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**Perinatal and familial risk factors
of youth suicidal behaviour**

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PROLOG

... und ich möchte Sie, so gut ich es kann,
bitten Geduld zu haben gegen alles Ungelöste in
Ihrem Herzen und zu versuchen, die Fragen selbst
liebzuhaben wie verschlossene Stuben und wie Bücher,
die in einer fremden Sprache geschrieben sind.
Forschen Sie jetzt nicht nach den Antworten, die Ihnen
nicht gegeben werden können, weil Sie sie nicht leben
könnten. Und es handelt sich darum, alles zu leben.
Leben Sie jetzt die Fragen. Vielleicht leben Sie dann
allmählich, ohne es zu merken, eines fernen Tages in
die Antwort hinein.

Rainer Maria Rilke

ABSTRACT

Completed suicide constitutes one of the leading causes of death in adolescents and young adults. Youth suicide attempt often precedes completed suicide and represents in itself a considerable public health problem in Sweden and in other European countries.

The aims of this study were to 1) scrutinise trends in suicide mortality in adolescents compared to trends in an older age group and in relation to changes in reporting practices in European countries, 2) investigate the relation of maternal, pre- and perinatal factors with subsequent suicidal behaviour in young adults, 3) analyse the association of foetal and childhood growth and their interaction with subsequent suicide attempt by violent and non-violent means, and finally 4) analyse the independent and interacting effects of familial and individual psychopathology as well as familial suicidal behaviour on suicide attempt in young adults.

For this purpose, the WHO mortality database has been used for the analysis of European suicide trends from 1979 to 1996 in Study I. For the investigation of pre- and perinatal, childhood and familial factors in relation to subsequent suicidal behaviour up to seven Swedish registers were linked: the Medical Birth register, the 1990 Population and Housing Census, the Inpatient Care Register, the Cause of Death Register, the Multi Generation Register, the Military Service Conscription Register and the Register of the Total Population. The birth cohort 1973-80 was followed up to 1999 using a cohort study design in Study II and III, including 713,370 individuals in Study II and 318,953 males in Study III. In paper IV all individuals, who were born 1968-80 and who had attempted suicide (14,440 cases) until 1999 were matched for gender, county and month of birth with 144,400 controls.

Suicide rates in adolescents increased for males in twenty-one and for females in eighteen of the thirty European countries during the 1980s and mid-1990s. These increases were generally accompanied by stable or decreasing trends in suicide rates of males and females of 20 years and over. In several countries changes in reporting practices affected to different degrees the temporal variations in adolescent suicide rates, primarily in males. Results from Study II revealed that teenage motherhood increased the risk of both suicide attempt and completion in adolescents and young adults. Multiparity and low maternal education predicted suicide attempt in young offspring. Preterm birth was a strong predictor for violent suicide attempt. Restricted foetal growth was associated with both suicide completion and attempt. The inverse association of foetal growth and suicide attempt did not seem to be modified by childhood growth (Study III). Decline in postnatal linear growth potential entailed an additional risk.

Familial suicidal behaviour, primarily suicide attempt, and familial psychopathology, mainly substance abuse and personality disorders, were significantly associated with an increased risk of suicide attempt in young adults. There seemed to be an effect of familial suicidal behaviour as well as familial psychopathology on youth suicide attempt beyond the transmission of mental illness. Familial suicidal behaviour had a stronger effect on suicide attempt of early onset and on boys. Individual psychopathology, primarily substance abuse, affective and personality disorders, emerged as the strongest risk factor for suicide attempt in young adults. Significant interactions were also observed between psychopathology in index subjects and familial suicidal behaviour.

Keywords: suicide, attempt, trends, perinatal, childhood, growth, familial, psycho-pathology

Papers

Mittendorfer Rutz Ellenor, Wasserman Danuta. Trends in adolescent suicide mortality in the WHO European Region. *European Child and Adolescent Psychiatry* 2004 Oct;13(5):321-331.

Mittendorfer Rutz Ellenor, Rasmussen Finn, Wasserman Danuta. Restricted foetal growth and adverse maternal, psychosocial and socioeconomic conditions as risk factors for suicidal behaviour of offspring: a cohort study. *The Lancet*. 2004 Sep;364(9440):1135-40.

Mittendorfer Rutz Ellenor, Rasmussen Finn, Wasserman Danuta. Foetal and childhood growth and the risk of suicide attempt – a cohort study of 318,953 young men (submitted)

Mittendorfer Rutz Ellenor, Rasmussen Finn, Wasserman Danuta. Familial clustering of suicidal behaviour and psychopathology in young suicide attempters– a register-based nested case control study (manuscript)

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INTRODUCTION

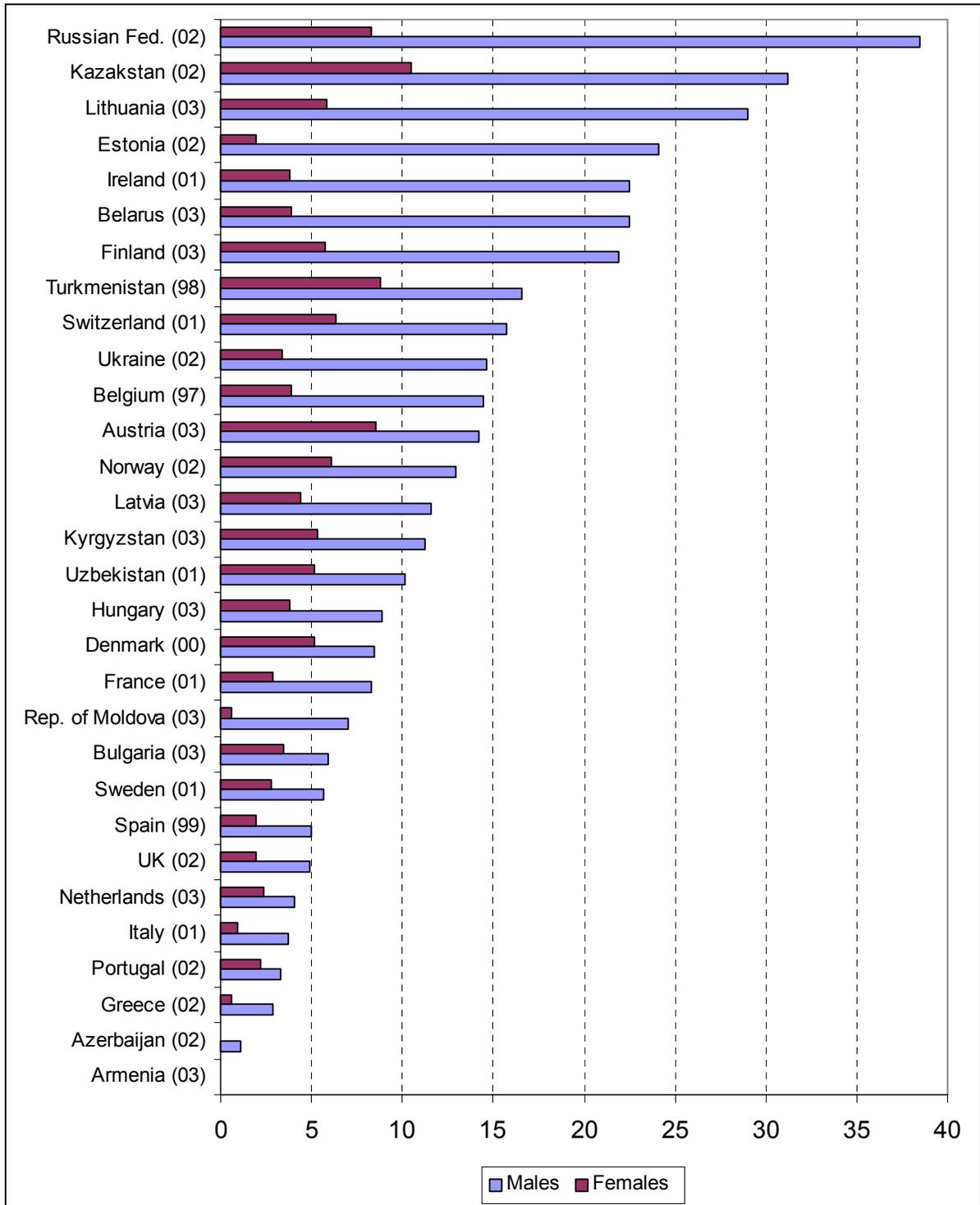
Epidemiology of youth suicide attempt

Based on a review of community surveys, the prevalence of youth suicide attempt in the general population ranges from 2% to 20% (Grossman et al., 1991; Harkavy Friedman et al., 1987; Smith et al., 1986; Rubenstein et al., 1989; Kienhorst et al., 1990; Andrews et al., 1992). In interpreting these prevalence data, the variability in definitions used for suicide attempt has to be taken into account. The definitions differ mainly in consideration of intent and medical severity of the attempt. In this thesis only those suicide attempts, that are followed by hospital admission have been considered. The proportion of adolescent suicide attempters receiving medical treatment ranges from 12 till 50% (Grossman et al., 1991; Harkavy Friedman et al., 1987; Smith et al., 1986). In Sweden 1,845 young people (15-24 years old) were hospitalised after a suicide attempt in 2002, reflecting a rate of 176 per 100,000. This rate is based on hospital discharge data obtained from the National Board of Health and Welfare. Suicide attempts are a major public health concern in Sweden not only due the size of the problem, but also due to the considerable increase in them since the 1980s, particularly in young girls.

Epidemiology of youth suicide completion

Youth suicide mortality varies considerably internationally (Figure 1). Based on latest available suicide mortality statistics from the WHO mortality database, suicide rates in male adolescents (15-19 years) ranged from below 5 per 100,000 in some Southern European countries to rates around 25 and even close to 40 per 100,000 in Northern and Eastern European countries. Suicide often ranks among the three most common causes of death in youth and accounted for 21 % of deaths in adolescents (15 to 19 years old) in Sweden (mean of proportion from 1999 to 2001) according to data from the WHO mortality database. This is high in an inter-European perspective and of particular concern as it increased from only 10% in the beginning of the 80s (mean 1979-81). As a comparison, the mean proportion of suicide deaths in the total number of deaths in adolescents from 2000 to 2002 in Greece was 4%.

