess comorbidity (both psychiatric and somatic), increased mortality (an average decreased lifespan of 20%), as well as extensive negative social, educational, familial and personal consequences even in the early phases of the illness (Isohanni *et al.* 2010). Schizophrenia accounts for 1.1% of the global burden of disease, which is similar to the contributions from diseases such as diabetes mellitus (1.0%), osteoarthritis (1.1%) and asthma (0.9%). It is listed as the 8th leading cause of disability-adjusted life years worldwide in the age group 15–44 (WHO 2001). Antipsychotic drugs relieve symptoms and prevent illness relapses, but have limited efficacy — especially for negative and cognitive symptoms — and also have neurological and metabolic side effects. Neither cure nor prevention is yet in sight. (Isohanni *et al.* 2010) Schizophrenia research in Finland has been very active during recent decades (Koskinen *et al.* 2004 a,b).

3.1 Definition, symptoms and diagnosis

Emil Kraepelin (1909) was the first to classify mental disorders into two groups: manic-depressive psychoses and dementia praecox (i.e. schizophrenia). Kraepelin defined dementia praecox as a disorder beginning early in life, leading to chronicity and characterized by hallucinations, delusions, stereotypes, thought disorder, negativism and blunted affect. Eugen Bleuler (1911) first introduced the term “schizophrenia”. Bleuler’s view was that the primary symptom of schizophrenia was cognitive impairment (such as thought disorder, loosening of associations, attention, autism). Schizophrenia symptoms can be classified into positive symptoms (including hallucinations, delusions, bizarre behavior, derailment, flight of ideas, and illogicality) and negative symptoms (flattened affect, impaired attention, poverty of speech, apathy, and asociality) (Lauronen 2007).

Currently two diagnostic criteria are used to classify schizophrenia: the American Psychiatric Association’s (APA) Diagnostic and Statistical Manual for Mental Disorders (DSM) and the World Health Organization’s (WHO) International Classification of Diseases and Causes of Death (ICD). The main

difference between these two criteria is the duration of symptoms: the DSM system (widely used for research purposes and in clinical use in, for example, the USA), requires the duration of symptoms for at least six months (APA 1994), whereas one-month duration of symptoms is needed for ICD diagnosis of schizophrenia (WHO 1993). To be classed as schizophrenic according to DSM-IV criteria a person has to have at least one of the following: bizarre delusions, third-person auditory hallucinations or running commentary, or two or more of the following: delusions, hallucinations, disorganized speech, grossly disorganized behavior or negative symptoms (APA 1994).

3.2 Epidemiology

In a large systematic review of 188 studies published around the world between 1965–2002 the point prevalence of schizophrenia was estimated to be 4.6/1,000 persons (10%–90% quantile 1.9–10.0), and life-time prevalence 4.0/1,000 persons (1.6–12.1) (Saha *et al.* 2005). The average prevalence of schizophrenia in Finland is approximately 1% (Lehtinen *et al.* 1990, Arajärvi *et al.* 2005, Perälä *et al.* 2007).

No single cause has yet been found that would cause schizophrenia and the etiology of this devastating illness is still to be discovered. There are several genetic and environmental risk factors and markers of increased risk for schizophrenia (Isohanni *et al.* 2005, Mäki *et al.* 2005, Isohanni *et al.* 2006, Isohanni *et al.* 2009, Welham *et al.* 2009). The risk of schizophrenia is higher in males compared to females (Kirkbride *et al.* 2006). Males also have slightly lower onset age, with the illness usually beginning at 15–25 years and for females at age 15–29. Females also have another peak in incidence at the time near to menopause (Räsänen 2001, Häfner 2003).

Some genetic, biological and developmental factors are associated with an elevated risk of schizophrenia; they may be markers of increased risk, or may even have some causal role in the etiology of the disorder. An adverse event during pregnancy and delivery, advanced paternal age, central nervous system infections in childhood and predisposition to infections in the prenatal period, early neuromotor abnormalities and developmental delays, as well as poor premorbid cognitive and scholastic performance have been associated with increased risk of schizophrenia. (Isohanni *et al.* 2005, Mäki *et al.* 2005, Lauronen 2007, Miller *et al.* 2010a)

3.3 Schizophrenia and suicide

Increased mortality of patients with schizophrenia is well-documented. The risk of premature death is heightened from both natural and unnatural causes (Brown 1997, Saha *et al.* 2007). Mortality is increased in all ages and both genders, largely due to suicides, unhealthy lifestyle factors (Brown *et al.* 1999) and poor quality of somatic treatment (Druss *et al.* 2001). In males, life expectation is 5.9–7.9 years shorter than in the general population (in ages 30–50), and in females 5.2–9.5 years shorter (Hannerz *et al.* 2001). Advanced paternal age, a well-replicated risk factor for schizophrenia (Miller *et al.* 2010a), is also a risk factor for increased mortality in psychosis (Miller *et al.* 2010b).

It is estimated that approximately 5% of schizophrenia patients die by suicide (Palmer *et al.* 2005). In Finland 7% of suicides are committed by people suffering from schizophrenia (Heilä *et al.* 1997). Pompili *et al.* (2005) reviewed timing of the suicide. Most suicides occur in the early phase of schizophrenia (Kua *et al.* 2003, Kuo *et al.* 2005), after acute discharge or between exacerbations (Dong *et al.* 2005, Lewis 2004). However, suicide risk is elevated during the whole course of illness (Heilä *et al.* 1997). Findings demonstrate that suicides committed at different points of the illness course may differ according to motivation. While acute phase suicides are most probably a direct consequence of psychosis (eg paranoia, hostility, erroneous insight), suicides following acute discharge or committed at a variable time period after discharge are mostly related to symptoms of depression (Lewis 2004).

Thus, the risk factors for suicide in schizophrenia vary during the course of the illness. According to a meta-analysis by Hawton *et al.* (2005), strong risk factors for suicide in schizophrenia are previous depressive disorders (OR=3.03), previous suicide attempts (OR=4.09), drug misuse (OR=3.21), agitation or motor restlessness (OR=2.61), fear of mental disintegration (OR=12.1), poor adherence to treatment (OR= 3.75) and recent loss (OR=4.03).

3.3.1 Suicide rate in schizophrenia

The view of the suicide rate among schizophrenia patients has changed in the past few years. In their meta-analysis of suicide risk in schizophrenia Palmer *et al.* (2005) concluded that the lifetime risk of suicide in this disorder is 4.9%. This is less than half of the 10–13% reported previously in review by Caldwell and Gottesman (1990). Also Heilä and Lönnqvist (2003) recently suggested in their

review that the previous estimation could have been too high. Several reasons may have accounted for this overestimation.

Of particular interest is the strong relationship between characteristics of the study sample and the observed suicide rate in the meta-analysis of Palmer *et al.* (2005). For example, the estimated lifetime suicide rate was nearly three times greater in follow-up studies on first-admission patients (5.6%) than on patients at various points of illness (1.8%). Largely derived from consecutive patients enumerated in clinics and hospitals, wide variation in both proportionate mortality and case fatality was, however, reported across the 32 studies included in the meta-analysis. Palmer *et al.* (2005) argued that first-admission and new-onset studies estimate suicide risk more accurately because they include the very first years of the illness when death by suicide is most likely.

4 Summary of literature

While being extensively studied, suicide is still a major individual, family, social and public health problem and effective preventive strategies are far from perfect. There is still a need for research into risk factors of suicide in order to clarify our view of why some people, especially the young, end their lives.

A mother's high parity and young age have been connected with suicide attempts or suicides in the offspring as well as linking single-parent families to suicides. There are, however, no studies of these factors that report gender differences or take into account parental psychiatric disorders. There are no studies of associations between maternal antenatal depression, smoking or unwanted pregnancy and attempted or completed suicides in the offspring.

There are no studies so far in which the association between adolescent regular smoking and committed suicides later in life has been studied at epidemiological level in birth cohort settings. In addition, some of the earlier studies have investigated only male populations (Miller *et al.* 2000, Hemmingson *et al.* 2003). Although it is well-known that smoking is associated with an increased risk of suicide, it is not yet known whether smoking in adolescence increases the risk of committing suicide at a younger age or whether it also influences the choice of a more violent method of suicide, since it is known to be associated with violence (Räsänen *et al.* 1998).

Although some support exists for the association between high educational achievements or high intellectual capacity and an elevated risk of suicide in psychoses, the results are still unclear. All of the past studies have been made with selected study samples. The measuring of subjects' educational achievements or intelligence has also varied considerably. Long-term prospective research on patients with new-onset schizophrenia is needed to verify the overall suicide risk as well as to identify the risk factors specific for the different course of the illness. Since 7% of all suicides are committed by people with schizophrenia, further studies are needed in order to prevent suicides of this specific section of the population.

Longitudinal population-based birth cohort offers possibilities to identify early and developmental risk factors (Welham *et al.* 2009) that might be useful in developing suicide prevention strategies.

5 Aims of the study

The aim of this study was to investigate risk factors, developmental pathways and the rates of attempted or completed suicide in a longitudinal population-based prospective Northern Finland 1966 Birth Cohort. Specific aims were to study:

1. Ante- and perinatal circumstances and the risk of attempted or completed suicide (original study I)
2. The association between early adolescent regular smoking and suicide (original study II)
3. The relationship between school performance and later suicide. Special focus was on the subjects suffering from psychoses, and the interaction between diagnosis and school performance in predicting suicide (original study III)
4. The suicide rate in schizophrenia until age 39 years and to analyse in what phase of the illness suicide occurs (original study IV)

6 Material and methods

6.1 Northern Finland 1966 Birth Cohort Study

This study is a part of the prospective, longitudinal Northern Finland 1966 Birth Cohort Study (NFBC 1966). The NFBC 1966 was founded by Professor Paula Rantakallio (Rantakallio 1969). Her aim was to investigate the risk factors for perinatal deaths and low birth weight. The original sample was collected from a geographically defined area of the two northernmost provinces of Finland and consisted of an unselected birth cohort of 12,058 live births covering 96.3% of all deliveries in Northern Finland in the year 1966 (Kantojärvi 2008).

Information on the sociodemographic characteristics of the mother and the family was collected at the antenatal clinic during midgestation (Rantakallio 1969). Three follow-up studies of the whole NFBC 1966 project have been conducted. The first follow-up was performed when the subjects were 1 year old during a routine postnatal clinic visit (1-year follow-up) (Rantakallio 1988). The second follow-up of the total cohort was performed at the end of 1980 and in early 1980 (14-year follow-up) by sending a postal questionnaire to the subjects (Rantakallio 1988). The latest follow-up for all cohort members, called the Northern Finland Health and Well-being Study, was conducted during 1997-98 (Sorri & Järvelin 1998, Järvelin *et al.* 2004).

In addition to whole cohort follow-ups, psychiatric field survey at the age of 34 years was conducted in 1999–2001. 104 non-psychotic controls and 91 subjects with a history of psychosis participated. The study protocol included interviews, questionnaires, cognitive tests and MRI scan. (Jääskeläinen *et al.* 2008, Haapea 2010)

Follow-up of NFBC 1966 continues in a 2008–2011 psychiatric field study with re-examination of 34 year follow-up participants and new subjects with psychosis and new controls. Also, a subsample of siblings of psychotic subjects is being invited. The new follow-up for the whole cohort is also going to be performed during the next few years.

