

UMEÅ UNIVERSITY MEDICAL DISSERTATIONS

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**From the Division of Psychiatry, Department of Clinical Science,
Umeå University, SE-901 85 Umeå, Sweden**

**SEASON OF BIRTH
IN
SUICIDOLOGY**

Neurobiological and epidemiological studies

Jayanti Chotai



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ABSTRACT

Chotai J (1999). *Season of birth in suicidology: neurobiological and epidemiological studies*. Umeå University, Department of Clinical Science, Division of Psychiatry, 901 85 Umeå, Sweden. ISSN 0346-6612 ISBN 91-7191-645-8.

Background: Several neuropsychiatric disorders have shown season of birth associations. Low cerebrospinal fluid (CSF) levels of the serotonin metabolite 5-HIAA and the dopamine metabolite HVA have been associated with suicidal behaviour, impulsivity, and aggression. This thesis investigated associations between the season of birth, the CSF levels of three monoamine metabolites (including MHPG of norepinephrine), the scales of the diagnostic interview for borderline patients (DIB), and psychiatric diagnoses. Also, the methods of suicide were investigated in relation to the season of birth.

Methods: We studied a clinical sample of 241 patients in Stockholm with mood, anxiety and adjustment disorders with respect to the CSF levels of monoamine metabolites in relation to the season of birth, and in relation to the DIB in an overlapping sample. We also analysed all completed suicides during the 42 years 1952 – 1993 in Västerbotten in northern Sweden (1466 cases) by multiple logistic regressions to relate suicide methods with season of birth, gender, age, urban-rural residence, marital status, year of suicide, and season of suicide. For the 20 years 1961 – 1980 (693 cases), psychiatric in-patient and out-patient records were also examined for any history of psychiatric contacts and psychiatric diagnoses. In two mutually independent samples, we investigated the DIB in relation to the season of birth.

Results: In the Stockholm sample, those born during February to April had significantly lower CSF levels of 5-HIAA, and those born during October to January had significantly higher CSF levels of HVA, HVA/5-HIAA, and HVA/MHPG, as well as (non-significantly) higher levels of 5-HIAA. Those with an intermediate score of section II (impulse action patterns) of the DIB had significantly higher CSF levels of 5-HIAA and HVA, and they were significantly more likely to have been born during October to January. In the Västerbotten register, those born during February to April were significantly more likely to have preferred hanging rather than poisoning or petrol gases, and conversely for those born during October to January. These associations with suicide methods were found for the total sample and for those without any history of psychiatric contacts, but not for those with psychiatric contacts.

Conclusions: Suicidal behaviour shows statistically significant variation according to the season of birth, most probably mediated by a variation in an independent trait of vulnerability to suicide based on neurodevelopmental parameters, particularly the serotonergic system. The suicidal process differs between those who seek psychiatric care compared to those who do not, reflecting differences in the diagnostic spectra and in the extent of mental illness.

Key words: season of birth, CSF monoamine metabolites, suicide method, borderline.

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In memory of
my beloved mother,
and my beloved teachers
Lars Erik Björkman and Andrejs Dunkels.

The history of discovery is full of arrivals
at unexpected destinations,
and arrivals at the right destination
by the wrong boat.

- *Arthur Koestler*

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LIST OF ORIGINAL PAPERS

This thesis is based on the following six papers, which will be referred to in the text by their Roman numerals.

- I Chotai J, Salander Renberg E & Jacobsson L (1999) Method of suicide in relation to some sociodemographic variables in northern Sweden. *Archives of Suicide Research*, in press.
- II Chotai J & Åsberg M (1999) Variations in CSF monoamine metabolites according to the season of birth. *Neuropsychobiology*, 39, 57 - 62.
- III Chotai J, Kullgren G & Åsberg M (1998) CSF monoamine metabolites in relation to the diagnostic interview for borderline patients (DIB). *Neuropsychobiology*, 38, 207 - 212.
- IV Chotai J, Salander Renberg E, Kullgren G & Åsberg M (1999) Season of birth variations in dimensions of functioning evaluated by the diagnostic interview for borderline patients. *Manuscript*.
- V Chotai J, Salander Renberg E & Jacobsson L (1999) Season of birth associated with the age and method of suicide. *Archives of Suicide Research*, in press.
- VI Chotai J, Salander Renberg E (1999) Season of birth variations in suicide methods with or without any history of psychiatric contacts. *Manuscript*.