Figure 1: Suicide rates for male and female adolescents 15 to 19 years old per 100,000 in latest available year (in brackets) in 30 countries of the WHO European Region



Characteristics of suicide attempt and completion

Suicide attempt and completion primarily differ in their age and gender pattern and in the intent and thereby in the choice of method for suicidal behaviour (Cantor, 2000; Kerkhof, 2000). In Western countries, young females are about twice as likely as males to attempt suicide, while young males commit suicide three to four times more often than their female counterparts (Kerkhof, 2000) (Figure 1). Contrary to suicide completion, suicide attempt is generally more frequent in youth than in the elderly. The choice of methods for suicidal behaviour reflects the availability of means and the intent behind the behaviour, which can range from a cry for help, revenge, relief of anxiety to a clear intent to die (Kerkhof, 2000). Non-violent methods (primarily self-poisoning) are most frequently found among suicide attempters, and violent means are more often chosen for completed suicide. There is also a gender difference in the choice of methods. Males are more inclined to use more drastic (violent) methods. This gender difference in the chosen methods is regarded as one of the reasons behind the gender paradox of suicidal behaviour. Violent suicidal behaviour can be regarded as more strongly associated with completed suicide, reflecting a progress in the suicidal process often starting with non-violent suicidal behaviour. Suicide attempt represents the strongest predictor for completed suicide. It is estimated that 5% of suicide attempters take their lives within 9 years after their attempt (Owens et al., 2002).

Stress diathesis model

From 60% to 90 % of young suicide attempters and completers have a mental illness at the time of the event (Andrews et al., 1992; Fergusson et al., 1995). However, not every patient with a mental illness attempts or commits suicide. In the stress-diathesis model suggested by Mann and co-workers, suicidality is proposed to result from a genetic and acquired vulnerability to suicidal behaviour (diathesis) interacting with an acquired susceptibility due to stress (Mann et al., 1999). Stress can arise from mental illness as well as adverse life events, psychosocial, interpersonal and socio-economic in nature. The diathesis of suicidality may be primarily characterised by impulsivity and aggression and reflects a propensity to experience more suicidal ideation. The factors involved in the diathesis of suicidal behaviour include chronic substance abuse, early physical and sexual

abuse, family history of suicidal acts, personality disorder and head injury. This thesis scrutinises a variety of risk factors, which may either influence the diathesis of suicidal behaviour or reflect modulating risk factors. The factors investigated include: early life exposures like pre-and perinatal factors, maternal psychosocial and socio-economic risk factors, childhood exposure measured by physical growth, individual psychopathology, as well as familial suicidal behaviour and familial psychopathology.

BACKGROUND

Trends in youth suicide rates in Europe

Increasing youth suicide rates, especially in males, have been reported in Western Europe during the 1980s and 1990s (Burton et al., 1990; Hawton, 1998; Kellerher, 1998; McClure, 2001). Possible explanations for these rising trends were suggested, ranging from loss of social cohesion (Diekstra, 1996; Hawton, 1998; Kellerher, 1998), increasing economic instability and unemployment (Gunnell et al., 1999, Prichard, 1992) and breakdown of traditional family structures (Moens et al., 1988; Kellerher, 1998; Hawton, 1998), to increases in the prevalence of depressive disorders (Diekstra, 1996; Fombonne, 1994) and changes in reporting practices (Kellerher, 1996; De Castro et al., 1989). A frequently proposed cause of the changes in suicide rates, both in the countries of the former Soviet Union (Wasserman et al., 1994) and in Western European societies in youth (Diekstra, 1996; Fombonne, 1998) has been the increased alcohol consumption. Males are supposed to be more vulnerable towards these societal changes, partly due to their weaker capacity to ask for help (Rutz et al., 1995; Hawton, 1998).

Pre- and perinatal factors and mental ill-health

Evidence of a relationship between obstetric and neonatal complications and mental disorder, primarily schizophrenia and depression, has been reported (Jones et al., 1998; Gale et al., 2004). A number of studies found an association between small size at birth and minor neurological abnormalities as well as subnormal psychological performance and stress tolerance later in life (Pryor et al., 1995; Hadders-Algra et al., 1988; Lundgren et al., 2001; Nilsson et al., 2004). Concerning an association between adverse obstetric, neonatal and maternal conditions, and elevated suicide risk in adolescents sparse and contradictory results have been reported. Salk et al. (1985) found a substantially elevated frequency of obstetric, neonatal and maternal complications among adolescents who committed suicide, compared with controls. Neugebauer et al. (1998) and Barker et al. (1995) failed to replicate such findings.

Hypotheses regarding underlying mechanisms

Relations between pre-and perinatal complications, and later psychiatric disorder, particularly schizophrenia, have been explained through neurodevelopmental impairment (Dalman et al., 1999). Other authors suggested that infants subjected to complications during pregnancy and at birth, might be more vulnerable to environmental stressors precipitating suicide (Salk et al., 1985). Barker et al. (1995) related elevated suicide risk to low rates of weight gain in infancy and proposed modified programming of hormonal systems affecting infant growth, as well as causing susceptibility to depression. Other hypotheses regarding the association of birth size with later disease have also been proposed, including confounding by genetic differences or by factors related to socio-economic status (Hubinette et al., 2001; Kramer et al., 1996).

Childhood growth

Short stature, reflecting various adverse exposures during childhood, has been associated with an increased risk of psychiatric morbidity, psychological impairment, stress susceptibility, suicide attempt and completion as well as overall mortality in male conscripts (Jiang et al., 1999; Magnusson et al., 2005; Allebeck et al., 1992; Tuvemo et al., 1999). The inverse association with suicide remained significant after adjustment for socio-economic status in one study (Magnusson et al., 2005) but not in another study, which additionally adjusted for health risk factors (Song et al., 2003). Growth in childhood and height in adults are often used as indicators of nutrition and well being and catch-up growth in low birth weight infants has been found to decrease the risk for subsequent subnormal intellectual and psychological performance as well as for the development of schizophrenia (Lundgren et al., 2001; Gunnell et al., 2003). The majority of children (87%) born with small size at birth catch-up in their growth during childhood and reach normal stature (Albertsson-Wikland et al., 1994).

Familial risk factors

Twin and adoption studies

Results from studies of adopted children (Wender et al., 1986; Schulsinger et al., 1979) and twins (Glowinski et al., 2001; Statham et al., 1998; Fu et al., 2002) have suggested

that suicidal behaviour might be partly genetically determined. In an adoption study undertaken in Denmark, Schulsinger and colleagues (1979) found a six-fold higher rate of suicide in the biological relatives of adoptees who committed suicide compared to controls and an absence of suicide in the adopted relatives. Several twin studies have reported higher rates of concordance for suicidal behaviour in monozygotic compared to dizygotic twins (Glowinsky et al., 2001; Statham et al., 1998). After adjustment for psychiatric disorders, combat history and sociodemographic variables, the genetic component of risk for suicide attempt has been suggested to be 17% (Fu et al., 2002).

Family studies

Familial suicidal behaviour

Familial clustering of suicidal behavior has been reported for adolescent suicide attempters. Table 1 gives an overview of surveys on familial occurrence of suicide attempt in young suicide attempters with a variety of study designs and samples (clinical setting, community-based and register-based). Odds ratios for suicide attempt in the case of a suicide attempt in a first-degree relative ranged from 2.9 to 5.7. Adjusting for socio-economic, socio-demographic and psychopathological factors decreased the odds ratios to 2.1 and 2.9. Only two out of the ten studies reviewed here reported non-significant results. Between 5.9% and 30% of suicide attempters had experienced a suicide attempt in the family. This variation is most likely due to differences in study design and study population. Information on family history of completed suicide was often not available (Pfeffer et al., 1994), was combined with suicide attempt (Christofferson et al., 2003; Johsson et al., 1998) or not significant when adjusted for other psychosocial factors and mental ill-health (Grossman et al., 1991).

Familial and individual psychopathology

Adolescent suicide attempters reportedly have higher rates of familial psychopathology than community and clinical controls, mainly affective, substance abuse and personality disorders (Johsson et al., 1998; Pfeffer et al., 1994; Garfinkel et al., 1982). Also, from population-based studies an association between familial mental illness, primarily

substance abuse, and suicidal behaviour in adolescents has been reported (Grossman et al., 1991; Rubenstein et al., 1989; Fergusson et al., 1995). A history of hospital admission due to psychopathology in a first degree relative was 2.3 to 3.7 times more common in youth suicide attempters than community controls (Christoffersen et al, 2003; Pfeffer et al., 1994). Individual psychopathology is a strong predictor for attempted and completed suicide. A predominance of substance abuse, affective and personality disorders in young suicide attempters has been reported (Andrews et al., 1992; Fergusson et al., 1995).

Modes of transmission

Familial aggregation of suicidal behaviour appears to be due to genetic factors such as transmission of a vulnerability to psychiatric disorders and personality traits (characterised by impulsivity and aggression), as well as due to environmental factors such as imitation, bereavement of a parent, shortcomings in care and attachment and exposure to family violence and discord (Brent et al., 2005). The occurrence of attempted suicide was found to be elevated in the relatives of completers (Brent et al., 1994) and the occurrence of completed suicide was increased in the relatives of attempters (Johnson et al., 1998). Therefore, it can be assumed that familial transmission of suicidal behaviour involves a common vulnerability for both attempted and completed suicides.