6.2 Study sample (original studies I-V)

The Northern Finland 1966 Birth Cohort (NFBC 1966) comprises of 12,068 pregnant women with expected dates of delivery in 1966, covering 96% of all

deliveries in the region, and their 12,058 live-born children, the cohort members (Rantakallio 1969, Poutska *et al.* 2010). The data used here was collected prospectively for 11,017 individuals who were alive and resident in Finland at the age of 16. Since a total of 83 individuals did not give their consent for the last follow-up, in 1997–98, the number of cohort members in the present study was 10,934. These were followed up until the end of 2005, when they were 39 years old. Due to missing data in single variable samples size varies in the analyses.

6.3 Variables

Variables used in each original study are presented in Table 1.

Table 1. Variables used in original studies I-IV

Variables	Original study I	Original study II	Original Study III	Original Study IV
Predictor variables	Antenatal depressed mood (no, yes); Unwantedness of pregnancy (no, yes); Mothers age at birth (<20, 20–35, >35); Mothers smoking during pregnancy (no, yes); Parity at birth (1, 2–5, >5); Socioeconomic status at birth (I-II, III-IV, V); Family type in 1966 (single parent family, two parent family);	Smoking at age 14 (never, experimental smoking, regular smoking)	School marks at age of 16 (the average of school marks below vs. over 8.5); Psychiatric diagnoses (schizophrenia, other psychosis, no)	Psychiatric disorder (schizophrenia, non-psychotic, no)
Covariates	Mothers' psychiatric disorder (no, yes); Fathers' psychiatric disorder (no, yes); Cohort member psychiatric disorder (no, yes). Above-mentioned predictor variables were selected to logistic regression models if they showed trend with p-values below 0.1 in cross-tabulations	Family type at age 14 (single parent family, two parent family); Parental social class 1980 (I-II, III-IV, V); School performance at the age of 14 (not in normal grade, in normal grade); Alcohol use at age 14 (never, experimental use, regular pattern of alcohol use); Other substance use at age 14 (never, occasional/regular use); Psychiatric disorder (no, psychotic, non-psychotic)	Gender (male, female); Socioeconomic status at age 14 (I-II, III-IV, V); Age of onset of psychotic disorder (≤20 vs. >20 years)	No
Outcome variables	Suicide attempt; Suicide (by the end of 2005)	Suicide attempt; Suicide (by the end of 2001)	Suicide (by the end of 2001)	Suicide (by the end of 2005)

6.3.1 Predictor variables

Antenatal depressed mood (I)

Data on depressed mood in the mothers during pregnancy was available for 10,705 offspring who were living in Finland at the age of 16 years. The mothers had been asked by the interviewing nurse at the antenatal clinic during mid-gestation (mainly between the 24th and 28th gestational weeks) whether they felt that their mood had been normal, depressed or very depressed during pregnancy. Altogether 13.9% of the mothers of offspring living in Finland at the age of 16 rated themselves as having been depressed (11.8%) or very depressed (2.1%) during pregnancy (Mäki *et al.* 2010). These two categories were considered as being ‘depressed’ for the purposes of the analysis.

Unwanted pregnancy (I)

During the same visit to the antenatal clinics in the sixth or seventh month of pregnancy the mothers were asked whether they had wanted the pregnancy, would have preferred it later or had not wanted it at all (Rantakallio 1974, Myhrman *et al.* 1996) For the analysis this variable was dichotomized into ‘wanted now or later’ and ‘unwanted’. 12% of the mothers had rated the pregnancy as unwanted, 25% as mistimed but wanted and 63% as wanted, implying that altogether 88% of the offspring had been the result of a wanted pregnancy (Rantakallio 1974, Myhrman 1992, Myhrman *et al.* 1996).

Mother’s age at birth (I)

The age of the mother at the time of the birth was obtained from the Population Register Centre. Mother’s age was classified into ‘under 20 years’, ‘20–35 years’ and ‘over 35 years’. Cut-off points were selected based on previous studies in the NFBC 1966 (Kemppainen *et al.* 2001 a,b).

Mother’s smoking during pregnancy (I)

Information on the mother’s smoking habits was collected during the same routine visit to the antenatal clinic and after delivery. Maternal smoking was classified as ‘yes’ if the mother had smoked more than one cigarette daily during

the pregnancy and ‘no’ if the mother did not smoke or had stopped before the pregnancy (Rantakallio 1978, Isohanni *et al.* 1995, Mäki *et al.* 2010).

Multiparity at birth (I)

Parity, assessed at birth, was categorized into three classes: ‘1’, ‘2–5’ and ‘over 5’. The ‘over 5’ class was termed ‘grand multiparity’ (GMP; Juntunen 1997, Kemppainen *et al.* 2000). The three classes were used to see if being a first-born or one of a large number of children increased the risk of attempted or completed suicide. GMP with the same cut-off point (over 5) has been found to be associated with schizophrenia and depressive disorders of offspring (Kemppainen *et al.* 2000). First-born status is associated with increased risk of schizophrenia in the NFBC 1966 (Kemppainen *et al.* 2001a).

Socioeconomic status at birth (I)

Socioeconomic status (SES), determined by the father’s occupation, had been assessed in 1966 (Mäkikyrö *et al.* 1997). When the father’s occupational status was not known the mother’s information was used instead. Classes I and II (“high social class”) and classes III and IV (“low social class”) were pooled for the purpose of the analyses. Social class V (farmers) was treated separately in the analysis. This categorization was based on previous studies in the NFBC 1966 (Sauvola *et al.* 2001b, Sauvola *et al.* 2002).

Single-parent family (I)

The mothers were asked about their marital status during the visit at the antenatal clinic and were classified as: 1) married, 2) divorced, 3) widowed, or 4) never married. The families were categorized for the analysis as ‘two-parent families’ or ‘single-parent families’ (Sauvola *et al.* 2001a).

Adolescent smoking (II)

The information on smoking habits was gathered from a questionnaire mailed to the children at the age of 14 years (Rantakallio 1983, Isohanni *et al.* 1995, Riala *et al.* 2009). Smoking habits were assessed by asking: Do you smoke? The following categories were constructed from the original 8 alternative responses:

1 Never; 2. Experimental smoking (tried once/tried twice or more/smokes occasionally/smokes about twice a week); and 3. Regular smoking (smoking 1–5 cigarettes/6–10 cigarettes/more than 10 cigarettes a day).

School data (III)

Data on school marks at the age of 16 were obtained from registers of the national application system for secondary education after compulsory schooling (Isohanni *et al.* 1998). Averages of school marks were used in this study, which included marks in all school subjects. The school marks range from 4 (fail) to 10 (excellent). Although they are scored (by teachers) using only whole numbers (4 to 10), individual scores are approximately normally distributed (Isohanni *et al.* 2004). Good school performance was set to be mean scores over 8.5, which had been reached by approximately 20% of cohort members. School grades were not available for 239 persons, of whom 39 (none psychotic subjects) had not attended school at all, 72 (3 psychotic subjects) were in special schools, 47 (2 psychotic subjects) had failed at least one grade and 81 (1 psychotic subject) were in a class appropriate for their age.

Diagnostic data (II-IV)

The Finnish Hospital Discharge Register (FHDR) covers all mental and general hospitals and health centers nationwide (Gissler & Haukka 2004, Miettunen *et al.* 2010). The ICD-8 was used in Finland between the years 1968–1986. During 1987–1995 the ICD-9 with DSM-III-R criteria was in use; since 1st January 1996 the ICD-10 has been the official classification. All cohort members over 16 years appearing on the FHDR until the end of 1997 for any mental disorder (ie ICD-8 codes 290-309, ICD-9 290-316, and ICD-10 F00-F69, F99) were identified. All case records were scrutinized and diagnoses were re-checked for DSM-III-R criteria (Isohanni *et al.* 1997, Moilanen *et al.* 2003). Until recently, most patients in Finland who had experienced an episode of schizophrenic psychosis were hospitalized and appear in the FHDR (Isohanni *et al.* 1997) and the proportion of hospital treated patients has remained relatively high (Arajärvi *et al.* 2005).

Altogether 155 subjects with known psychotic episodes in their life up until age 31 were detected. One hundred subjects met the DSM-III-R criteria for schizophrenia (295, except 295.4 and 295.7). The group of other psychoses includes 55 subjects (26 men). DSM-III-R diagnoses in this group were 295.40

schizophreniform disorder (n=16); 295.70 schizoaffective disorder (4); 296.24 major depression, single episode, with psychotic features (5); 296.34 major depression, recurrent, with psychotic features (1), 296.44; bipolar disorder, manic, with psychotic features (6); 296.54 bipolar disorder, depressed, with psychotic features (1); 296.64 bipolar disorder, mixed, with psychotic features (1); 297.10 delusional (paranoid) disorder (10); 298.8 brief reactive psychosis (2); 298.9 psychotic disorder NOS (9). The non-psychotic psychiatric diagnoses group included 322 subjects (DSM-II-R codes 296 except 296.24, 296.34, 296.44, 296.54, 296.64, 300-316).

6.3.2 Covariates

Original study I

Predictor variables were selected to logistic regression models if they showed a trend with p-values below 0.1 in cross-tabulations.

- Parental psychiatric disorder. Information on mental disorders in the mothers and fathers according to the International Statistical Classification of Diseases, 8th revision (ICD-8 codes 290-309), was gathered from the FHDR, which covers all mental and general hospitals and health centers nationwide, for the period from 1972 to 1984, when the offspring were in the age range 6–18 years. Diagnoses were not available from the FHDR before 1972. The cut-off point was set at 1984 to ensure that the parent’s hospital treatment occurred before the offspring’s suicide or attempted suicide. This variable was dichotomized in the analyses in the form ‘psychiatric disorder’ or ‘no psychiatric disorder’.
- Psychiatric disorder in the offspring. All cohort members over 16 years appearing in the FHDR up to the end of 1997 on account of any mental disorder (ie ICD-8 codes 290-309, ICD-9 290-316, and ICD-10 F00-F69, F99) were identified. All case records were scrutinized and diagnoses were re-checked against the DSM-III-R criteria (Isohanni *et al.* 1997, Moilanen *et al.* 2003). This variable was dichotomized as ‘psychiatric disorder’ or ‘no psychiatric disorder’. Organic psychiatric disorders were excluded from analyses.

Original study II

The following variables were extracted from the 14-year postal questionnaire:

- Primary family type; two-parent family with both biological parents vs. other family types.
- Parental social class; I-II vs. III-IV vs. V. Social classes I-II included those with the highest social standing/professional status, classes III and IV were skilled and unskilled workers, respectively, and class V comprised farmers.
- School performance at the age of 14 years; not in normal grade (grade below age-appropriate level or special school) vs. in normal grade (grade appropriate for age level or above).
- Alcohol use was assessed by asking: *Do you drink alcohol?* The following categories were constructed from the original 5 alternative answers 1. Never; 2. Experimental use (tried once/tried twice or more often); and 3. Regular pattern of alcohol use (alcohol use at some time every month/every week).
- Information on other substance use was assessed based on the question: Have you used other substances (eg solvents or drugs)? The following two categories were constructed from the original 4 alternatives due to rarity of regular use: 1. Never; and 2. Occasional/regular use (tried once/tried twice or more often/regular use).

Original study III

We included the following potential confounding variables in the analyses: gender, age of onset of psychotic illness and fathers' social class in 1980:

- Gender is known to be associated with school performance (Isohanni *et al.* 1998, Koivusilta 2000) and suicide risk (Hawton *et al.* 2005). In this sample (n=10,585), gender was associated with school performance (11.0% of males and 28.6% of females scored above 8.5, $p<0.001$) and with suicide risk (0.8% of males and 0.2% of females committed suicide, $p<0.001$).
- Social class is known to be associated with school performance (Kuusinen 1986) and it may also be associated with suicide risk (Steenland *et al.* 2003). In NFBC 1966 (n=10,585), social class was associated with school performance (in highest social class 29.4%, in middle social class 14.6% and in lowest social class 19.4% scored above 8.5, $p<0.001$), but not with suicide

risk (in highest social class 0.4%, in middle social class 0.6% and in lowest social class 0.3% committed suicide, $p=0.291$).