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ABBREVIATIONS

ANOVA	analysis of variance
APA	American Psychiatric Association
BPD	borderline personality disorder
CSF	cerebrospinal fluid
DIB	diagnostic interview for borderline patients
Section I	social adaptation
Section II	impulse action patterns
Section III	affects
Section IV	psychosis
Section V	interpersonal relations
DSM	diagnostic and statistical manual of mental disorders (by APA)
DSM-III	the third edition of DSM, 1980
DSM-III-R	the third, revised, edition of DSM, 1987
5-HIAA	5-hydroxyindoleacetic acid (a serotonin metabolite)
HVA	homovanillic acid (a dopamine metabolite)
ICD	international statistical classification of diseases (by WHO)
ICD-8	the eighth edition of ICD, 1967
ICD-9	the ninth edition of ICD, 1977
MHPG	3-methoxy-4-hydroxyphenylglycol (a norepinephrine metabolite)
WHO	World Health Organization

BACKGROUND

Introduction

It has been known for many years that schizophrenia is associated with season of birth, showing an excess of births for winter-spring months and a deficit of births for autumn months in the Northern Hemisphere when compared to the general population. Some studies show season of birth associations for the corresponding winter-spring and autumn months in the Southern Hemisphere, although these are less striking (McGrath et al, 1995; Torrey et al, 1997; McGrath et al, 1999). Also, several studies have compared schizophrenic patients born during different seasons with each other without reference to the general population to try to identify etiologic subgroups or to relate season of birth with clinical features, family history, and obstetric complications (discussed below). Several other psychiatric and neurological disorders have also shown season of birth associations, although no general consistent unifying patterns have emerged (for reviews see Torrey et al, 1997; Castrogiovanni et al, 1998).

In this thesis, we show that season of birth plays a significant role also in suicidology. We do not make comparisons with the birth pattern in the general population, but rather compare different seasons of birth with each other, firstly in a register of completed suicides, and secondly in a sample of patients who took part in a psychobiological investigation. In the process, we also derive other results of interest in suicide research and in suicide prevention, which include the relationship between the methods of suicide and sociodemographic variables, differences in the suicide victims with or without any history of psychiatric contacts, and the relationship between season of birth, neurotransmitters, and areas of functioning involving impulsivity, affects, and psychosis.

Suicide and suicidal behaviour

Suicide constitutes a major health problem in many countries. In the 33 countries of Europe, totally about 150 000 persons commit suicide each year (World Health Organisation Database for 1995), and the corresponding figure for the USA is 30 000 (Mann, 1998; Mann, Oquendo et al, 1999).

Suicide rates vary considerably between countries, from 40 per 100 000 population in Hungary to 3.8 per 100 000 in Greece (World Health Organization, 1989). In almost all societies for which data are available, suicide rates are higher for males than females, they tend to increase with age, and are higher for single, divorced and widowed persons (Diekstra, 1993; La Vecchia et al, 1994).

The introduction of the concept of undetermined manner of death (codes E980 – E989) in ICD-8 has resulted in an underestimate in the reported number of determined suicides (codes E950 – E959) from 1969 by 5 – 10% in different countries (O’Carrol, 1989; Ohberg & Lönnqvist, 1998). Sweden has a relatively high proportion of those with undetermined suicides among the aggregate of determined and undetermined suicides (over 20%), and so the aggregated group is often employed in suicide research in Sweden (Kolmos, 1987; Beskow *et al*, 1993). In 1991, the suicide rates for Sweden per 100 000 population when considering only the determined cases, were 24.1 for males versus 10.1 for females, giving a sex-ratio of 2.4. If also the undetermined cases are included, this gives the rates as 32.5 for males versus 14.5 for females, yielding a sex-ratio of 2.2 (quoted from Ottosson, 1995). For the county of Västerbotten in northern Sweden studied in this thesis, the annual suicide rates per 100 000 pooling the determined and undetermined cases, on average for the 20 years 1972 – 1993, were approximately 18 in all, 14 for males, 4.5 for females, and a sex ratio of 3.0.

Suicidal behaviour spans a spectrum that ranges from completed suicide to suicide attempts and, at the mildest end, suicidal ideation. Different domains of risk factors studied in suicide and suicide attempts include social, psychiatric, psychological, and familial (for references see Mann, Waternaux et al, 1999).

Suicide attempts are more complex than completed suicides since they include a medical damage dimension as a consequence of the suicide attempt, and often a second dimension involving suicidal intent (Mann, 1998). The problem of attempted suicide (“deliberate self-harm”, “parasuicide”), includes any intentional act of self-poisoning or self-injury, irrespective of the intended outcome. Although a substantial proportion of such acts are motivated by significant degrees of suicidal intent, others are not and may include complex multiple motivation (Hawton, 1997; Linehan, 1997).