Table 1: Studies analysing occurrence and odds ratios for suicide attempt in relation to suicide attempt in first degree relatives

First author	Year	Cases	Controls	N cases/ controls	Age	% fam. affected	OR
Garfinkel	1982	Emergency Room SA	Emergency room non SA	505/505	6-21	5.9	5.4
Smith	1986	Students with SA	Students without SA	33/117	Mean 16.5**	9.1	ns
Harkavy Friedman	1987	Students with SA	Students without SA	33/146	Mean 16**	29+	3.2
Rubenstein	1989	Students with SA	Students without SA	60/240	13-19**	n.i.+	2.9*
Grossman	1991	Community SA	Community non-SA	971/5,666	Grade 6-12	n.i. +	5.0 (2.8*)
Lewinsohn	1993	Students with SA	Students without SA	121/1,589	14-18**	ni	ns
Pfeffer	1994	Inpatient SA	Community non-SA	25/54	Pre-pubertal	30	4.3
Johnson	1998	Inpatient SA	Inpatients non-SA	62/70	13-19	16.8†	2.3 (2.1*)
Christoffersen	2003	SA (register based)	Non-SA (register based)	867/83,898	14-27	6.3 ‡†	3.5
Cerel	2005	Community SA	Community non-SA	207/5,844	11-19	12 ^{&}	5.7

*adjusted for socio-demographic and socio-economic factors and mental illness; ‡ parents; & year before the survey; ns ... non significant; ni. ... no information; + no detailed information on family members included; † familial attempt and completion, ** high school students

AIMS

The aims of this thesis were to

- 1) scrutinise trends in suicide mortality in adolescents compared to trends in an older age group and in relation to changes in reporting practices in European countries from 1979 to 1996
- 2) investigate the relation of maternal, pre- and perinatal factors with subsequent suicidal behaviour in young adults
- 3) analyse the association of foetal and childhood growth and their interaction with subsequent suicide attempt by violent and non-violent means
- 4) analyse the independent and interacting effects of familial and individual psychopathology as well as familial suicidal behaviour on suicide attempt in young adults.

MATERIAL AND METHODS

Data sources

Study I

World Health Statistics Annuals of the World Health Organisation

The World Health Statistics Annuals of the World Health Organisation collect mortality data reported annually from its member states. Data are included only for countries reporting vital statistics properly coded according to the International Classification of Diseases (ICD). This WHO mortality database represents, to date, the only source of data for international comparison.

Study II to IV

The Medical Birth Register (MBR)

The MBR is nationwide in coverage (99% of all birth in Sweden), and its validity has been assessed as good (Cnattingius et al., 1990). This register was established in 1973 and comprises data on complications during pregnancy, delivery and the neonatal period from standardised forms used at all antenatal clinics and delivery units throughout Sweden.

The Cause of Death Register (CDR)

The CDR kept by the National Board of Health and Welfare contains data on the date and cause of death of all deceased persons registered in Sweden, irrespective of where the death occurred. This register has also been evaluated, and it was found that information on the cause of death was missing in 0.6% of all deaths in 2002 (National Board of Health and Welfare, 2005).

The Inpatient Care Register (ICR)

The Swedish ICR provides information on the date and diagnosis of individual hospital care for overnight patients based on the assessment of the responsible clinician. National coverage was achieved in 1987. The annual dropout rate in main diagnoses is estimated to be less than 1 percent in general (National Board of Health and Welfare, 2005). Within

psychiatry, however, missing information on the main diagnoses has increased from 0.1% between 1975 and 1983 till 8% in 1999 and in 2003 (National Board of Health and Welfare, 2005).

Multi-Generation Register (MGR)

The MGR is kept by Statistics Sweden and contains links between children and parents, both biological and adoptive. It is a population register with national coverage since 1968. Less than 2% of individuals born in Sweden after 1950 have no link to their parents (Statistics Sweden, 2001).

1990 Population and Housing Census (PHC)

Information on country of birth, age, socio-economic status, including education level, and housing situation was collected through the population and housing census in 1990. The majority of the households (94%) are reported to be correctly classified.

The Military Service Conscription Register (MSCR)

The MSCR contains data from compulsory, structured and standard military enlistment examinations for physical and mental health including information on height and weight from conscripts born from 1946 and onwards.

The Register of the Total Population (RTP)

The RTP is kept by Statistics Sweden and includes information on date of emigration and immigration.

Table 2: Overview of Studies

Study	Design	Subjects	Data	Outcome measures	Covariates
I	Trend analysis	Adolescents 15-19 years old in European countries	WHO mortality data base, cross-sectional data	Suicide and undetermined causes of death	
II	Cohort study	713,370 singletons born in Sweden 1973-80, followed-up till 1999	Swedish registers merged: MBR, ICR, CDR, 1990 PHC, MGR, RTP; longitudinal data	“Determined” and “undetermined”* suicide and suicide attempt	Birth weight and length, gestational age, parity, maternal age and education, complications during pregnancy and at birth
III	Cohort study	318,953 young men born in Sweden 1973-80, followed-up till 1999	Swedish registers merged: MBR, ICR, CDR, 1990 PHC, MGR, RTP, MSCR	“Determined” and “undetermined”* suicide attempt	Birth weight and length, gestational age, adult weight and height, maternal age, parity and education
IV	Case-control study	14,440 cases and 144,400 controls born in Sweden 1968-80, matched for age, gender and county, end of observation: 1999	Swedish registers merged: ICR, CDR, 1990 PHC, MGR, RTP; longitudinal data	“Determined” and “undetermined”* suicide attempt	Familial suicide attempt and completion, familial and individual admission due to mental illness (clustered in diagnostic groups)

*see definition in Main outcome measures, page 23

Study design

In order to contrast trends in adolescents (15 to 19 years old) with trends in adults (≥ 20 years old), statistics for suicides for 30 of the 52 countries in the WHO European Region were obtained from the latest available World Health Statistics Annuals of the World Health Organisation (Study I). Furthermore, trends in deaths due to undetermined causes (*see Main outcome measures, p 23*), which were available for 17 countries, were compared to trends in adolescent suicide in order to estimate how changes in the classification could have affected the strength of temporal trends in suicide rates. The remaining twenty-two countries were excluded because their populations were too small for the purpose of this study or because of too many missing data in the study period.

Register linkage

By means of the Swedish national registration number assigned to every resident of Sweden, various available registers of good quality can be linked and offer a unique opportunity for epidemiological research. Datasets in Studies II to IV are based on register linkages.

Study II and Study III

All individuals born in Sweden between 1973 and 1980 and identified in the MBR (N=783,821) were followed up prospectively by register linkage with respect to the ICD codes for determined and “undetermined” (*see Main outcome measures, p 23*), suicide and attempted suicide in the CDR and the ICR, respectively (Study II). This made it possible to examine the association of foetal growth, complications during pregnancy and at birth, and maternal factors with the risk of suicidal behaviour. To further investigate the interaction between foetal and childhood growth and the risk of suicide attempt, information from the MBR (birth weight and length) of all males from the mentioned birth cohort (1973-1980) was linked to the MSCR (adult height and weight) and the ICR (Study III). The study sample was based on 403,191 males resident in Sweden when they were conscripted into military service at age 18-19 years in 1991-1999. We only considered suicide attempts occurring after the conscription medical examination and therefore excluded 798 subjects with attempted suicide prior to the date of their conscription examination (Study III). These analyses were carried out separately for violent and non-violent suicide attempt.

Exclusion criteria

Cut-offs were set for all anthropometric measures (birth weight and length, adult height and weight) as well as for gestation age based on evidence of misclassification and biological implausibility of extreme values (Niklasson et al., 1991). Where data on any of the variables were missing, records were excluded. Of all individuals identified in the MBR, 9% and 20.9% were excluded from the analyses primarily due to missing data in Study II and III, respectively. The study population included 713,370 subjects (366,704 men and 346,666 women) in Study II and 318,953 males in Study III after exclusion.

Study IV

With the purpose of investigating familial clustering of suicidal behaviour and psychopathology, we carried out a nested case-control study through register linkage. Cases and controls comprised singletons born in Sweden between 1968 and 1980 (drawn from the MGR), for whom both parents could be identified. Cases represent all individuals who were registered for inpatient hospital care due to determined and “undetermined” attempted suicide from their tenth birthday to the end of follow up (31.12.1999) in Sweden. We randomly selected ten controls for each case and matched them for gender, month of birth and county (drawn from the 1990 PHC). If a case had died before 1990, the county was taken from the ICR instead of from the 1990 PHC. Only individuals who were still alive at the end of 1999 and who had never emigrated during the study period were sampled as controls. Controls were drawn without replacement so that each control could only be matched to one case.

Dependent and independent variables

Main outcome measures

In all four papers, deaths due to undetermined causes (“undetermined” suicides) have been included in the analyses. This is based on the observation that the verdict “death due to undetermined causes” is preferably used to conceal suicide deaths. Underreporting of suicide statistics in adolescents is estimated to be around 30 percent and even more (Madge et al., 1999; Moens et al., 1988). A number of factors contribute to this underreporting: reluctance to classify deaths as suicides (mainly due to religious and social reasons), lack of uniformity of ascertainment procedures, and variability in the training of those who certify the causes of death.

Underreporting of suicide is suggested to vary between countries and over time (Kellerher et al., 1996; DeCastro et al., 1989). There also seems to be a gender bias in the proportion of adolescents receiving a suicide verdict due to differences in lethality of the chosen methods (Madge et al., 1999). Females use more often poisoning as method for suicide and deaths due to drugs are those most likely not to be identified as a suicide death. Furthermore, differences in cultural norms – female suicide seems to be less accepted – may affect those responsible for ascertainment (Murphy, 1998).

Statistics on suicide attempt and completion from the WHO mortality database as well as from the CDR and ICR have been registered according to the International Classification of Diseases (ICD). ICD-8 was introduced in Sweden in 1969 and used up until 1987, when ICD-9 was implemented. The latest version ICD-10 was used in Sweden since 1997. The following ICD codes have been used for determined suicide and suicide attempt: ICD-7 (E970-979), ICD 8 and 9 (E950-E959) and ICD 10 (X60-X84). Furthermore, “undetermined” suicide and suicide attempt have been registered as ICD-8 and ICD-9 (E980-E989) and ICD 10 (Y10-Y34).