- The age of onset of psychotic disorder has been associated with suicide risk (De Hert *et al.* 2001). Early onset of psychotic illness may also be related to patient's school marks (Helling *et al.* 2003). In this sample of psychotic patients ($n=145$), age of onset was not significantly associated with school performance (in early onset group 18.8% and in late onset group 12.4% scored above 8.5, $p=0.304$) or with suicide risk (in early onset group 6.3% and in late onset group 7.2% committed suicide, $p=0.829$).

6.3.3 Outcome variables

Suicide attempts (I, II)

Data on suicide attempts was gathered from the FHDR, which usually includes severe suicide attempts requiring hospital treatment. All cohort members over 16 years appearing in the FHDR up to the end of 2001 (original study II) and by the end of 2005 (original study I) on account of a suicide attempt were identified (ICD-8-9 E950-E959, ICD-10 X60-X84). There were 5 males with a suicide attempt followed later by suicide who were excluded when studying the attempts. In this study suicide attempt includes only serious acts that have led to hospital treatment. The main focus is on completed suicide.

Suicides (I-IV)

Causes of death up to Dec 31st, 2001 (original studies I and IV) and up to Dec 31st, 2005 (original studies II and IV), were obtained for 2.4% ($N=271$) of the study population from the national Cause of Death Statistics maintained by Statistics Finland. These were divided into two main categories according to the ICD 8-10th revisions: suicide (ICD-8-9: E950-E959, ICD-10: X60-X84, Y87.0) and other causes. No suicides had occurred before the cohort members were 18 years old. NFBC 1966 members who had died of other causes were excluded from the analyses, leaving a population of 10,742 offspring. The method of suicide was classified as violent (hanging, shooting, drowning, wrist-cutting, deliberate traffic accident, or jumping from a high place) or nonviolent (poisoning

or gas) according to potential immediate lethality of the method (Maes *et al.* 1993).

6.3.4 Statistical methods

Original Study I

Cross-tabulations and risk calculations (odds ratio, OR) were used to assess the relation between potential early risk factors and attempted and completed suicides among the offspring. The significance of differences appearing in the frequency tables were tested using Pearson's Chi-square test or Fisher's exact test as appropriate. All the variables that showed trends to statistical significance with p-values below 0.1 were selected for inclusion in logistic regression models. All the analyses were performed separately for males and females and for attempted and completed suicides. Due to the low number of female suicides no logistic regression model was constructed for this group. All the analyses were performed using SPSS software package version 17.0 (SPSS 2008).

Original Study II

Statistical significance of group differences between categorical variables was assessed with Pearson's Chi-square test and in continuous variable with the analysis of variance (ANOVA). A Cox proportional hazards regression model was used to test the effect of each characteristic on the hazards for dying from a suicide after the subject's 14th birthday. All analyses were performed using SPSS 13.0 for Windows. Statistical significance was set at $\alpha = 0.05$ level and all tests were two-tailed.

Original Study III

Crude and adjusted hazard ratios (HR) and their 95% confidence interval (95% CI) for suicide by school performance were computed using Cox regression which takes the time to the event (suicide) account. Information of patients with other causes of deaths was censored in survival analysis at the time of the death. The exposure variables included were the variable of interest (school mark) and potential confounders (gender, age of onset of psychotic illness and fathers' social

class in 1980). Onset age of psychotic symptoms was dichotomized to early onset (at age of 20 years or earlier) and late onset cases. This categorization was also used in an earlier study in the Northern Finland 1966 Birth Cohort (Moilanen *et al.* 2003). Fathers' social class in 1980 had three categories: high (I-II) vs. low (III-IV) and farmers (V). Subjects with missing school mark data (233 in non-psychotic group and 6 in psychotic group) were excluded from the analysis. 12 non-psychotic cases were censored before the earliest event in a stratum. The final sample for Cox regression analysis was 149 psychotic patients and 10,546 non-psychotic control subjects.

Original study IV

Survival analysis with Log Rank test statistics was used to study time to suicide after first discharge from psychiatric hospital for schizophrenia and non-psychotic psychiatric disorders.

7 Ethical considerations and personal involvement

The Ethics Committee of the University Hospital of Oulu keeps the study design of the Northern Finland 1966 Birth Cohort under review. The research plans for the 31-year follow-up of the NFBC 1966 study were accepted by the Ethical Committee of Oulu University, Faculty of Medicine on June 7th 1996, the 34-year psychiatric follow-up on March 30th 1998, and the 43-year follow-up on February 18th 2008. Data protection has been scrutinized by the Privacy Protection Agency, as well as by the principles from the Ministry of Health and Social Affairs in 1994, when the permission to have information on the study sample was obtained. Informed consent was inquired from all the participants, and those subjects who declined use of their data have been excluded from the study.

The author of this thesis has participated in the Northern Finland 1966 Birth Cohort study as a researcher since 2003. Due to the longitudinal nature of the NFBC 1966 study the author has not participated in collection of data used in the original studies, but has been designing and collecting data in the ongoing 2008–2011 psychiatric field study acting as a member of a management group from 2007 and as a field manager in 2008–2009. As a field manager the author has been responsible for practical realization of the field study including planning the study protocol, selecting, training and supervising workers and making arrangements of study materials and environments. The age 43–45 follow-up which will be performed in 2008–2011 includes structural and functional MRI and an extensive clinical examination, cognitive battery and register update.

The author has participated in the designing of all the original studies. Statistical analyses of original articles I, III and IV have been made by the author together with adjunct professor Jouko Miettunen. The author has written the first and final versions of the original articles I, III and IV and has participated in interpreting the data and writing of the original article II in all phases and especially in its discussion section. The author has been the corresponding author in original studies I, III and IV and has led the whole resubmission process.

8 Results

8.1 Early family factors and risk of attempted suicides or suicides in offspring (I)

A total of 121 suicide attempts (57 males and 64 females) and 69 suicides (56 males and 13 females) had occurred among the offspring during the follow-up period up to the end of 2005 (ie by 39 years of age). The numbers of cases and unadjusted odds ratios (OR) and p-values for the associations between suicide attempts and the various potential early risk factors are presented for males and females separately in Table 2 and similar data for suicides in Table 3.

Table 2. Association between early family factors and suicide attempts in the Northern Finland 1966 Birth Cohort (N=10742) (original study I Table 1).

Variable	Males (n=5445)		Females (n=5292)	
	yes n/N (%)	OR (95% CI)	yes n/N (%)	OR (95% CI)
Antenatal depressed mood				
no	46/4583 (1.0)		51/4424 (1.2)	
yes	10/730 (1.4)	1.37 (0.69-2.72)	11/727 (1.5)	1.32 (0.68-2.54)
Unwanted pregnancy				
wanted now or later	42/4674 (0.9)		49/4544 (1.1)	
unwanted	13/631 (2.1)	2.32 (1.24-4.35)	13/602 (2.2)	2.03 (1.09-3.75)
Mother's age at birth				
under 20	6/372 (1.6)	1.40 (0.59-3.29)	7/352 (2.0)	1.63 (0.73-3.62)
20-34	40/4052 (1.0)	Ref.	48/3953 (1.2)	Ref.
35 or over	11/1021 (1.1)	0.93 (0.48-1.80)	9/987 (0.9)	0.74 (0.36-1.50)
Mother's smoking during pregnancy				
no	42/4434 (0.9)		47/4342 (1.1)	
yes	14/795 (1.8)	1.86 (1.02-3.40)	13/736 (1.8)	1.63 (0.89-3.00)
Parity at birth				
1	12/1736 (0.7)	0.54 (0.28-1.04)	16/1705 (0.9)	0.68 (0.38-1.23)
2-5	39/3076 (1.3)	Ref.	40/2927 (1.4)	Ref.
6 or more	6/624 (1.0)	0.76 (0.32-1.79)	8/652 (1.2)	0.90 (0.42-1.93)
Socioeconomic status at birth				
I-II	3/410 (0.7)	Ref.	4/373 (1.1)	Ref.
III-IV	40/4009 (1.0)	1.37 (0.42-4.44)	51/3850 (1.3)	1.24 (0.45-3.45)
V	14/1006 (1.4)	1.92 (0.55-6.70)	8/1042 (0.8)	0.71 (0.21-2.38)
Family type in 1966				
two-parent family	48/5257 (0.9)		63/5101 (1.2)	
single-parent family	9/188 (4.8)	5.46 (2.64-11.29)	1/191 (0.5)	0.42 (0.58-3.05)
Mother's psychiatric disorder				
no	55/5237 (1.1)		57/5074 (1.1)	
yes	2/208 (1.0)	0.95 (0.22-3.78)	7/218 (3.2)	2.92 (1.32-6.48)
Father's psychiatric disorder				
no	52/5140 (1.0)		55/4943 (1.1)	
yes	5/305 (1.6)	1.63 (0.65-4.11)	9/349 (2.6)	2.35 (1.15-4.80)
Offspring's psychiatric disorder				
no	37/5158 (0.7)		45/5134 (0.9)	
yes	20/284 (7.0)	10.49 (6.00-18.32)	19/154 (12.3)	15.92 (9.07-27.94)

OR = unadjusted Odds Ratio. Statistically significant Odds ratios are in **bold**

Table 3. Association between early family factors and suicide in the Northern Finland 1966 Birth Cohort (N=10742) (original study I Table 2).

Variable	Males (suicides/total n=56/5450)		Females (suicides/total n=13/5292)	
	yes n/N (%)	OR (95% CI)	yes n/N (%)	OR (95% CI)
Antenatal depressed mood				
no	42/4588 (0.9)		10/4424 (0.2)	
yes	12/730 (1.6)	1.81 (0.95-3.45)	3/727 (0.4)	1.83 (0.50-6.66)
Unwanted pregnancy				
wanted now or later	44/4678 (0.9)		11/4544 (0.2)	
unwanted	10/632 (1.6)	1.69 (0.85-3.38)	2/602 (0.3)	1.37 (0.30-6.21)
Mother's age at birth				
under 20	8/373 (2.1)	2.20 (1.02-4.73)	1/352 (0.3)	1.03 (0.13-7.97)
20-34	40/4055 (1.0)	Ref.	11/3953 (0.3)	Ref.
35 or over	8/1022 (0.8)	0.80 (0.37-1.70)	1/987 (0.1)	0.36 (0.047-2.83)
Mother's smoking during pregnancy				
no	44/4439 (1.0)		9/4342 (0.2)	
yes	9/795 (1.1)	1.14 (0.56-2.35)	3/736 (0.4)	1.97 (0.53-7.30)
Parity at birth				
1	19/1738 (1.1)	1.35 (0.74-2.46)	3/1705 (0.2)	0.57 (0.16-2.11)
2-5	25/3078 (0.8)	Ref.	9/2927 (0.3)	Ref.
6 or more	12/625 (1.9)	2.39 (1.20-4.78)	1/652 (0.2)	0.50 (0.06-3.94)
Socioeconomic status at birth				
I-II	4/411 (1.0)	Ref.	0/373 (0)	Ref.
III-IV	45/4013 (1.1)	1.15 (0.41-3.23)	13/3850 (0.3)	-
V	7/1006 (0.7)	0.71 (0.21-2.45)	0/1042 (0)	-
Family type in 1966				
two-parent family	52/5262 (1.0)		12/5101 (0.2)	
single-parent family	4/188 (2.1)	2.18 (0.78-6.09)	1/191 (0.5)	2.23 (0.29-17.25)
Mothers' psychiatric disorder				
no	50/5241 (1.0)		13/5074 (0.3)	
yes	6/209 (2.9)	3.07 (1.30-7.24)	0/218 (0)	-
Fathers' psychiatric disorder				
no	50/5145 (1.0)		13/4943 (0.3)	
yes	6/305 (2.0)	2.05 (0.87-4.81)	0/349 (0)	-
Offspring's psychiatric disorder				
no	37/5161 (0.7)		8/5134 (0.2)	
yes	19/286 (6.6)	9.86 (5.59-17.37)	5/154 (3.2)	21.50 (6.95-66.51)

Statistically significant Odds ratios are in **bold**.