In line with previously published research (Hulten et al., 2000), violent suicide attempts used for Study III were defined as including following methods: hanging, use of firearms or knives, jumping from height or in front of vehicles and drowning (ICD-8 and ICD-9 codes: E953-957 and 983-987; ICD 10: X70-X82 and Y 20-Y32 for determined and undetermined violent suicide attempt, respectively). ICD codes for determined non-violent attempted suicide were E950–E952 in ICD-8 and ICD-9, X60–X69 in ICD-10; and ICD codes for “undetermined” non-violent attempted suicide were E980–E982 in ICD-8 and ICD-9, and Y10–Y19 in ICD-10.

In Study I trends in determined and “undetermined” suicide have been compared. In Studies II to IV determined suicide or suicide attempt have been combined with “undetermined” suicide or suicide attempt after thorough evaluation that showed that hazard ratios of all covariates were similar for both verdicts. Only suicides and suicide attempts occurring after the tenth birthday of index subjects and family members were analysed, as it was deemed that suicidal acts before the age of ten may be misclassified (Study II-IV). Suicide attempts in index subjects in Study II and in family members in Study IV followed by completed suicide within the inclusion period, were

only considered as completed suicide in the analyses.

Independent variables

Education

Mothers were identified by means of the MGR and information on maternal education level, used in Study II and III as an indicator for socioeconomic status (SES), was obtained from the 1990 Population and Housing Census (PHC). Although data on maternal education in 1970 were available, using them would have introduced selection bias owing to the substantial proportion of missing data. Education levels in 1970 and 1990 proved to be strongly correlated, although the correlation was weaker for the youngest mothers, who were able to catch up with their education. Maternal education was categorised as “up to nine years compulsory schooling”, “upper-secondary schooling” (10 to 12 years altogether), and “university or higher education” (13+ years), with the highest education being the reference group.

Pre-and perinatal factors

Birth weight was grouped in five categories and entered as an indicator variable. Low birth weight (< 2500g) was compared to normal (close to the mean) birth weight (3500 to 4000g). The same procedure was used for short birth length (< 47cm), which was compared to the reference group of normal birth length (50 to 51 cm). Gestational age in weeks was grouped in 3 categories in Study II: $\leq 37w$, $\leq 40w$, $\geq 41w$. In Study III an additional category of below 34 weeks of gestation was introduced based on evidence of a strong association of particularly violent suicide attempt with preterm birth.

Several additional pre-and perinatal and maternal factors have been investigated in Study II: Parity (1, 2-3, 4-9) and mother’s age at child birth in years ($\leq 19y$, $\leq 29y$, $>29y$) were categorised and introduced as indicator variables and bleeding during pregnancy (ICD-8 codes 632, 651), preterm rupture of the membranes (ICD-8 codes 635.95, 661.0), cephalo-pelvic disproportion (ICD-8 codes 654, 655), hypertensive diseases during pregnancy (ICD-8 codes 637, 401), Apgar scores at 1 minute (0–6/7–10), uterine atony (ICD-8 codes 657.0, 657.1), caesarean section and asphyxia (ICD-8 codes 661.7, 661.8, 776) were entered as dichotomous variables (0= no diagnosis, 1= diagnosis).

Conscription factors

Weight at conscription ($\leq 55\text{kg}$, $\leq 65\text{kg}$, $\leq 75\text{kg}$, $\leq 85\text{kg}$, $> 85\text{kg}$) and height at conscription ($\leq 170\text{m}$, $\leq 176\text{m}$, $\leq 181\text{m}$, $\leq 186\text{m}$, $>186\text{m}$) were also introduced as indicator variables in the univariate analyses in Study III. We analysed the interaction of birth weight and birth length with adult height by using tertiles of the mentioned variables in relation to the reference groups (long birth length and tall adult height and high birth weight and tall adult height).

Familial factors

The following risk factors were studied for cases and controls: Parental factors were hospital admission due to psychiatric and personality disorders and suicide attempts (ICR; 1964 – 1999), suicides and deaths due to other reasons (CDR; 1967 – 1999). Sibling factors were hospital admission due to psychiatric and personality disorders and suicide attempts (ICR; 1968 – 1999), suicides and deaths due to other reasons (CDR; 1968 – 1999). Index subject (cases and controls) characteristics were hospital admission due to psychiatric and personality disorders (ICR; 1968 – 1999). All familial and individual events for cases and controls were only included in the analyses if they occurred before the date when the index case attempted suicide so as to limit reverse causality.

For each individual, psychiatric and personality disorders (main and side diagnoses) at all admissions during the observation period were available. In order to have mutually exclusive groups and limit collinearity, we used the main diagnosis at the latest available hospital admission within the inclusion period (up until the date of index attempt). The main diagnosis at the last available admission was chosen for two reasons: first, the main diagnosis reflects the primary condition causing the hospital admission and second, using the last admission takes the course of mental ill-health into consideration. Of fathers, mothers and index subjects (cases and controls) admitted to a hospital due to mental illness, 36%, 41% and 53% had only one admission, and 79%, 83% and 69% only one diagnosis recorded, respectively. These proportions were somewhat lower (approximately by 1%) for suicide attempters than controls.

Familial and individual main diagnoses at latest available hospital admission were categorised in clusters, based on ICD-10 structures. The following diagnostic groups were formed: schizophrenia and non-affective psychoses; affective disorders; substance abuse disorders; neurotic, stress-related and somatoform disorders; organic disorders; emotional, behavioural and developmental disorders; and personality disorders. These diagnostic groups were compared to the reference groups of “no history of hospital admission due to psychopathology”. The vast majority of parents (88% in cases and 95% in controls) and index subjects (74% in cases and 99% in controls), have never been hospitalised. In siblings, a diagnosis was assigned if at least one sibling was admitted with the respective diagnosis. Familial suicide attempts were entered as dichotomous variables (0=no attempt, 1= attempt). Familial vital status was categorised (suicide, death by other reason, alive).

Statistical analysis

Study I

Analysis of trends

Linear regression was performed on the country- and gender-specific logarithmised suicide rates and rates of undetermined causes of death (per 100,000) for adolescents 15-19 years and individuals of 20 years and older. The years 1979 - 1996 were included for countries with available data (Study I). A two-tailed t-test was performed to test the hypothesis of a significant slope. Based on the regression coefficients, annual changes in suicide rates and rates of death due to undetermined causes were estimated for adolescents and the older age group. These were then contrasted.

Changes over time in adolescent suicide rates were compared to rates of undetermined causes of death by calculating mean rates per 100,000 for the two three-year bands: 1979-81 and 1994-96. This also allowed changes in male: female ratios of adolescent suicide rates to be examined. Where data for specific years were not available, two-year or three-year bands for the preceding or subsequent years have been used. To estimate time trends in undetermined causes of death in relation to suicide, ratios of ratios (see computation below) were calculated. A ratio of ratios above 1, for example, means that rising rates of deaths due to undetermined causes were

accompanied by declining or a reduced incline in suicide rates, or that despite declining trends in deaths due to undetermined causes, rates of suicide showed even stronger decreases. The ratio of ratios is equal to:

Rate of suicide in 1979-81 / Rate of undetermined causes in 1979/81

Rate of suicide in 1994-96 / Rate of undetermined causes in 1994/96

Study II

Using Cox proportional-hazard regression, suicide and attempted suicide were entered as the outcome variables and univariate and multivariate hazard ratios with 95% CIs were estimated for the periods from birth to whichever came first: the suicide or suicide attempt (events, ICR, CDR), death from another cause (censored, CDR), first emigration to a foreign country (drawn from the RTP) or 31 December 1999 (censored). The proportional hazard assumption was adequately tested (Hosmer et al., 1999). Owing to the gender differences in rates of suicide and attempted suicide and in anthropometric birth data, all analyses were adjusted for gender.

For multivariate model development, we used purpose selection of covariates (Hosmer et al., 1999). In the variable selection process, the partial likelihood ratio test was used to identify covariates that significantly contributed to the model, with significance levels set at $p < 0.05$. Besides adjusting for gender, multivariate models were adjusted for gestational age due to the known association with birth weight and length. The Attributable Proportion (AP) was calculated as follows: $AP = [(HR-1)/HR] * f$, where HR denote the Hazard Ratios and f the proportion of exposed among all who committed/attempted suicide.

Study III

We estimated crude hazard ratios for the independent variables associated with suicide attempt from proportional-hazard regression models for the periods from conscription to whichever came first: the suicide attempt (event), death from another cause (censored), first emigration to a foreign country or 31 December 1999 (censored). Then, we fitted multivariate Cox models analysing the interaction of foetal and childhood growth with respect to suicide attempt, with adjustment for gestational age and putative maternal confounding factors (age at child-birth,

parity and education). We used the partial likelihood ratio test to test for interaction and for trend.

Study IV

We applied conditional logistic regression to determine odds ratios and 95% confidence intervals, for the independent variables associated with suicide attempt. As the likelihood to have an affected sibling increases with the number of siblings, the analyses were adjusted for this (1, 2, 3, 4+). The partial likelihood ratio test was used to identify interaction. Independent contributions of familial and individual variables were tested in two steps of mutual adjustments. In the first step, the independent effect of the various diagnostic groups (psychopathology) from the suicidal history and vice versa, was assessed separately for father, mother and siblings and the effect of individual psychopathology was adjusted for familial suicidal history. In the second step, two additional independent effects - family history of psychopathology and suicidal behaviour from psychopathology in index subjects, and psychopathology in the index subjects from the effect of familial psychopathology - were scrutinised.

RESULTS

Trends in adolescent suicide rates

Study I scrutinised trends in adolescent suicide rates in European countries and investigated if these trends were unique for teenagers and to what extent they could have been affected by changes in reporting practices.

Increasing trends

Suicide rates increased, in most cases significantly, in twenty-one of the 30 studied countries in male adolescents and in eighteen countries, in some cases significantly, in female adolescents. Highest increases in young males occurred in Ireland, Spain, Belarus and Kazakhstan. In the majority of countries the male: female ratio increased. The highest increases in female adolescent suicide rates, and decreases in male: female ratios as a consequence, occurred in Norway and Ireland.

An additional analysis using latest available data from the WHO mortality database (up until 2003) revealed that in the majority of the 21 countries with increasing male adolescent suicide rates from 1979 to 1996, rates remained stable on the plateau reached in the mid-90s. In Belarus, Ireland, Lithuania and the Russian Federation, however, there were tendencies towards a further increase up until 2001/03. Only in Bulgaria and Latvia could decreasing trends be observed. With respect to the 18 countries with increasing female adolescent suicide rates, fourteen countries witnessed suicide rates levelling off at the rates reached in the mid-90s. In Norway and Ireland, trends to further increases up until 2002 could be found, while in Ukraine and Estonia, however, female adolescent suicide rates seemed to decline from the mid-90s to 2002.

The use of the undetermined causes of death category, primarily in male adolescents varied widely across European countries ranging from 0% to 81% of the rate of undetermined causes and suicide combined in Greece and Portugal, respectively. Compared to trends in adolescent suicide rates in females, trends in males have been affected by changes in reporting practices. Five countries with rising male adolescent suicide rates witnessed greater increases in the rates of undetermined causes over time, while in four other countries, including Sweden, the opposite occurred. The countries with increases in adolescent suicide rates had varying results with

respect to suicide rates for individuals of 20 years and over. Decreases or stable trends were found in nine countries for males and in fifteen countries for females, among them Sweden. Increases, but to a much lesser extent than for adolescents, were found in twelve countries for males and three countries for females.

Decreasing trends

Adolescent suicide rates showed declining or stable annual trends in nine countries for males and in twelve countries for females. Countries like Austria, Hungary and Denmark, with considerable decreases in female adolescent suicide rates, exhibited most pronounced increases in male: female ratios.

In all countries with decreasing suicide rates in male adolescents, rates stabilised at the levels reached in the mid-90s up until 2000/03. For adolescent females the recent trends looked somewhat different. While rates from the mid-90s to 2000/03 remained stable in seven of the twelve countries, that had previously shown a decrease, they further decreased in Bulgaria and the Republic of Moldova, and showed tendencies to increase in Austria, Switzerland and Finland.

The use of the undetermined causes of death category increased in three countries for males and decreased in two and four countries, for males and females, respectively. Neither the countries involved, nor the direction of change of reporting practices was similar for young males and females. Only in Switzerland the practice of classifying deaths as “of undetermined cause” increased for both genders. In Portugal, the declining trend in male adolescent suicide rates would be reversed if the increase in underreporting would be considered. Decreasing and stable trends in adolescents were accompanied by increases or less substantial decreases in the comparison age group in seven countries for females and in eight countries for males. In the remaining countries greater decreases in the age group of 20 years and over for both genders occurred.

Characteristics of youth suicide behaviour

The mean duration of follow-up was 22.7 years (SD 3.4) in Study II, and 2.3 (SD 1.9) and 2.5 (SD 1.8) years for violent and non-violent suicide attempters, respectively, in Study III. Among all suicide attempts, 78 % were determined attempts in Study II and IV, compared to 67% in Study III. The majority (82%) of completed suicides were ascertained as determined (Study II). Suicide attempters primarily used poisoning: 87% in Studies II and IV and 74% in Study III. For suicide, the preferred method was hanging and strangulation (30%), followed by poisoning (28%). Cutting (57%) was the predominant method for violent suicide attempters (Study III). The mean age of suicide attempters was 19.1 years (SD 3.6) in Study IV, and 19.7 (SD 4.4) and 17.8 (SD 2.8) for suicide and suicide attempt, respectively, in Study II. The maximum age in individuals included in Studies II and III compared to IV was 26 and 31 years, respectively.

Maternal factors

Compared with subjects delivered by mothers aged 20 to 29 years, there was a significant two-fold rise in the risk of suicide and suicide attempt among offspring born to **teenage mothers**. This inverse association of teenage motherhood and suicidal behaviour in offspring was only marginally altered in the multivariate analysis, when maternal education and parity, gender and foetal growth were included in the model. Maternal age at childbirth of 29 years and above was significantly protective for offspring's suicide attempt. **Low maternal education** was associated with a slight increase in risk for suicidal behaviour in offspring, relative to higher maternal education. After adjustment for other risk factors, however, maternal education of maximum 9 years remained significantly associated with suicide attempt but not suicide completion. **Multiparity** (4th to 9th birth order) was significantly associated with subsequent suicide attempt in the uni-and multivariate analysis, compared with subjects being born of second and third birth order (reference group). **Hypertensive diseases** during pregnancy and **caesarean section** were significantly associated with a slightly elevated risk of attempted suicide in offspring, although only in univariate analysis.

Neonatal factors

In the univariate analysis, **low birth weight** (below 2,500 g) adjusted for gestational age, was significantly associated with suicide and suicide attempt in relation to the reference category of

normal birth weight. The association was strongest (more than a two-fold increase in risk) for suicide and violent suicide attempt (Study II and III). Additionally, **short birth length** (below 47cm), relative to the reference category (50-51 cm), was also found to be associated with an increase in risk of completed suicide and attempted suicide, both by violent and non-violent methods in the univariate analysis (Study II and III). The risk for suicidal behaviour decreased with rising birth weight and length. After further adjustment for maternal factors, low birth weight adjusted for gestational age remained associated with the two-fold increase in risk of suicide completion, while short birth length adjusted for gestational age continued to increase the risk of attempted suicide. Owing to collinearity, only birth length for suicide attempt and birth weight for suicide were introduced in the final models (Study II). **Preterm birth** was particularly important for violent suicide attempt. The risk was increased four-fold for infants born before the 34th week of gestation, compared with gestational age of 38 to 40 weeks. This large increase in risk decreased only slightly after adjustment for maternal and anthropometric factors (Study III).

Childhood growth

We found a significantly elevated risk of suicide attempt for subjects, who were short at conscription (< 170cm) relative to the reference category of normal height (177-181cm). The risk of attempt decreased considerably with increasing adult height and weight. Tall adult stature and being overweight were significantly protective. These patterns were similar for non-violent and violent suicide attempt, although only the inverse association of adult height and non-violent attempt was found to be significant.

Foetal and childhood growth interaction

When gestational age and maternal factors were included in the model, the interaction between birth length and adult height was found to be of borderline significance ($p_{\text{interaction}} = 0.06$) with respect to suicide attempt and significant ($p_{\text{interaction}}=0.03$) with respect to non-violent suicide attempt. The interaction between birth weight and adult height, however, was not significant ($p_{\text{interaction}} = 0.72$) for suicide attempt. All associations between foetal and childhood growth, and suicide attempt, are in relation to the reference group (highest tertile of birth weight or birth length with highest tertile of adult height).

Across all tertiles of adult height, the risk of suicide attempt (violent and non-violent) was increased for men with short birth length and low birth weight. The highest risk of attempt (in general and by non-violent means) was found for subjects with medium birth length/high birth weight, and short adult height. For these subjects the risk of suicide attempt decreased significantly with increasing adult height. The risk of violent suicide attempt in short adults, however, deviated from this pattern as it fell with increasing birth weight. Low birth weight in short adults was associated with a two-fold increase in risk of violent suicide attempt. The interaction of birth weight with adult height with respect to the risk of violent suicide attempt was not found to be significant ($p_{\text{interaction}} = 0.72$).

Familial suicidal behaviour

Of the 14,440 cases (suicide attempters), 12% and 2% had a history of suicide attempt and suicide in the family, respectively. Having two or more family members, who have attempted or completed suicide, raised the risk for suicide attempt more than two-fold compared with having only one family member with suicidal behaviour. We observed a significant interaction with gender for familial suicide completion ($p=0.012$). The odds ratio for attempting suicide with paternal or sibling's suicide completion was higher for boys than for girls, with a non-significant gender difference for maternal suicide completion. There was also a significant interaction of age with familial suicidal behaviour ($p=0.018$). The effect increased with decreasing age of onset and was strongest for maternal attempt, particularly for young girls.

Suicide attempt in siblings (OR 4.5), mothers (OR 4.2) and fathers (OR 3.3) was strongly associated with suicide attempt in index subjects in the univariate model. Familial suicide completion increased the risk for suicide attempt in the index cases compared to controls, from 2.7 times in siblings to 3.1 times in the mothers. Familial suicide attempt generally increased the risk of suicide attempt in young adults to a greater extent than familial suicide completion. Maternal and paternal death other than suicide raised suicide attempt risk by 50%.

Adjustments for familial mental illness decreased the odds ratios related to familial suicidal history considerably, greatest for paternal suicide attempt, and maternal and sibling's suicide completion. Further adjustment for individual mental illness marginally altered the effect of

familial suicidal behaviour in the final model. Maternal suicide attempt remained considerably more important than paternal attempt. Suicide attempt in the siblings emerged as the strongest familial risk factor for attempted suicide in young adults. Parental suicide completion continued to be significant as a risk factor for subjects' suicide attempt. Parental death other than suicide remained marginally important and significant.

Familial hospital admission due to mental illness

A history of hospital admission due to mental illness in a first degree relative was present in 23% of cases. As for familial suicidal behaviour, the risk of suicide attempt increased considerably if two or more family members, rather than only one, had a history of admission due to psychopathology. In the crude analysis, odds ratios ranged between 1.8 and 5.9 for the various diagnostic groups of mental illness in fathers, mothers and siblings. We found highest odds ratios for familial personality and substance abuse disorders and lowest for the group of "behavioural, emotional and developmental disorders".