8.1.1 Suicide attempts

Unwanted pregnancy, mother's smoking, a single-parent family and psychiatric disorder in the offspring were significant risk factors for suicide attempts in males before adjustment (Table 2), while those for females were unwanted pregnancy, psychiatric disorder in the mother and/or father and psychiatric disorder in the offspring. Maternal depressed mood during pregnancy, mother's age and multiparity were not associated with suicide attempts in either the male or female offspring, nor was socioeconomic status during childhood.

The logistic regression models for suicide attempts and suicides among males and suicide attempts among females are shown in Table 4. Risk factors were included if they showed a trend toward association (the significances of the associations had p-values below 0.1) in Table 1 (suicide attempts) or 2 (suicides). The first model does not contain hospital-treated mental disorders in the subjects themselves, while the second model includes these. A single-parent family (OR 3.71, 95% confidence interval 1.62–8.50) was the only significant risk factor for suicide attempts in the males in addition to psychiatric disorder in the subject (OR 10.50, 6.11–18.05), but a maternal or paternal hospital-treated psychiatric disorder (OR 2.67, 1.19–5.97, and OR 2.18, 1.06–4.48, respectively) were significant risk factors in the females. When a psychiatric disorder in the subject was included among possible risk factors for suicide attempts, it alone remained significant (OR 15.55, 8.78–27.53).

8.1.2 Suicides

The risk factors for suicide in males in the unadjusted analyses were mother's age under 20 years, grand multiparity, mother's hospital-treated psychiatric disorder and a psychiatric disorder in the subject (Table 3). Only the last-mentioned was a significant risk factor for suicide in females. Mothers' depressed mood and smoking during pregnancy and unwantedness were not associated with suicides in the male and female offspring, nor was socioeconomic status during childhood.

The first model showed mother's age under 20 years (OR 2.41, 1.02–5.71), multiparity (OR 2.74, 1.19–6.29) and a psychiatric disorder in the mother (OR 2.87; 1.21–6.82) to be significant risk factors for suicide in males (Table 4), but after adjustment for a psychiatric diagnosis in the cohort member only multiparity (OR 2.67; 1.15–6.18) remained significant. A psychiatric disorder in the subject himself was a robust risk factor for suicide in men, OR 8.31 (4.62–14.96).

Table 4. Adjusted odds ratios (OR) for suicide attempts in males and females and suicide in males (original study I Table 3).

Variable	Logistic regression analysis					
	Suicide attempts males		Suicide attempts females		Suicide males	
	OR ¹ (95% CI)	OR ² (95% CI)	OR ¹ (95% CI)	OR ² (95% CI)	OR ¹ (95% CI)	OR ² (95% CI)
Antenatal depressed mood					1.65 (0.85-3.19)	1.44 (0.73-2.83)
Unwanted pregnancy	1.45 (0.74-2.84)	1.39 (0.70-2.77)	1.85 (1.00-3.44)	1.53 (0.80-2.91)		
Mother's age						
under 20					2.41 (1.02-5.71)	2.21 (0.92-5.33)
20-34					Ref.	Ref.
35 or over					0.42 (0.17-1.07)	0.40 (0.16-1.03)
Mothers smoked during pregnancy	1.77 (0.99-3.17)	1.63 (0.90-2.96)				
Parity at birth						
1					1.00 (0.51-1.96)	0.97 (0.49-1.91)
2-5					Ref.	Ref.
6 or more					2.74 (1.19-6.29)	2.67 (1.15-6.18)
Single parent family	4.02 (1.80-8.95)	3.71 (1.62-8.50)				
Mother's psychiatric disorder			2.67 (1.19-5.97)	1.95 (0.83-4.56)	2.87 (1.21-6.82)	2.38 (0.97-5.83)
Father's psychiatric disorder	1.75 (0.74-4.13)	1.34 (0.55-3.27)	2.18 (1.06-4.48)	1.83 (0.86-3.87)		
Offspring's psychiatric disorder		10.50 (6.11-18.05)		15.55 (8.78-27.53)		8.31 (4.62-14.96)

¹ All the variables that showed trends with p-values below 0.1 in unadjusted analysis (see Table 3 and Table 4) were selected for the logistic regression models. Odds Ratios (OR) with 95% confidence intervals (95% CI) are presented for all variables included in each model.

² Adjusted for the same variables as in model 1 and also for psychiatric disorder in the offspring

8.2 Smoking at age 14 and suicide risk (II)

In Table 5 the survival status at the end of follow-up and other background variables are presented by 14-year smoking status for males and females separately. Male adolescents with regular daily smoking at the age of 14 years were more likely to commit suicide by the age of 34 years ($\chi^2 = 15.8$, $df = 2$, $p < 0.001$). A corresponding association was not found among females. There were 66 males and 70 females who had undergone hospital treatment because of suicide attempts until the end of 2001. The proportion of suicide attempts among boys who smoked regularly was 3.3%, while it was 1.3% for experimental smokers and 0.8% for non-smokers ($\chi^2 = 11.8$, $df = 2$, $p = 0.003$). The corresponding percentages among girls were 4.2% for regular smokers, 1.4% for experimental smokers, and 0.8 for nonsmokers ($\chi^2 = 24.41$, $df = 2$, $p < 0.001$).

The survival estimates according to their smoking status at the age of 14 are presented for male and female cohort members in Figures 2 and 3, respectively. In males the mean survival time after the 14th birthday was statistically significantly lower among regular smokers (mean 21.32 years, std 1.36 years) compared to experimental smokers (mean 21.45, std 0.77) or non-smokers (mean 21.46, std 0.62); ($F=3.95$, $df=5073$, $p = 0.019$), while in female subjects no difference in survival time was observed. After adjusting for sociodemographic factors in adolescence and psychiatric morbidity, regular male smoker were at 4.05-fold hazard (95% CI 1.18–13.93, $p = 0.026$) for committing suicide at a younger age (Table 6). Non-conventional family type ($p = 0.003$) and psychiatric hospitalization (psychotic disorders, $p < 0.001$; non-psychotic disorders, $p < 0.001$) independently increased the risk of suicide among males as well. Correspondingly, among female cohort members adolescent smoking status was not associated with the risk to commit suicide at a younger age (Table 6). However, hospital-treated psychiatric disorders (psychotic disorders, $p < 0.001$; non-psychotic disorders, $p < 0.001$) increased the risk of suicide among females.

Of the 40 male suicide victims 32 (80%) used a violent method. The use of violent suicide method was not statistically significantly more common among those being regular smokers at the age of 14 years (7 out of 8 suicides: 87.5%) than among experimental smokers or non-smokers. Of the female suicide victims, 7 of 15 (46.7%) used a violent method, but their smoking status did not associate with the choice of suicide method.

Table 5. Sample characteristics of male and female adolescent non-smokers, experimental and regular daily smokers from the Northern Finland 1966 Birth Cohort (original study II Table 1).

Characteristics ^a	Males					Females						
	Non-Smokers		Experimental Smokers		Regular Daily Smokers	Non-Smokers		Experimental Smokers		Regular Daily Smokers	Statistic	p Value
	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)			
Survival status at end of follow-up, % (N)												
Alive	99.6 (1430)	99.2 (3309)	97.4 (295)	97.4 (295)	99.7 (1863)	99.7 (2846)	99.4 (328)	99.4 (328)	99.4 (328)	$\chi^2 = 1.1$ (df = 2)	0.564	
Suicide	0.4 (6)	0.8 (26)	2.6 (8)	2.6 (8)	0.3 (5)	0.3 (8)	0.6 (2)	0.6 (2)	0.6 (2)			
Family type, % (N)												
Two-parent family	86.0 (1235)	82.1 (2727)	68.0 (206)	68.0 (206)	86.1 (1608)	79.6 (2273)	63.9 (211)	63.9 (211)	63.9 (211)	$\chi^2 = 97.2$ (df = 2)	< 0.001	
Other type of family	14.0 (201)	17.9 (598)	32.0 (97)	32.0 (97)	13.9 (260)	20.4 (581)	36.1 (119)	36.1 (119)	36.1 (119)			
Social class, % (N)												
I-II (Highest)	31.1 (449)	31.5 (1051)	27.4 (83)	27.4 (83)	32.9 (614)	28.7 (820)	23.3 (77)	23.3 (77)	23.3 (77)	$\chi^2 = 49.8$ (df = 4)	< 0.001	
III-IV (Lowest)	54.7 (785)	56.4 (1881)	65.0 (197)	65.0 (197)	52.9 (983)	59.3 (1692)	70.9 (234)	70.9 (234)	70.9 (234)			
V (Farmers)	14.1 (202)	12.1 (403)	7.6 (23)	7.6 (23)	14.5 (271)	12.0 (342)	5.8 (19)	5.8 (19)	5.8 (19)			
School performance, % (N)												
At normal level	93.5 (1343)	94.7 (3159)	91.7 (278)	91.7 (278)	96.2 (1797)	98.1 (2801)	97.9 (323)	97.9 (323)	97.9 (323)	$\chi^2 = 17.2$ (df = 2)	< 0.001	
Below average level	6.5 (93)	5.3 (176)	8.3 (25)	8.3 (25)	3.8 (71)	1.9 (53)	2.1 (7)	2.1 (7)	2.1 (7)			
Use of Alcohol, % (N)												
Never	76.1 (1093)	28.5 (949)	5.6 (17)	5.6 (17)	75.7 (1414)	23.6 (674)	2.7 (9)	2.7 (9)	2.7 (9)	$\chi^2 = 2145.4$ (df = 4)	< 0.001	
Experimental	23.9 (343)	70.6 (2356)	75.6 (229)	75.6 (229)	24.1 (4511)	74.1 (2116)	67.9 (224)	67.9 (224)	67.9 (224)			
Regular pattern of use	0 (0)	0.9 (30)	18.8 (57)	18.8 (57)	0.2 (3)	2.2 (64)	29.4 (97)	29.4 (97)	29.4 (97)			
Use of substances, % (N)												
Never	100.0 (1436)	99.2 (3309)	92.7 (281)	92.7 (281)	100.0 (1868)	99.5 (2841)	91.2 (301)	91.2 (301)	91.2 (301)	$\chi^2 = 273.9$ (df = 2)	< 0.001	
Tried/Used	0 (0)	0.8 (26)	7.3 (22)	7.3 (22)	0 (0)	0.5 (13)	8.8 (29)	8.8 (29)	8.8 (29)			

Characteristics ^a	Males				Females				p Value
	Non-Smokers		Smokers		Non-Smokers		Smokers		
	Experimental	Regular Daily	Statistics	p Value	Experimental	Regular Daily	Statistics	p Value	
Hospital-treated Psychiatric Disorders, % (N)			$\chi^2 = 41.4$	< 0.001			$\chi^2 = 4.1$		
None	96.4 (1384)	95.0 (3168)	88.4 (268)		97.2 (1815)	97.3 (2777)	96.7 (319)		0.389
Psychoses	1.3 (19)	1.3 (44)	1.7 (5)		1.4 (26)	0.9 (25)	1.2 (4)		
Non-psychotic disorders	2.3 (33)	3.7 (123)	9.9 (30)		1.4 (27)	1.8 (52)	2.1 (7)		

^a Family type, Social class, School performance and Use of Alcohol was assessed at 14 years of age, while information on Survival Status and Hospital-Treated Psychiatric Disorders reached up to 31 years of age among the cohort members

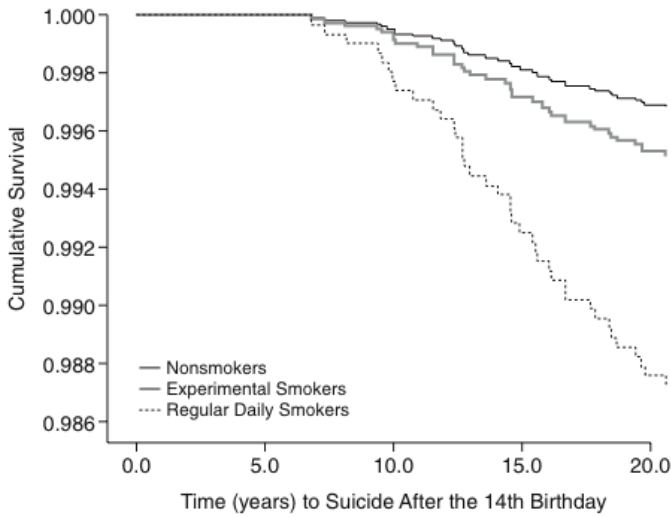


Fig. 2. Proportion of male cohort members who died from suicide after their 14th birthday according to smoking status at 14 years of age (original study II Figure 1).