The majority of diagnostic groups were associated with higher odds ratios in the mother compared to the father, particularly organic disorders, schizophrenia and non-affective psychoses, and substance abuse disorders. The effect of paternal personality disorder was stronger for male than female suicide attempts (OR 5.4 vs. 3.2). Maternal affective disorders influenced female suicide attempts more strongly than male attempts (OR 2.7 vs. 1.9). These interactions with gender were, however, of borderline statistical significance ($p=0.056$ and $p=0.054$, respectively).

Odds ratios of familial psychopathology were not considerably affected when controlling for familial suicidal behaviour, with the exception of maternal and sibling's substance abuse and personality disorders. The effect of familial mental illness was considerably decreased after taking individual mental illness into consideration. Familial personality and substance abuse disorders, and maternal organic disorders among all diagnostic groups, remained the strongest risk factors for suicide attempt in index subjects in the final model.

Individual hospital admission due to mental illness

Only 26% of suicide attempters had been admitted to a hospital due to psychopathology before their attempt. The frequency of individual hospital admission in cases was 33 times more common compared to controls. There were strong interactions ($p < 0.001$) between individual hospital admission due to psychopathology in index subjects and familial hospital admission due to psychopathology as well as familial suicidal history (attempt and completion combined). For example, the odds ratio of being both admitted to a hospital with a psychiatric or personality disorder and having a family member with suicidal behaviour (OR 64), clearly exceeded the additive risk of both factors separately (OR 37 and OR 3.5). This excess in risk in case of familial suicidal behaviour was observable for all diagnostic groups in index subjects (data not shown).

Hospital admissions due to psychopathology in the index subjects themselves were undoubtedly the strongest risk factors and were only marginally attenuated after adjustment for familial risk factors. Substance abuse, affective, and personality disorders represented the strongest predictors for youth suicide attempt. We found gender differences for individual psychopathology. With the exception of substance abuse disorders and organic disorders all other diagnostic groups were associated with higher odds ratios in females compared to males.

DISCUSSION

Methodological considerations

The considerable number of countries involved in the analyses of trends in adolescent suicide rates is a strength of Study I. So too are the coinciding analyses of changes in reporting practices and changes in suicide rates in an older comparison age group. As a limitation of this Study, the international differences in the validity and reliability of official suicide mortality statistics reported to the WHO need be mentioned (Phillips et al., 1993; O' Carroll et al., 1989; Sainsbury et al., 1982 and 1983). Non-uniformity in ascertainment and classification procedures as well as differing religious and social stigma, result in varying degrees of underreporting between countries. These variations have to be taken into account when interpreting the data (WHO, 1973; Wasserman et al., 1998; Phillips et al., 1993; O'Carroll et al., 1989; Sainsbury et al., 1982 and 1983). In an attempt to limit the influence of inter-country variance in reporting practices, death by undermined causes, the verdict predominantly used to conceal suicides, has been included in the analyses.

Studies II-IV

The strengths of these register-based studies are the large samples yielding high statistical power for sub-group analyses, with a long follow-up and analyses of a rare outcome. Due to the quality of the registers used and due to the fact, that data was obtained from independent information sources, we could avoid differential misclassification of exposure or outcome. In Studies II and III, 9% and 20.9% of records were excluded, respectively. We then analysed each variable for those subjects with available data and found these findings similar to the findings for the study sample. It therefore seems unlikely, that our results are biased by selection. We further limited non-differential misclassification of anthropometric data by excluding extreme values. Owing to the historical prospective study design based on information from professional health examinations, recall bias and bias due to self-reporting could also be avoided.

The quality of the data in various registers in Sweden has been assessed previously (Dalman et al., 2002; Cnattingius et al., 1990; Allebeck et al., 1991; National Board of Health and Welfare, 2005). In a study evaluating causes of death among conscripts in Sweden, Allebeck et al. (1991)

found 19% of officially recorded undetermined suicides (E980–E989) to be re-evaluated into determined suicides (E950–E959). International estimates of underreporting of suicide in adolescents reach 30 percent and even more (Madge et al., 1999). These suicides are often reported as undetermined causes of death (“undetermined suicides”). For this reason, “undetermined” suicides were included in Studies II till IV. We have also analysed attempted suicides, as they reflect suicidal behaviour and are strong predictors of future suicides. For the analyses of attempted suicide, both determined and undetermined attempts have been included. Hazard ratios were found to be similar for the independent variables for determined and “undetermined” suicide attempt and suicide completion.

The choice of main diagnosis at latest available admission has been validated against a hierarchical system, where the diagnosis considered for a patient was the one assigned at any admission as the main or side diagnosis. This way of coding yielded predominantly similar results without any change in the priorities of the various diagnostic groups. The proportion of co-morbidity in index cases (32%) was considerably lower than results from earlier research showing 79% co-morbidity in young suicide attempters (Wunderlich et al., 1998) and may reflect underreporting of side diagnoses in the ICR.

Some limitations of the study and considerations when interpreting our findings are important to mention. First, using data on attempted suicide from inpatient care registers excludes individuals who were not hospitalised after their suicide attempt. The proportion of adolescent suicide attempters receiving medical treatment ranges from 12 to 50% (Grossman et al., 1991; Friedman et al., 1987; Smith et al., 1986). Our analyses most likely included suicide attempts, which were medically more severe. Another inherent limitation of register-based research is potential variability in the degree of reporting across categories of exposure variables. The propensity to seek hospital care after a suicide attempt or the tendency of hospital staff to keep intentionally injured individuals, may be unevenly distributed across social background (maternal education or age) or psychosocial support system (familial psychic ill-health). We are, however, unable to assess the extent and direction of this bias.

Individuals who were not hospitalised for mental illness are also excluded when using data from ICR. Hospital admission for mental illness from the ICR is affected by differences in access to mental health care and in help seeking behaviour by time, region and gender. Furthermore, national coverage of data on hospital admission was not complete until 1987. We believe we have overcome most of these limitations by the case control study design matching for gender, age and county.

The Multi-Generation Register used for identification of cases, controls and their families in Study IV also includes adoptive parents. In the data-set used, the identification of adoptive parents was not possible. However, information from other analyses revealed that from the 1,362,694 children born in Sweden 1968-1980 there were 3,311 children (0.2 %) registered as having both parents as adoptive parents. It therefore seems unlikely, that our results of familial transmission of suicidal behaviour and psychopathology have been affected by missing information on adoption.

Interpretations

Changes in adolescent suicide mortality

The results of Study I show predominantly increasing trends in suicide mortality in male adolescents in various areas in the WHO European Region over the observed period. Female adolescent suicide rates increased in fewer countries than for their male counterparts and the increases were in general less marked, with a few exceptions (e.g., Norway and Ireland). Results from a longitudinal WHO European multi-centre study on attempted suicide suggest that the recent increase in attempted suicide rates in young male subjects in several European countries might signal a further increase in suicide rates, as attempted and completed suicide co-vary (Hawton et al., 1998a). Part of the explanations for this finding might be a shift to suicide methods with higher lethality particularly in young males in recent years, in countries with increasing suicidality (Ohberg et al., 1996; Hulten et al., 1992; Madge et al., 1999). Several other reasons which might have contributed to the increasing suicide rates, like increases in unemployment, in the prevalence of depression and alcohol abuse, in family discord as well as general societal changes have been proposed to have affected young males more than young females (Kellerher, 1998; Hawton, 1998; Diekstra, 1996; Fombonne, 1998). Males are proposed

to be more dependent on a job to assume a social role and consequently more susceptible to unemployment, they are less likely to seek help, their depression might be different to diagnose and finally they might be more affected by societal changes due to the loss of role models (Rutz et al., 1995; Oliver et al., 2005; Kellerher, 1998; Hawton, 1998).

The increases in adolescent suicide rates, however, are accompanied by a decrease or reduced incline in trends in individuals of 20 years and older. The gap between increasing adolescent rates and decreasing rates in the older comparison group were strongest in the Scandinavian countries, including Sweden, the Central Asian Republics, the United Kingdom and the Netherlands. This observation deserves the attention of public health specialists. Birth cohort analyses in several countries have reported a shift of suicide mortality towards younger ages, especially for young men (Åsgard et al., 1987; Etzersdorfer et al., 1996; Häfner et al., 1985; Surtees et al., 1989). Changes in rank orders of suicide rates in adolescents and young adults in European countries, witnessed by relative stability in adults, have also been reported (Mäkinen et al., 1997). The authors comment that the reason for the disproportionate effect on young people may be that any socio-cultural changes might have affected the unsettled, youngest group the most.

Trends in adolescent gender-specific suicide rates were also compared with trends in rates of undetermined causes of death for those countries with available data. Changes in the use of undetermined causes of death affected temporal trends in suicide rates in males more strongly than in females. Without considering improved gathering of statistical information, increases in male adolescent suicide rates would have been overestimated in Sweden, Ireland and Greece, and decreasing male suicide rates underestimated in Denmark and Austria. Disregarding increases in underreporting, however, would have lead to an underestimation of increases in male adolescent suicide rates in Finland, Belgium and the United Kingdom, an overestimation of decreases in Switzerland in both genders and misinterpretation of decreasing trends in Portugal in young males. The conclusion of some earlier studies that classification practices are stable over time should therefore be revised, particularly in studies of young male suicides (Sainsbury et al., 1982).

Maternal education

In Study II, maternal educational level in 1990, used as an indicator for socioeconomic status, proved to be significantly and inversely associated with the risk of attempted suicide, but not suicide, in offspring after adjusting for other maternal and neonatal factors. Our findings are in line with earlier studies on stronger childhood socioeconomic differences in the risk of suicide attempt than suicide completion in youth (Andrews et al., 1992; Hjern et al., 2002). When interpreting our results, one has to keep in mind though, that maternal education in 1990 does not entirely tally with the mother's education at the time of childbirth (1973 to 1980). It is important to stress here, that 10.3% of cases would be attributed to low maternal education, if it were causally associated with the risk of suicide attempt.