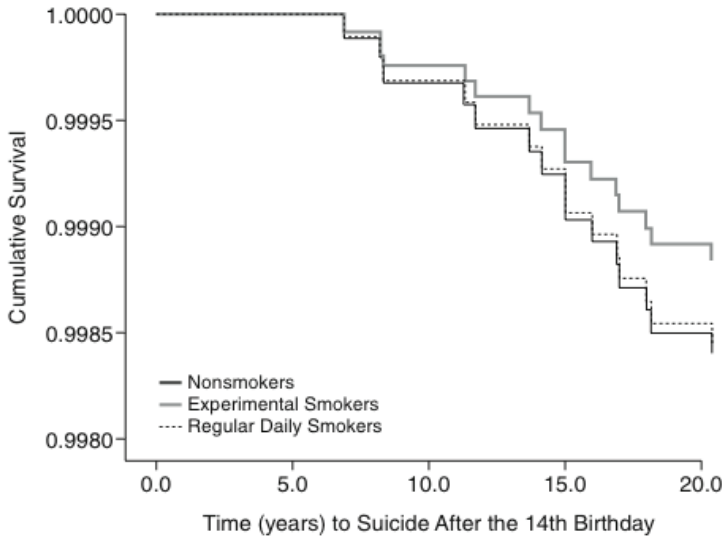


Fig. 3. Proportion of female cohort members who died from suicide after their 14th birthday according to smoking status at 14 years of age (original study II Figure 2).

Table 6. Proportional Hazards (HR) for suicide after 14th birthday among subjects from the Northern Finland 1966 Birth Cohort (original study II Table 2).

Characteristics	Males			Females		
	HR ^a	95% CI	P value	HR ^a	95% CI	p Value
Smoking at 14 years						
Non-Smokers	ref.			ref.		
Experimental Smokers	1.53	0.58 to 4.03	0.395	0.72	0.20 to 2.59	0.615
Regular Daily Smokers	4.05	1.18 to 13.93	0.026	0.97	0.12 to 7.65	0.976
Family type at 14 years						
Two-parent family	ref.			ref.		
Other type of family	2.89	1.44 to 5.74	0.003	0.63	0.16 to 2.40	0.498
Father's social class at 14 years						
I-II (Highest)	ref.			ref.		
III-IV (Lowest)	0.84	0.40 to 1.78	0.657	3.15	0.70 to 14.29	0.137
V (Farmers)	1.48	0.51 to 4.32	0.472	1.31	0.12 to 14.52	0.826
School performance at 14 years						
At normal level	ref.					
Below average level	0.95	0.33 to 2.77	0.926	^b	^b	^b
Use of alcohol at 14 years						
Never	ref.			ref.		
Experimental	1.19	0.54 to 2.63	0.659	2.04	0.54 to 7.72	0.296
Regular pattern of use	0.66	0.07 to 6.00	0.712	2.09	0.14 to 31.95	0.595
Use of substances at 14 years						
Never	ref.			ref.		
Tried or used at least once	^b	^b	^b	4.71	0.44 to 49.95	0.198
Hospital-Treated psychiatric disorders Healthy in adulthood						
None	ref,			ref,		
Psychotic Disorders	13.66	5.18 to 36.05	< 0.001	19.49	4.18 to 90.77	< 0.001
Non-Psychiatric Disorders	6.62	2.99 to 14.65	< 0.001	17.93	4.71 to 68.30	< 0.001

^a The Cox Proportional Hazards Regression Model was used to test the effects of each characteristic on the hazards for dying from suicide after 14th Birthday. Adjusted for sociodemographic factors in adolescence and psychiatric morbidity.

^b Not estimable.

8.3 School performance and risk of suicide (III)

A total of 58 suicides occurred during 1982–2001, 45 (78%) males and 13 (22%) females. Fifty-five had valid school marks. Thirty-three of these did not have psychiatric diagnosis in FHDR. A total of 12 had a diagnosis of non-psychotic

mental disorder, 7 suffered from schizophrenia and 3 had a psychotic disorder other than schizophrenia (DSM-III-R diagnoses 295.40, female; 296.44, male; and 298.80, male).

Of the psychotic patients who had shown good school performance (one male and one female in the schizophrenia group and two males in the other psychoses group) 18% committed suicide compared to 4.8% of the psychotic patients with low or average school performance, HR 4.08 (95% CI 1.15–14.46) (Table 7). Of the psychotic patients who committed suicide 40% (4/10) had shown good school performance, compared to only 6.1% (2/33) of those with no psychiatric diagnosis.

Suicide risk was particularly high in the other psychosis category, but the number of cases is small and confidence interval includes unity. In the non-psychotic population (97% without psychiatric hospitalization) HR was 0.19 (95% CI 0.05–0.78). In a Cox regression model that included the effect of gender, social class and age of onset of illness, the interaction between school performance and psychiatric diagnosis (psychoses vs. non-psychotic population) in predicting suicide remained statistically significant (Wald Chi-square test 6.70, $p = 0.01$). In the whole cohort, 0.6% with average school marks under 8.5 committed suicide compared to 0.3% with good school performance; however, this result is statistically inconclusive, HR 0.50 (95% CI 0.21–1.17).

Table 7. Number and percent of suicides and hazard ratio for suicide in different diagnostic groups by school performance assessed using mean school marks at the age of 16 years in the Northern Finland 1966 Birth Cohort. School marks range from 4 (fail) to 10 (excellent) (original study III Table 1).

Diagnostic groups	Mean school marks under 8.5		Good school performance (mean school marks over 8.5)		Hazard Ratio* (unadjusted)	Hazard Ratio** (adjusted)
	Suicides/all	%	Suicides/all	%		
All non-psychotic (N=10546)	43/8470	0.5	2/2076	0.1	0.19 (0.05-0.78)	0.28 (0.07-1.16)
No diagnosis ¹ (N=10242)	31/8189	0.4	2/2053	0.1	0.26 (0.06-1.07)	0.36 (0.84-1.53)
Non-psychotic disorder ² (N=304)	12/281	4.3	0/23	0	-	-
All psychoses (N=149)	6/127	4.7	4/22	18.0	4.08 (1.15-14.46)	3.56 (0.97-13.05)
Other psychosis (N=54)	1/47	2.1	2/7	28.6	15.75 (1.42-174.40)	9.52 (0.46-195.60)
Schizophrenia (N=95)	5/80	6.3	2/15	13.3	2.07 (0.40-10.67)	2.14 (0.40-11.50)
Total	49/8597	0.6	6/2098	0.3	0.50 (0.21-1.17)	0.72 (0.30-1.71)

Test for interaction between diagnosis (psychoses vs. no diagnosis and school mark): Wald Chi-square test 6.70, p=0.01.

* Crude hazard ratio for suicide, reference group is school mark under 8.5.

** Adjusted (gender, age of onset and social class at 1980 in psychoses; gender and social class at 1980 in non-psychotic group) hazard ratio for suicide, reference group is school mark under 8.5.

¹ Never hospitalized due to any psychiatric disorder.

² Hospitalized due to non-psychotic psychiatric disorder.

Short case summaries of psychotic patients with good school performance who committed suicide (Appendix in original study III)

Patient 1. He was a member of a very talented and problematic family. He showed excellent performance at school and in military service, as well as during the first 2 years of studies at university. His life changed dramatically at the age of 22 years when his mother and a close, alcoholic relative died. The patient gave up his studies and developed schizophrenia. His illness became chronic and he adopted a homeless lifestyle. He committed suicide when he was 28 years old.

Patient 2. She had an excellent school performance and graduated from university. She had her first psychotic symptoms at the age of 27 and received a schizophrenia diagnosis. After a couple of years' struggle in a demanding job she became permanently disabled and unable to work, and six months later she committed suicide at the age of 32 immediately after discharge from psychiatric hospital.

Patient 3. He was the first-born child and was very dependent on his family. He had a psychosis when he was 20 years old. He thought of himself as a loser because he was unable to get on with his life and was afraid of becoming a burden to his parents. He committed suicide three weeks after he was discharged from a psychiatric hospital.

Patient 4. He placed enormous pressures on himself to succeed in everything. The patient had two hospital-treated psychotic episodes, the first one when he was 20, and received the diagnosis of manic bipolar disorder with psychosis in our validation. He committed suicide when he was 25 after his second attempt at trying to study at university failed.

8.4 Suicide rate in schizophrenia (IV)

At the end of 2005 (age 39), 7 of 100 schizophrenia patients had committed suicide. Thus, the case fatality (number of suicides divided by number of subjects) of the cohort was 7%. It was 2.9% (1/35) for women and 9.2% (6/65) for men. Seven men and none of the women died from a cause other than suicide. Thus, proportionate mortality (number of suicides/number of deaths) is 50% for all schizophrenic persons. Furthermore, 71% of suicides in schizophrenia occurred during the first three years after onset of illness.

Figure 4 shows survival curves for suicide after first psychiatric discharge for schizophrenia and non-psychotic psychiatric patients. Suicide rate of schizophrenia patients was nearly 2-fold higher (3.1% vs. 6.0%, OR=2.0, 95% CI 0.7–5.6) six years after first discharge from psychiatric care compared to hospital-treated patients with non-psychotic psychiatric diagnoses (number of suicides 14). When comparing survival curves the difference was statistically significant (Log Rank = 7.74, df=1, p = 0.0054).