Teenage motherhood

Teenage motherhood in our study was found to be a strong and an equally important predictor for suicide and suicide attempt, independent of other maternal risk factors. These findings are in accordance with previous results, relating teenage motherhood to attempted and completed suicide in adolescents and young adults (Lewinsohn et al., 1994; Fergusson et al., 1999; Ekeus, 2004). It is possible that young motherhood is associated with an adverse psychosocial home environment, inadequate social support, inadequate child-rearing practices, the stress burden of single motherhood and consequently superimposed long-term socioeconomic problems. These conditions may exacerbate the risk of the offspring's mental ill-health and subsequently the risk of suicidal behaviour (Olausson et al., 2001; Fergusson et al., 1999; Elster et al., 1983).

Women who are pregnant in their teens are more likely to have been exposed to parental separation, abuse or neglect, foster care and parental substance abuse than older childbearing women (Christoffersen, 2005; Elster et al., 1983). Teenage motherhood is also found with increased frequency in women suffering from a mental disorder, primarily personality disorder and substance abuse disorders (Lier et al., 1989). Among adolescent mothers, those who had been victims of child physical abuse constitute a high-risk group for abusing their own children (De Paul et al., 2000). Child abuse and neglect appears to be one central part in the association of teenage mothers and later outcome of their offspring (Fergusson et al., 1999).

Multiparity

Multiparity significantly increased the risk of attempted suicide but not completed suicide in offspring. Comparable studies relating multiparity to suicidal behaviour in offspring are sparse. However, multiparity has been related to an increased risk of major suicide risk factors like schizophrenia, other psychoses and depressive disorders in offspring (Jones et al., 1998; Kempainen et al., 2000). It seems plausible that stress and depressed mood perceived by multiparous mothers, as well as their lack of time for adequate child rearing, may adversely affect a child's psychosocial and socioeconomic environment (Gurel et al., 2000). Our finding of an increased risk of suicide attempt in the youngest children in multi-child families should be cautiously interpreted as they might be biased by the fact that some of their older siblings were less likely to be included in the study because they were born before the inclusion period. We are unable to estimate the extent of this bias on the basis of our dataset.

Neonatal factors

In this study we found an inverse association of **birth weight** and **birth length** adjusted for gestation age with subsequent risk of completed and attempted suicide, particularly by violent means. This is in line with earlier findings that mental disorders – strong predictors of suicidal behaviour - like depression and schizophrenia, but also sub-optimal psychological functioning and increased stress susceptibility as well as mental health care use have been found to be associated with low birth weight and short birth length (Nilsson et al., 2004; Gale et al., 2004; Jones et al., 1998; Wahlbeck et al., 2001; Gunther et al., 2003). However, Barker et al. (1995) and Li et al. (2003) failed to find an association between birth weight and suicide. Explanations for these discrepancies in findings may be due to differences in study design, in study samples, in categories of birth weight and in length of follow-up. **Preterm birth** was strongly inversely associated with violent suicide attempt. Prematurity at birth has also been linked to an increased risk of depressive disorder, anorexia nervosa and schizophrenia (Patton et al., 2004; Dalman et al., 1999; Cnattingius et al., 1999).

Differences appear to exist in factors influencing foetal linear growth and foetal weight gain. In fact, restrictions in linear foetal growth and foetal weight gain have been previously proposed to

represent two different responses to foetal adverse conditions with different long-term consequences (Forsen et al., 1999). Support for these findings is lent by observations from some (Bernstein et al., 1997), but not all ultrasound studies (Kramer et al., 1989), showing that linear foetal growth and foetal weight gain could be primarily determined in early versus late gestation. These authors suggest that the reason behind the differences in the associations of body proportions at birth with subsequent health outcome could originate in differences in the time of gestation, in which the underlying adverse effect occurred. Interesting in this context are the findings from the Dutch Hunger winter, where an association of maternal starvation during second trimester and affective disorder, a major suicide risk factor, in the offspring was reported (Brown et al., 1995).

Underlying mechanisms

A hypothetical pathway underlying the association of prenatal exposures and subsequent suicidal behaviour is an alteration of the serotonin metabolism in foetal life. The serotonin metabolism is supposed to be more specifically associated with the diathesis of suicidal behaviour than with any underlying psychiatric morbidity (Mann et al., 2001). The importance of serotonin metabolism for brain development as well as pre-and postnatal growth has been reported (Bercu et al., 1987; Sodhi et al., 2004). Children, born preterm, show damages in various parts of the brain, including the amygdaloid nuclear complex, hippocampus and the prefrontal cortex (Luciana, 2003). The prefrontal cortex has been reported as a site of alterations in the serotonin metabolism in suicide completers (Mann et al., 2001). It is possible that serotonin function and growth hormone metabolism are altered by the hypoxia induced by preterm delivery (Kim et al., 1994; Luciana, 2003; Bercu et al., 1987). Serotonin metabolism is also affected by other factors leading to foetal growth restriction or preterm birth, like maternal prenatal alcohol, drug and nicotine abuse, stress and malnutrition (Sodhi et al., 2004; Luciana, 2003). Furthermore, impulsivity and aggression, which are well known features of suicidal behaviour and associated with low serotonin levels, have been reported for preterm born children (Mann et al., 2001; Luciana, 2003).

Are the effects independent?

Teenage mothers are more inclined to have many children and their babies are more often born preterm and with a lower birth weight (Otterblad Olausson, 2000). They are more likely to smoke during pregnancy and come more often from a lower socio-economic background (Odlind et al., 2003). They themselves do not reach similar educational achievements as older mothers do (Otterblad Olausson, 2000). In our analyses maternal age, parity, education and birth weight/length have been adjusted for each other and their effects on suicidality in young adults seem to be independent from each other.

Differences in antenatal care could confound the reported association of foetal growth restriction and teenage motherhood with suicidal behaviour in offspring. Routines for antenatal care were, however, standardised in Sweden in 1970 and the vast majority of pregnant women is known to follow antenatal routines (Aberg et al., 1992). Prenatal care and obstetric routines can also be assumed to be similar during the inclusion period (1973 – 1980). Maternal adverse lifestyle may also have contributed to the observed relation of foetal growth restriction and preterm birth with suicidal behaviour. Maternal smoking and alcohol and drug abuse are known to contribute to restricted foetal growth and preterm birth as well as affect the central nervous system (Wollmann et al., 1998; Kramer, 1987; Luciana, 2003; Sodhi et al., 2004). Information on maternal smoking, alcohol and drug abuse, however, was not available in the MBR.

The reported associations of foetal growth restriction, preterm birth and adverse maternal conditions (low age, low education and multiparity) with suicidal behaviour in offspring could however also be due to maternal psychiatric disorders and aggregation of suicide in the family. Maternal mental ill-health may affect foetal growth, prematurity, socioeconomic position and increase the risk of teenage pregnancies and multiparity as well as exacerbate the risk of psychiatric disorders in their offspring, which further increases the risk for suicidal behaviour (Bennedsen et al., 1999, Kessler et al., 1997; Lier et al., 1989). A recent analysis of Swedish register data, however, reported that the increased risk of suicide attempt and completion in offspring to teenage mothers was independent from parental psychiatric disorders and substance abuse as well as socioeconomic status, single parenthood and child welfare intervention (Ekeus, 2004). This suggests that teenage motherhood per se is a risk factor for suicidal behaviour in

offspring. Further research is required to disentangle the effect of the maternal (multiparity, education and age) and neonatal factors from the effect of maternal mental illness on the risk of suicidal behaviour in offspring.

Childhood exposures

Suicide attempt risk was increased for men with low birth weight and short adult stature. In the absence of a comparable study examining associations of foetal and childhood growth with suicidal behaviour, it is interesting to refer to studies with psychosocial and psychiatric outcome. Increased risk of schizophrenia was seen for low birth weight subjects who became short adults (Gunnell et al., 2003), or had low body mass indexes at age 7 years (Wahlbeck et al., 2001).

We could not find a modifying effect of childhood linear growth on the association of reduced foetal growth with suicide attempt. This is in contrast to earlier research with different forms of mental health outcome. Subjects with impaired foetal growth not only benefited from linear postnatal growth, but also weight gain, with respect to psychological performance and reduced likelihood to develop schizophrenia in childhood and adulthood (Gunnell et al., 2003; Lundgren et al., 2001; Cheung et al., 2002). It is important to keep in mind that the group of subjects with “low birth weight” and “short birth length” in the current work, consisted of individuals in the lowest tertiles (<50cm, < 3370g), similar to those in Gunnell et al. (2003). Thus, they were not individuals with foetal growth restriction, often measured as 2 standard deviations below the mean of the population adjusted for gestation. Further research is needed as regards to possible effects of postnatal growth on outcomes primarily related to brain function.

Additional risk was found in subjects with postnatal linear growth below their expected genetic potential, namely men with adequate prenatal growth and short adult stature. Adult height is both genetically determined as well as influenced by prenatal growth and the physical, psychosocial and socio-economic conditions during childhood and adolescence (Gunnell, 2002). The increased risk for men with adequate foetal growth and short adult stature probably reflects an adverse psychosocial situation and stress during childhood, which have been associated with

linear postnatal growth failure and unfavourable mental development (Bercu et al., 1987). Children of parents, who sought care at a psychiatric hospital showed failure to thrive without an apparent organic cause, possibly reflecting psychosocial instability in the families (Larsson et al., 1982). Besides this so-called psychosocial dwarfism, several associations between mental disorder and its treatment through for example, neuroleptics, and growth suppression have been reported (Bercu et al., 1987). Particularly anorexia nervosa, manic depression and psychotic disorders are known to be associated with growth hormone neurosecretory dysfunction (Bercu et al., 1987).