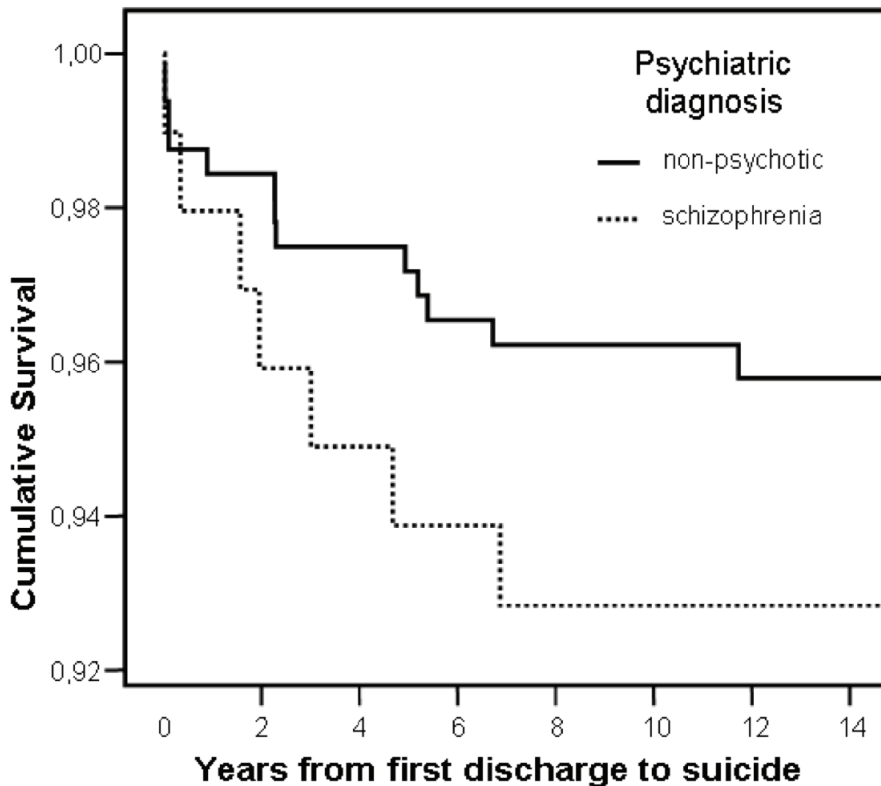


Fig. 4. Cumulative survival for suicide in schizophrenia (n=100) and in non-psychotic psychiatric diagnoses (n=322) in the Northern Finland 1966 Birth Cohort (Figure 1 in original study IV).

9 Discussion

9.1 Main findings

The single parent family was a risk factor for suicide attempts and grand multiparity for suicides among males even after adjusting for their own and parental mental disorders. Antenatal factors which have not previously been studied in this context were not related to suicide attempts or suicides in male and female offspring after adjustment.

Regular smoking in early adolescence independently increased the risk of hospital-treated suicide attempts in both genders, while increasing the risk of committed suicides only among male cohort members during a follow-up period up to the age of 34 years. A novel finding is that male cohort members with regular daily smoking in adolescence committed their suicides at a younger age compared to victims who were experimental smokers or non-smokers. However, smoking status in adolescence did not relate to the choice of suicide method in either gender. The gender ratio for suicides in this cohort was equal to the rate found in the official statistics of Finland during the period 1980 to 1995 for the whole country. In Finland, 3 out of 4 suicides are committed by males.

Good school performance was a protective factor against suicide in general population. However, among those individuals who later developed psychosis, good school performance was a risk factor for suicide. In a population-based cohort the case fatality rate in schizophrenia was 7% by the age of 39. Suicide risk was high especially for men and particularly in the early phase of the disease. Two thirds of suicides occurred within three years after the onset of illness.

9.2 Discussion of results

9.2.1 Early family factors and risk of attempted suicides or suicides in offspring (I)

In this study any depressed mood in the mother during pregnancy is unlikely *per se* to increase the risk of attempted or completed suicide in the offspring, even though it showed a slight tendency to increase the risk of suicide in male offspring. This was a rather surprising finding, since a previous study of the male offspring of antenatally depressed mothers in the NFBC 1966 had pointed to a

slight but significant increase in criminality, especially in violent criminality and recidivism (Mäki *et al.* 2003). Violent criminality has already been connected to suicides in the NFBC 1966 (Räsänen *et al.* 1998). On the other hand, there are no previous reports concerning the association between a mother's antenatal depression and suicidal phenomena in their offspring. Further studies with other samples might clarify this possible association.

There was an association between unwanted pregnancy and suicide attempts in both the males and females, but this was attenuated after adjustment for other early risk factors. Unwantedness was not statistically significantly associated with suicide in either the males or the females. There are no previous studies of the unwantedness of pregnancies in relation to the risk of suicide attempts or suicides in the offspring. However, there are probably several reasons why pregnancy is unwanted and might cause problems later in life.

This is the first study to consider the relationship between maternal antenatal smoking and the risk of suicide attempts or suicides in the offspring. Antenatal smoking was not connected with an elevated risk of either suicide attempts or actual suicides after adjustment, but it was associated with an elevated risk of suicide attempts in male offspring before adjustment for other factors.

In contrast to earlier findings (Mittendorfer-Rutz *et al.* 2004) a mother giving birth at a young age was not a statistically significant risk factor for suicide attempts, although it was associated with suicides in males before adjustment to the offspring's own mental disorder, a factor which is in agreement with the results of an earlier Scottish register study (Riordan *et al.* 2006). The young age of the mother was not associated with suicide attempts or suicides in the female offspring.

Birth into a single-parent family remained a risk factor for attempted suicide in males, increasing the risk nearly 4-fold even after adjustment for other early risk factors, namely mental disorders in the parents or offspring. A high suicide risk in males from single-parent families in the NFBC 1966 cohort by the age of 28 is previously reported (Sauvola *et al.* 2001), and an increased mortality has also been found in other settings (Romelsjö *et al.* 1992, Judge & Benzeval 1993, Schwartz *et al.* 1995). It should be noted, however, that Sauvola *et al.* (2001) used a different criterion for the single-parent family, including all types of single-parent families (mother was unmarried during pregnancy; parents had divorced or were not living together by the time the child was 14 years old; the mother, father or both had died before the child was 14 years old), while in this study only those who birth into a single-parent family were studied.

Environmental adversities may be connected with maternal effects by programming the capacity for defensive responses, such as adjustments in the emotional and endocrine system in response to increased sensitivity to adversity in children (Zhang *et al.*, 2006). The correlation between maternal and foetal cortisol and adverse functioning of the HPA axis might help to explain the effects of antenatal maternal stress on the foetus (Gitau *et al.* 1998). Maternal stress during the second trimester has been shown to increase depression in the offspring (Huizink *et al.* 2007), and single or teenage motherhood might increase maternal stress levels during pregnancy. On the other hand, antenatal depressed mood was not connected with suicidal phenomena. Inheritable personal traits (mainly cluster B) might also be associated with single or teenage mothers and thereby be further associated with suicide and suicide attempts in the offspring (Brent *et al.* 1994, Yen *et al.* 2009). There may be gene-environment interactions, too (Rutter *et al.* 2006).

Grand multiparity (over 5 previous children) was a risk factor for suicide in males. This confirms the results of an earlier study (Riordan *et al.* 2006). On the other hand, observation that grand multiparity was not associated with suicide attempts contradicts a previous finding in a Swedish register study (Mittendorfer-Rutz *et al.* 2004). Grand multiparity was not connected with suicide attempts or suicides in females. This study contains the first analysis of this issue stratified by gender. Problems in the early caretaker-infant relationship may be a risk factor for disadvantages affecting the offspring later on in life (Nemeroff 1999). Maternal depression is associated with grand multiparity (Brown & Harris 1978), and this may have a negative effect on development of the HPA axis and psychological development in the children. A feeling of rejection and neglectful parenting is found to increase the risk of suicide attempts in female offspring (Ehnavall *et al.* 2008), and this kind of parenting may be more prevalent in children with many older siblings.

Low or high socio-economic status (SES) at birth was not statistically significantly associated with suicide attempts or suicides in either gender, which was rather unexpected and in contrast to some previous findings, although earlier results have in general been inconsistent. The risk of suicide in a Scottish population sample was found to be elevated in the offspring of parents in skilled and unskilled occupational groups as compared with the offspring of members of the professions (Riordan *et al.* 2006), and low childhood SES was also linked with a high suicide risk in another British study (Neeleman *et al.* 1998) and with a high risk of suicide attempts in New Zealand (Fergusson *et al.* 1995). Meanwhile,

it was found in a Norwegian register study that high SES in childhood was connected with elevated suicide mortality in adulthood, especially in females (Strand & Kunst 2006). High social class at birth was also a risk factor for suicide in a sample consisting of people with a high risk of schizophrenia in Denmark (Silverton *et al.* 2008). These observations suggest that the effect of childhood SES on attempted and completed suicides might be culturally determined. SES in adulthood is nevertheless probably a more important factor for suicidal phenomena than SES in childhood (Qin *et al.* 2003).

Parental mental disorders are known to be risk factors for suicide attempts (Christoffersen *et al.* 2003, Mittendorfer-Rutz *et al.* 2008) and for suicides (Qin *et al.*, 2002 & 2003, Agerbo *et al.* 2002, Gould *et al.* 1996, Brent *et al.* 1996). The present results confirm this association and suggest that there might be gender differences in the influence of mothers' and fathers' psychiatric disorders on male and female offspring. Both mothers' and fathers' hospital-treated psychiatric disorders were risk factors for suicide attempts in female offspring and mothers' psychiatric disorders for suicide in males. This might be partly explained by heritability of mental disorders, since this association was attenuated after adjustment for psychiatric disorders in the offspring themselves.

This study did not focus on mental disorders in those who attempted or completed suicide, since this association is already well-known (Hawton & van Heeringen 2009), but it was evident in NFBC 1966 that hospitalization for any psychiatric disorder increased the risk of suicide attempts over 10-fold in males and over 15-fold in females, and that of actual suicide nearly 10-fold in males and over 20-fold in females. These figures are fairly similar to those quoted in a previous meta-analysis, where the risk of suicide was 9-fold greater in males and 13-fold greater in females among people with mental disorders in any treatment setting (Harris & Barraclough 1998). Also, including common mediating and causal factors - mental disorder of the study subject - to the logistic modeling may cause overadjustment; that is why the results of a logistic model without mental disorder are of interest. In a population-based sample, a non-significant result does not prove the null-hypothesis, but may reflect either small effect size or inadequate power (Kraemer *et al.* 2001).

9.2.2 Smoking and suicide (II)

Smoking is known to be a risk factor for subsequent onset of depression both in adolescent and adult populations (Wu & Anthony 1999, Breslau *et al.* 2004).

Although results were adjusted for hospital-treated psychiatric disorders in statistical analyses, it is possible that some suicide victims of this study were suffering from non-diagnosed depression or were treated in outpatient settings. However, the smoking-depression link does not explain the findings of a gender difference. In this study, adolescent smoking increased the risk for committed suicides only among males. It is well known that depression is more prevalent among females (Kessler *et al.* 1994), and adolescent smoking in this birth cohort was even more common among females than among males. Therefore the effect of gender on the smoking-suicide association is important and deserves further study.

At least two putative biological mechanisms behind these findings are worthy of note: first, Roggenbach *et al.* (2002) have suggested that reduced 5-HIAA concentrations in cerebrospinal fluid (CSF) might be related to increased depressive symptoms and changes in impulsivity. When measuring CSF 5-HIAA levels in depressed subjects Malone *et al.* (2003) found that CSF 5-HIAA levels were negatively correlated with the amount of cigarette smoking, but were not related to suicide attempter status. Furthermore, the number of cigarettes smoked correlated positively with aggression scores. Thus, according to Malone *et al.* (2003) nicotine may have both biological and behavioral effects in the brain that increase the probability to suicidal behavior in depressed patients.

Secondly, subjects with a background of frequent impulsive behaviour, alcoholism and suicide attempts have been found to have higher levels of free testosterone in CSF compared to healthy volunteers (Virkkunen *et al.* 1994). Furthermore, higher levels of serum testosterone and free testosterone were found among male smokers compared to ex-smokers or non-smokers (Trummer *et al.* 2002). The effect of high testosterone levels on impulsive behaviours may be mediated by serotonin, as there exists an inverse relation between testosterone levels and brain 5-HT levels. Furthermore, lack of brain 5-HT is known to lead to increased aggression (Giammanco *et al.* 2005). However, the direction of causality between smoking and higher levels of serum testosterone remains unclear. For example, men having a high level of testosterone as opposed to a low level have been found to be more often engaged in health risk behaviours (Booth *et al.* 1999).

Since smoking is associated with higher levels of aggression impulsivity, which are associated with the choice of a violent method of suicide (Dumais *et al.* 2005), one might assume that smokers choose violent suicide methods more often than non-smokers. In this study the choice of suicide method did not differ

between smokers and non-smokers. However, a violent method has in general been used in Finland by more than 80% of male suicides for decades (Hakko *et al.* 1998). The rather small number of suicides in NFBC 1966 does not allow us to draw strong conclusions on the association between smoking and choice of suicide method.

9.2.3 School performance and suicide (III)

This study was able to show in a population-based sample that high premorbid scholastic achievement increased the risk for suicide specifically in psychoses. This study was too small to declare good school performance as a risk factor for suicide in psychosis but it confirms the earlier findings and conclusions (Farberow *et al.* 1966, Sletten *et al.* 1972, Drake *et al.* 1984, Dingman *et al.* 1986, Nyman & Jonsson 1986, Apter *et al.* 1993, Fenton 2000, De Hert *et al.* 2001) of high suicide risk in the group of psychotic patients with high premorbid intellectual functioning or high educational achievements. On a general population level, good school performance was a protective factor against suicide. This latter finding is similar to that presented in a study with some 900,000 Swedish young conscripts where each unit increase in IQ score resulted in a decrease in suicide risk by 12% (Gunnell *et al.* 2005).

Replication of this study in a larger Swedish sample with IQ and school performance measurements at age 13 showed similar results (Andersson *et al.* 2008). High childhood IQ was associated with reduced risk of suicide in males, while in those males with a history of psychosis it was associated with an increased risk of suicide. Among females there was no significant association between IQ and suicide risk. There was no significant association of school performance and the risk of suicide either in males or in females. Furthermore, in a sample consisting of over 500 adolescent (12–17 years) psychiatric inpatients in Northern Finland there was an elevated risk of suicidal ideation and of psychotic disorders among boys performing well in school (Tikkanen *et al.* 2009). Similar association was not observed in girls.

It was previously found that in the Northern Finland 1966 Birth Cohort excellent school performance could be a risk for developing schizophrenia (Isohanni *et al.* 1999). Similar findings have been made by Davidson *et al.* (1999). However, low performance also predicted schizophrenia in NFBC 1966 (Isohanni *et al.* 1998). Also, other recent studies suggest that schizophrenia is associated with lower school performance and IQ (Maccabe 2008, Maccabe *et al.* 2008).

Bipolar disease could be associated with good school performance and IQ, especially high scores in arithmetic reasoning (Zammit *et al.* 2004, Tiihonen *et al.* 2005, Maccabe *et al.* 2010).

Good school performance can be seen as a marker of good general ability (Spilerman 1977, Wiersma *et al.* 1983). Correlation of school performance and intelligence tests has been studied in Finland at the time this study population received their school marks. The study by Kuusinen and Lehtinen (1986) showed that correlation between intelligence measured by ITPA (The Illinois Test of Psycholinguistic Abilities) and students' school performance measured by school marks given at the age of 16 was 0.45. Correlation depended on the students' social class and was strongest in students from the middle class (Kuusinen 1986).

Good school performance as a risk factor for suicide in patients with psychosis may reflect the impact of a dramatic drop in cognitive and general capacity. In a study by Drake and co-workers (1984), a high suicide rate among college graduates was partly considered to be the consequence of their high expectations of themselves that were in line with their good premorbid functioning. In that study awareness of pathology and fears of mental disintegration were also associated with increased risk of suicide. Drake *et al.* (1984) also suggested a downward drift as a modifying factor: college educated individuals commit suicide when they find themselves among the poor in the public mental health facility. It may also be much more difficult for someone who has managed well earlier in life and has learned to trust their own capability to appeal for help. Intelligent people suffering from psychosis may also be able to hide their suicidal ideas and their psychotic symptoms. Their suicidality may thus be underestimated by nursing staff (Isohanni 1976).

It has also been suggested that an advantaged socioeconomic status may confer paradoxical disadvantage in coping with the vocational losses consequent to schizophrenia (Lewis 2005). This study (also cases presented in 7.3 in the appendix of original study III) shows the effect of the inevitable social drift (Dunham 1965, Dohrenwend *et al.* 1992, Aro *et al.* 1995, Isohanni 2000) from the group of successful students in the school to becoming a burden on society that happens when psychosis strikes.

This sample was too small to study the relationship between school performance and the risk of suicide stratified by gender. It has, however, been shown that after falling ill males more often have deteriorating academic performance (28% for females vs. 40% for males) (Norman *et al.* 2005). Thus, compared to women, male schizophrenia cases with high premorbid academic

performance and higher tendency for drop from that level may be at greater risk of suicides.

In this study the number of cases was small, especially in stratified analyses. Especially in this situation statistical testing is important, because it is intended to decide whether a hypothesis about the distribution of variables should be rejected or accepted.

9.2.4 Suicide rate in schizophrenia (IV)

To the author's knowledge, this was the first study of suicide risk in a prospectively followed population-based cohort of individuals with schizophrenia. If one accepts that an epidemiologically based cohort provides the best estimate of suicide rate, then the meta-analysis of Palmer *et al.* (2005), largely based on samples of convenience at various stages of illness, may underestimate the lifetime risk of suicide in schizophrenia.

Although two-thirds of suicides in this sample occurred within three years of hospital discharge, other data suggest that suicide risk may remain high over the course of illness. An examination of all suicides of patients with schizophrenia in Finland over a 12-month period found that one third (30/92) of schizophrenia suicide victims were over the age of 45 (Heilä *et al.* 1997). Thus, continued follow-up of the NFBC 1966 will be useful in clarifying the trajectory of risk over the course of schizophrenic illness.

Constant monitoring of suicide rates in schizophrenia is essential also when evaluating the effects of new treatments. Suicide rate in schizophrenia had increased from less than 0.5% in 1875–1924 to 4.7% in 1994–1998 in North Wales (Healy *et al.* 2006). This rise may be explained by deinstitutionalization and advanced psychopharmacology, which may improve patients' insight (Healy *et al.* 2006). However, in contrast, a Finnish study comparing more contemporary suicide rates one year after discharge found that suicide risk in schizophrenia was greater in 1985–1991 than 1995–2001 (RR=1.26, CI=1.17–1.36) (Pirkola *et al.* 2007). During this period there have been significant structural changes in Finland in mental health services downsizing inpatient care.

Adequate treatment with antipsychotic drugs, especially with clozapine, have been proved to be essential in lowering the overall mortality and suicide prevention of schizophrenia patients (Meltzer *et al.* 2003, Tiihonen *et al.* 2006 & 2009). In a Finnish study of relative risk (RR) for suicide among patients not

using any antipsychotic medication the result was 37.4 (95%CI 5.1–276) compared to those patients using medication (Tiihonen *et al.* 2006).

9.3 Strengths and limitations of the study

9.3.1 Strengths of the study

The sample considered here was large, comprising more than 10,000 cohort members, and the subjects were representative, with all the members born in the same year and in a geographically defined area. The sample is population-based, which is essential in order to study risk factors for suicide attempts and suicides in the general population. The Finnish registers of mortality and hospitalizations are reliable and accurate (Lahti & Penttilä 2001, Arajärvi *et al.* 2005, Miettunen *et al.* in press). The psychiatric diagnoses for the entire sample were re-checked twice by professionals (Isohanni *et al.* 1997, Moilanen *et al.* 2003). Finnish suicide certification procedures are reliable and comparable to other developed countries (Huusko & Hirvonen 1988, Öhberg & Lönnqvist, 1998 Rockett & Thomas 1999, Chishti *et al.* 2003).

The NFBC 1966 was followed up prospectively from the foetal period to adulthood. This provides the opportunity to study factors that are difficult to study in other settings. As far as the author knows, no follow-up studies on the association between maternal depressed mood and smoking during pregnancy or unwanted pregnancies and attempted or completed suicides on the part of the offspring in adolescence and adulthood have been reported before. This was also the first study so far to compare the suicide methods between those who are regular smokers in adolescence and those who are experimental smokers or non-smokers. Further, this was the first study of suicide risk in a prospectively followed population-based cohort of individuals with schizophrenia.

The school record method has the advantage that the research data is collected in adolescence before the subjects suffer from any mental disorders. This means that neither the providers of the data nor the relatives or the subjects themselves know that they are to have mental disorders later, and most likely none, or only very few of them, will have been influenced by the epiphenomena of the illness.

At the general level, population-based birth cohort studies are effective for determining longitudinal risk factors, incidences and developmental trajectories

of different illnesses and outcomes (Welham *et al.* 2009). Birth cohort data are usually collected prospectively, which improves reliability and validity and diminishes recall bias, especially in cases of repeated measurements. Birth cohorts are also less likely to be affected by selection bias because study samples (cases and controls) represent the population.

9.3.2 Limitations of the study

This study also has some limitations. The subjects in the cohort were relatively young (35–39 years at the end of the follow-up). Even though the NFBC 1966 is large, the rarity of suicide attempts and suicides means that Type II statistical errors are possible. Considerable effort is put into Type I error control in epidemiological studies but in relatively small association studies there is a danger of Type II statistical errors: rejection of the null-hypothesis is not evident and large effects are probably worth considering even when the results do not reach the threshold of statistical significance (Isohanni *et al.* 2004). In a population based sample, a non significant result does not prove the null-hypothesis, but it may reflect either small effect size or inadequate power (Kraemer *et al.* 2001). The number of suicide attempts is underestimated, and biased towards more difficult cases, since data was available only on severe attempts requiring hospital treatment. Also, the suicide attempts and actual suicides occurred over a long period of time (1984–2005).

The maternal depression referred to here was not necessarily a clinical condition, but reflects the mothers' reports of feeling depressed (Mäki *et al.* 2010), although it must be said that the prevalence of antenatal depressed mood was in the same range as in earlier reports (Evans *et al.* 2001). Data on parents' psychiatric hospitalizations were only available after the year 1972, and thus there was no knowledge of the situation during early childhood. Likewise, data was available only on periods spent in hospital, but no information on outpatient care, which is where most cases of depression are treated.

The information on smoking habits was based on a self-report questionnaire, which may cause bias due to underestimates on smoking habits. The adolescent smoking status was measured at only one point in time. Therefore information on the temporal development of smoking habits later in adolescence and in adulthood was lacking. It was not possible to investigate the putative confounding effect of adult psychiatric disorders treated in outpatient settings or being in child psychiatric care or psychotropic medication. Additionally, recognition and

adequate diagnostics of attention deficit hyperactivity disorder were developed in Finland after the 1990s. It is therefore possible that results of this study could partly be affected by comorbid lifetime hyperactivity or conduct problems. It is also well known that a majority of subjects suffering from hazardous alcohol use never end up receiving inpatient treatment. From the methodological point of view however, these problem users are likely to be found both in suicidal and non-suicidal populations as well.

Selection of the cut-off point of school marks may also have an influence on results when sample sizes are small, an effect commonly seen in birth cohort studies (Sørensen *et al.* 2005). The school records method has the handicap that one must utilize whatever data is available, rather than designing it to suit the purposes of research.