Familial psychopathology

Our findings are comparable to results from clinical and population-based studies showing that the risk of suicide attempt in adolescents and young adults tends to be associated with familial psychopathology, particularly substance abuse and personality disorders (Johnsson et al., 1998; Pfeffer et al., 1994; Garfinkel et al., 1982). A history of hospital admission due to psychopathology in a first degree relative was 2.3 to 3.7 times more common in youth suicide attempters than community controls (Christoffersen et al., 2003; Pfeffer et al., 1994). This is in keeping with our finding of a 2.9 times increase of suicide attempt with familial hospital admission. Furthermore, odds ratios from earlier research for antisocial personality disorder (5.3), substance abuse (3.1), double depression (2.8) and panic disorder (2.1) in first degree relatives are in accordance with our findings (Pfeffer et al., 1994; Johnson et al., 1998).

All parental diagnoses were significantly associated with an increased risk of suicide attempt in the final model with the exception of the group of emotional, behavioural and developmental disorders. The main difference between maternal and paternal diagnoses was the elevated odds ratio for maternal organic disorders, which were often preceded by earlier admissions for affective and non-affective psychoses. The fact that maternal organic disorders, schizophrenia and non-affective psychoses were associated with higher odds ratios for attempted suicide compared to paternal, suggests a greater vulnerability to maternal psychoses in the index subjects.

Individual psychopathology

Our finding that hospital admission was 33 times more common in cases (young suicide attempters) than in controls, is in line with a Danish register study, reporting an odds ratio of 30 for individual hospital admission (Christoffersen et al., 2003). The hospitalisation of 26% in young cases prior to index attempt, however, is in contrast to clinical studies where 80% to 90% of young suicide attempters meet criteria for any psychiatric disorder (Andrews et al., 1992; Fergusson et al., 1995). This suggests that a majority of young suicide attempters in Sweden do not obtain treatment for their mental health problems before they receive clinical attention for their suicide attempt. In this context, it is necessary to keep in mind that from the suicide attempters who are admitted to a hospital after their attempt, those with violent and repetitive attempts are most likely to be recommended aftercare based on a recent, detailed European analysis (Hulten et al., 2000).

The predominance of substance abuse, affective and personality disorders in young suicide attempters is in accordance with previously published work (Andrews et al., 1992; Fergusson et al., 1995). All diagnostic groups were associated with a significantly and most of them with a greatly increased suicide attempt risk in our study. This calls for active approaches in early detection and treatment of children and young adults at risk for mental ill-health. We found a higher risk of suicidal behaviour associated with depressive and neurotic disorders in girls, and substance abuse in boys, which is consistent with previous research on suicidal behaviour in teens (Marttunen et al., 1995; Shaffer et al., 1988; Wunderlich et al., 2001).

Familial suicidal history

In Study IV, 13% of the cases had a parent or sibling who had completed or attempted suicide. The occurrence of suicidal behaviour in first-degree relatives of young people who have attempted suicide ranged from 6.3% to 16.8% in earlier studies (Johnson et al., 1998; Christoffersen et al., 2003). It is likely that this variation is primarily explained by differences in study population and methods.

Our findings are consistent with clinical and community surveys showing that the risk of youth suicide attempt tends to be associated with familial suicidal behaviour, primarily familial suicide attempt (Garfinkel et al., 1982; Pfeffer et al., 1994; Johnson et al., 1998; Cerel et al., 2005). In these studies odds ratios for index suicide attempt ranged from 2.3 to 5.7 if a first degree relative attempted suicide. This is in accordance with our findings of an odds ratio of 4.0 for familial suicide attempt. Similar results to our study, of stronger increased odds ratios in case of maternal compared to paternal suicide attempt, and the strong effect of sibling's suicide attempt have been reported previously (Sørensen et al., 1991; Pfeffer et al., 1994).

We could further show that a familial history of suicide completion had a stronger effect for boys than girls, and a stronger effect in the case of a father's rather than a mother's suicide. We speculate that gender differences in genetic transmission of suicidal behaviour may explain this finding. Our results showing that a family history of suicidal behaviour has a stronger effect on early onset suicide attempt, may also suggest that a history of familial suicidal behaviour could be an indicator of a genetic predisposition to suicidal behaviour. Similar findings were reported earlier (Roy, 2004; Brent et al., 2003). These authors concluded that familial loading for suicidal behaviour might affect the age of onset of suicidal behaviour. However, younger people might also be less capable of coping with adverse familial environmental influences associated with familial suicidal behaviour and might be more inclined to imitate parental behaviour.

Independent and interacting effects of familial and individual factors

Familial and individual psychopathology

In Study IV, familial psychiatric disorders (particularly substance abuse disorders) and personality disorders remained significant predictors of subjects' suicide attempts after adjustment for individual mental illness. This suggests that parental mental ill-health, in addition to increasing the risk for mental ill-health in the offspring, might contribute to risk for offspring's suicide attempt partly through hereditary and partly through environmental factors. Hereditary factors include genetically determined personality traits characterised by impulsivity and aggression. Environmental factors comprise poor and inappropriate parenthood, family

disruption or child abuse and neglect (Christoffersen et al., 2003a; Goodman et al., 2004). Brent and co-workers (1994) reported similar findings of an elevated risk of adolescent suicide completion in offspring of parents with depression, after adjusting for offspring's psychopathology. Part of the explanation can also be unobserved and under-diagnosed mental illness among index subjects.

Suicidal behaviour and psychopathology

In accordance with clinical studies (Johnsson et al., 1998), population-based studies (Goodwin et al., 2004), register-based studies (Christoffersen et al., 2003) and twin studies (Fu et al., 2002; Statham et al., 1998), our findings suggest that familial suicidal behaviour remains important for subject's suicide attempt even after controlling for familial and individual mental disorder. Furthermore, individual psychopathology in index subjects strongly interacted with familial suicidal behaviour, which increased the odds ratios for all diagnostic psychopathological groups. In interpreting these findings a potential effect of under diagnosed mental illness has to be taken into account. However, our observations provide further evidence for the additional effect of familial suicidal behaviour over and above and interacting with the diagnosed familial and individual mental illness.

Public health and clinical implications

We could show that offspring have an increased risk for subsequent suicidal behaviour if they are born to young mothers; to multiparous mothers or mothers with a low socio-economic status; or to mothers with suicidal behaviour and mental illness, particularly personality and substance abuse disorder. Offspring that were born preterm or with low birth weight/short birth length are also at increased risk. These at-risk pregnancies are often associated with psychological, economical and parenting stress that is likely to impact on the parent-child relationship. Screening of and support for these mothers as well as the fathers may therefore start as early as during ante- and post-natal care. The antenatal care system in Sweden covers the vast majority of pregnant women. Therefore, it appears to be an ideal arena for screening for psychosocial, psychiatric and physical risk factors and for delivering appropriate psychosocial and educational measures to these families.

This study suggests that the risk for suicide attempt in young adults is associated with parental suicidal behaviour and mental ill-health. Both inheritable and psychosocial factors related with parental psychopathology may contribute. Effective collaboration between the various sectors within health care and social services is crucial for early detection and adequate intervention with regards to the psychosocial and mental problems these children may have to face, and to the consequent prevention of suicidal behaviour. This collaboration should include ante- and postnatal health care services, schools, and child and adult psychiatry services.

Mental illness, particularly substance abuse, affective and personality disorders, emerged as the strongest predictor for suicidal behavior in youth. By early recognition and adequate treatment of individual mental illness, a considerable proportion of suicide attempts could be prevented. Due to the strong interaction between individual psychopathology and familial suicidal behaviour with regard to suicide attempt in youth, it is vital to look at the history of suicidal behaviour in the whole family when assessing the suicide risk in adolescents with mental ill-health.

CONCLUSIONS AND IMPLICATIONS FOR FUTURE RESEARCH

Suicide rates in adolescents increased for males in twenty-one, and for females in eighteen, of thirty European countries during the 1980s and mid-1990s. These increases were generally accompanied by stable or decreasing trends in suicide rates of males and females of 20 years and over. In several countries, changes in reporting practices affected to different degrees the temporal variations in adolescent suicide rates, primarily in males. Further research elucidating the various causes behind the changes in youth suicide rates is necessary in order to develop tailor-made prevention programmes. This seems to be particularly required in those countries, where increasing adolescent suicide rates were accompanied by decreasing trends in suicide rates in older age groups. However, preventive measures, for example in health care services after a suicide attempt and early recognition in schools, can be applied already in order to mitigate the hardships of today's teenagers.

Teenage motherhood increased the risk of both suicide attempt and completion in adolescents and young adults. Multiparity and low maternal education predicted suicide attempt in young offspring. Preterm birth was a strong predictor for violent suicide attempt. Restricted foetal growth was associated with both suicide completion and attempt in offspring. Further research is warranted to disentangle the effect associated with restricted foetal growth, preterm birth, poor socio-economic background as well as being born to a teenage or multiparous mother on suicidal behaviour in young adulthood, from the effect of maternal mental ill-health, which might underlie the observed associations.

This inverse association of foetal growth and suicide attempt did not seem to be modified by childhood growth. Decline in postnatal linear growth potential entailed an additional risk. Further research is needed as regards to possible effects of postnatal growth on outcomes primarily related to brain function.

Familial suicidal behaviour, primarily suicide attempt, and familial psychopathology, mainly substance abuse and personality disorders, were significantly associated with an increased risk of suicide attempt in young adults. There seemed to be an effect of familial suicidal behaviour as

well as familial psychopathology on youth suicide attempt beyond the transmission of mental illness. Individual psychopathology was the strongest risk factor for suicide attempt in young adults. Significant interactions were also observed between psychopathology in index subjects and familial suicidal behaviour. Familial suicidal behaviour had a stronger effect on suicide attempt of earlier onset and on boys. Further studies are needed to explore the mechanisms of transmission of suicidal behaviour in families.

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