10 Conclusions

10.1 Main conclusions

Early family structure (a single-parent family or grand multiparity) was associated with suicide attempts and actual suicides even after taking mental disorders in the parents and offspring into account. Maternal antenatal depression, smoking and unwanted pregnancy were connected with suicidal phenomena in the offspring but the association became diluted after adjustment. Parental psychiatric disorders are risk factors for suicide attempts in female offspring and a disorder in the mother for suicide in males. This may be partly explained by the heritability of mental disorders, since this association was attenuated after adjustment for psychiatric disorders in the offspring themselves.

Both a single-parent family and a family with many older children seemed to predispose male offspring to suicidality and may constitute pathways to suicide attempts and suicides. However, even though significant early risk factors were found, a later psychiatric disorder was the major risk factor for both attempted and completed suicide. Nevertheless, suicide seems to be a long process that begins in early life. Adolescent regular smoking was found to be associated with increased risk of suicide among male cohort members. This finding is important, since even as many as one out of five adolescents in the Finnish general population are known to be smokers at the age of 14 years today (Rimpelä *et al.* 2003). The prevalence of suicides of almost 3% among male adolescent smokers can thus be considered high at epidemiological levels. Based on the results from this and other studies, psychotic patients' premorbid intellectual capacity and school performance should be checked when they get ill. Premorbid educational achievement (or school performance) should be taken into account, along with other relevant characteristics, when considering suicide risk in patients with psychotic condition. The suicide rate for patients with schizophrenia followed until the age of 39 is high. The great majority of the suicides took place during the first years of the onset of illness.

10.2 Implications of the study

This study was mainly focused on risk factors for suicide and to a lesser extent on attempted suicide. Results improve our understanding of developmental

trajectories or pathways that lead to suicide. They also increase our knowledge of these factors and thus are valuable in the suicide risk assessment of individual patients.

10.2.1 Pathways leading to suicide in schizophrenia

The stress-diathesis model of suicide (Figure 1) is one way to illustrate the relationship between risk factors for suicide. Other more detailed and more longitudinally oriented approaches could be pathways as presented in Figure 5 (modified from Alaräisänen *et al.* 2007), something which was originally inspired by the system theory model published by Isohanni and co-workers (2009). These pathways are partly hypothetical and overlapping. Their aim is to help in clinical work as well as to give rise to new ideas of using the life-span view in research. Lacking knowledge of lifespan development also makes it difficult to formulate evidence-based trajectories. Linking genetic data to pathways is partly speculative and the evidence limited.

PATHWAYS LEADING TO SUICIDE IN SCHIZOPHRENIA

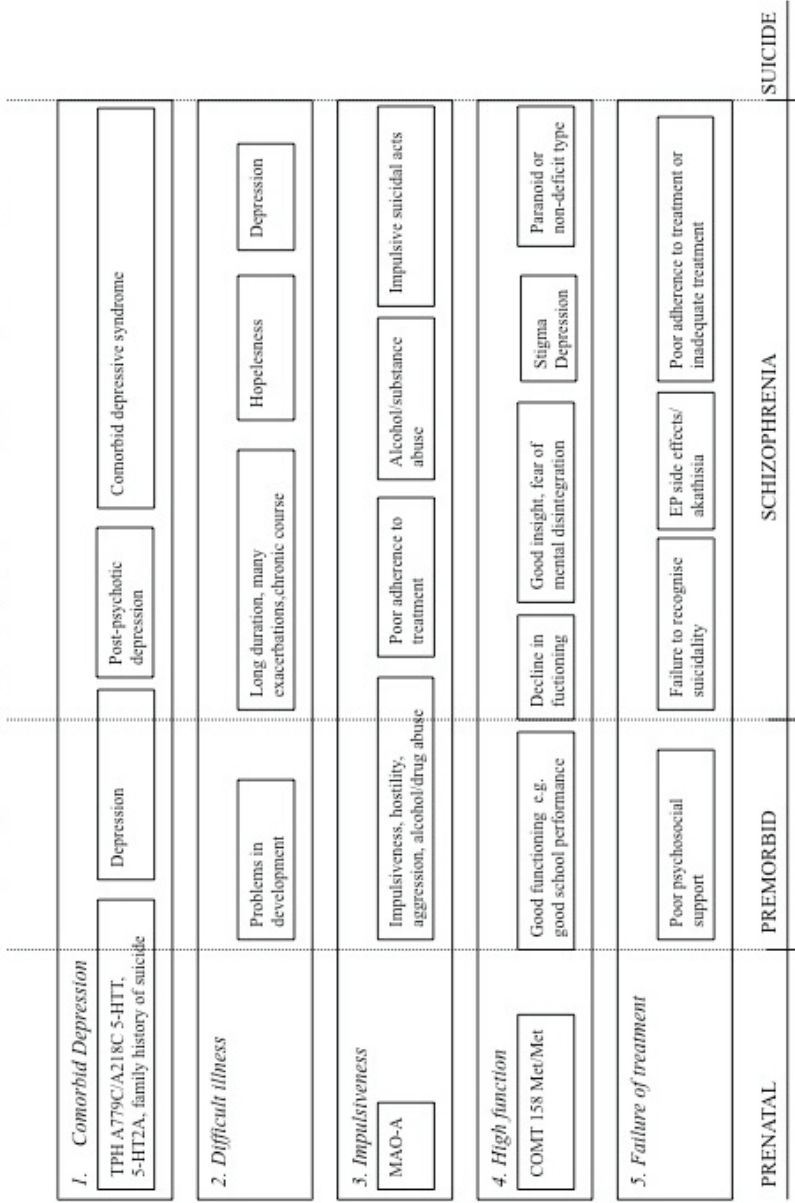


Fig. 5. Life-span model of the developmental pathways to suicide in schizophrenia (modified from Alaräisänen et al. 2007).

Comorbid depression pathway. Since comorbid depression is such a widely reported and acknowledged risk factor for suicide also in schizophrenia (Kelly *et al.* 2004, Hawton *et al.* 2005, McGirr *et al.* 2006, Kasckow *et al.* 2010) it should be recognized as a separate pathway to suicide, although it probably plays a role in every pathway. There is no clear evidence that family history of suicides is associated with comorbid depression, but one could assume so since the genetic influence is high in both suicide and depression.

Difficult illness pathway. This is a group of patients with a chronic course of illness and many relapses and exacerbations. Patients in this chronic course group lose their hope progressively over time. They may also suffer from comorbid depression and alcohol abuse. (Montross *et al.* 2005, Acosta *et al.* 2006, Kaneda *et al.* 2006)

Impulsiveness pathway. Patients (mostly young males) with impulsivity, dysphoric affect and substance abuse are also at elevated risk of suicide. In this group suicides can also be due to auditory or other hallucinations or some other psychotic reasons. Comorbidity with substance use is likely (Haw *et al.* 2005). Low levels of MAO activity and mutations in the MAOA gene have been associated with violent, criminal, or impulsive behaviour (Meyer-Lindenberg *et al.* 2006). Adolescent smoking might also be associated with this pathway.

High premorbid function pathway. There is also a relatively small but theoretically interesting and clinically important group of mainly young patients whose premorbid functioning and intellectual capacity is above average. For this high premorbid functioning group of patients psychosis may mean a dramatic drop of cognitive and general capacity. It also destroys their high expectations about their future. It may also be more difficult to appeal for help among people who have managed well earlier in life and have learned to trust their own capabilities. Intelligent people suffering from psychosis may also be able to hide their suicidal ideas and their psychotic symptoms, leading to underestimation of their suicidality (De Hert *et al.* 2001, Alaräisänen *et al.* 2006). Their insight is probably also better than other patients' right after the first psychotic episode. This might also elevate their suicide risk by producing stigma and depression (Pompili *et al.* 2004a). The COMT met/met genotype might be associated with this group of patients. COMT polymorphism (VAL108/158MET) accounts for a 4-fold variation in enzyme activity and dopamine catabolism, with both prefrontally mediated cognition and prefrontal cortical physiology. In their study Egan *et al.* (2006) showed that the load of the low activity met allele predicted enhanced cognitive performance. It has been shown that the met/met allele is also

associated with higher aggression levels in schizophrenia patients (Han *et al.* 2004). This pathway is one way to illustrate the results of the original study III.

Failure of treatment pathway. Lack of psychosocial support, inadequate pharmacological therapy, failure to detect suicidality, unmet need of a contact person, extrapyramidal side-effects and/or akathisia, and patient's own disappointment with treatment received could lead to suicide. (Pompili *et al.* 2004 b & 2007, Tidemalm *et al.* 2005).

10.2.2 Clinical implications for suicide prevention

This study provides some useful information for suicide prevention. Intensive treatment and careful suicide risk assessment should be especially focused for those psychotic patients who have good premorbid functioning. However, there are as yet no evidence-based treatment strategies addressed specifically for this patient group. Suicide prevention should be intensive in the early phase of schizophrenia after the first hospital treatment. Having many older siblings increases the risk of suicide in males. Smoking at early adolescence is a marker of increased suicide risk.

10.3 Future research

In future, it would be interesting to see in NFBC 1966 how suicide rates and risk factors for suicide evolves when cohort members get older. Does suicide in older age differ from those accomplished in younger age? Especially in schizophrenia patients constant monitoring of suicide rates is interesting. The most accurate estimates of suicide rates can be made with birth cohort studies and first-admission patient studies (Palmer *et al.* 2005). In future studies it would be interesting to see how suicide rate and timing in schizophrenia differs by gender and by other specific subgroups of patients. While the whole lifespan data is lacking, data gathered until age 39 has now been reported in this study.

Further studies are needed to investigate the effects of smoking on neurobiology of depression, self-damaging aggression and impulsivity. The association of smoking habits with nonviolent suicide attempts should also be investigated.

Larger studies are needed to investigate what kind of psychotic patients with good school performance are at especially high suicide risk. In this study risk was higher in other psychosis group (including bipolar disorder) than in schizophrenia.

One potentially beneficial strategy to suicide research in psychotic patients could be to identify symptom profile for those people who are at particular risk of suicide using, for example, OPCRIT (Craddock *et al.* 1996).

Further studies are also needed to clarify the effects of early factors on suicides and suicide attempts. Within NFBC 1966 data there are lot of potential risk factors for attempted and completed suicide that could be investigated in future studies: eg substance use, somatic morbidity, somatic and psychiatric comorbidity, psychiatric symptoms (measured by eg PANSS), military intelligent ratings, employment status, birth complications, birth weight, motor development, structural and functional magnetic resonance images, genetic data, cognitive tests and seasonality. Some potential protective factors, and the health of those who attempted suicide and survived, could also be studied including eg use of psychotropic medication and psychiatric treatment history (hospitalisations, inpatient versus outpatient treatment). Development of evidence-based pathways leading to suicide not only in schizophrenia but also in the general population might improve existing suicide prevention strategies. They might help to identify risk groups and periods and guide the interventions for the right groups at the right time.

In general, the NFBC 1966 study combines the unique advantages of a large population-based birth cohort, detailed longitudinal phenotyping and DNA availability in a cohort setting, but also provides clinical data and registers which allow the study of both genetic and environmental components in the evolution and course of disorder. This study gives the unique possibility of analyzing the natural course and current state of care in schizophrenic psychoses in middle adulthood. In expanding to the age of 43 years and reanalyzing the progression of disease, it is possible to study age regression slopes. Relapses, exacerbations, somatic risks and suicidal development are all possible, as are amelioration and adaptation to this severe illness. The study sample, follow-up period and timing are globally unique. The results will provide new insights into the disorder's developmental, diagnostic and treatment aspects; thus, the project has expansive clinical relevance and importance for translational research paradigms.

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