The risk of completed suicide following an episode of attempted suicide is likely to vary between different countries, but is estimated in the United

Kingdom as being 1% in the first year following the episode (a risk 100 times that of the general population) and approximately 3% in the eight years after an episode (Hawton & Fagg, 1988; Hawton, 1997). In other studies, the life-time risk of completed suicide by suicide attempters who are in contact with health-care services is estimated to be 10-15% (Cullberg et al, 1988; Maris, 1992). Conversely, in a study investigating the past history of the victims of completed suicides in Finland, Isometsä & Lönnqvist (1998) found that 56% of the suicide victims had died at their first suicide attempt (62% in males and 38% in females). At the population level, a multicentre study involving 13 European countries showed that there were positive correlations between rates of attempted suicide and suicide rates among young people in both sexes, which were statistically significant for males (Hawton, Arensman et al, 1998).

Some studies categorize the suicide methods into a "non-violent" group (for example drug overdose, poisoning) versus a "violent" group (usually the remaining) (Åsberg et al, 1976; Träskman et al, 1981; Mann & Malone, 1997), into "passive" versus "active", into "non-repeaters" versus "repeaters", or into "late repeaters" versus "early repeaters". Divisions into such groups are not always consistent among different authors, nor are the criteria and the reasons for grouping always well-defined.

Thus, the relationships between various aspects of suicide and suicidal behaviour are confounded by an interplay between the availability, acceptability, and lethality of different suicide methods. Different levels of analysis may be used to study this interplay.

One commonly used level is based on ecological data, where one studies the covariation of method-specific or overall suicide rates in relation to the availability of various methods of suicide, either in the same community over time or among different communities (Marzuk et al., 1992; Cantor & Baume, 1998; Hawton, Arensman et al, 1998). For example, an increasing availability of motor vehicles and drugs has been accompanied by a rise in the frequency of suicide by petrol gases (Cantor & Baume, 1998), and by drug poisoning (Gunnell et al., 1997; Hawton, Fagg et al., 1997).

Several studies indicate that reducing the availability of a suicide method often leads to a decrease in the overall suicide rate. Thus, the replacement of toxic coal gas by non-toxic natural gas in the households in the UK was followed by a significant reduction in overall suicide rates (Kreitman, 1976). Other examples include the decline in suicide rates following the reduction in

barbiturate prescriptions (Oliver & Hetzel, 1972; Whitlock, 1975; Carlsten et al., 1996), and reduced availability of firearms by a variety of firearm control laws (Hawton, Fagg et al., 1998; Lambert & Silva, 1998).

Other studies suggest that reducing the availability of a suicide method may lead to a partial substitution by other, more available, suicide methods in certain individuals, as implied by studies on suicide by firearms (Rich et al., 1990; Sloan et al., 1990; Beautrais et al., 1996; Kaplan & Geling, 1998).

Preference for a suicide method depends on its availability as well as on its acceptability. Thus, the abolition of judicial hanging in Britain in 1965 was followed by an increased acceptability of hanging as a suicide method (Pounder, 1993). More generally, acceptability reflects partly the sociocultural norms of a community, but it may also depend on the particular personality and sociodemographic circumstances of the individual. Isometsä & Lönnqvist (1998) report that 82% of the suicide victims with previous suicide attempts had used at least two different methods in their suicide attempts (the fatal included), indicating that method-switching is not an uncommon event. However, since the circumstances and the characteristics of suicide attempters are likely to be somewhat different from those with suicidal ideation or death wishes at the population level, the relevance of this result as regards the suicide preventive effects of reducing the availability of common suicide methods in the general population, is not straightforward.

Successful preventive strategies need to co-ordinate interventions, facilitate communication, and incorporate effective monitoring and evaluation programs (Gunnell & Frankel, 1994; Taylor et al., 1997). Both high-risk preventive strategies that identify groups that are at increased risk of suicide, as well as population strategies, are useful (Lewis et al, 1997). The greatest potential in suicide prevention seems to arise from the population strategy that limits the availability of methods commonly used for suicide (Gunnell & Frankel, 1994; Gunnell & Nowers, 1997; Lewis et al., 1997). Economic policies that reduce unemployment may also reduce the population suicide rate (Lewis et al, 1997).

In any case, development of more effective and successful suicide preventive strategies requires still more extensive information on the complex interplay between the availability, acceptability and lethality of suicide methods also at the individual level. Thus, besides the ecological approach, also other levels of analysis are used. One such approach includes population-based register data, where information is obtained on several relevant variables for

each individual from different records and registers. Complementing the register information is the information obtained by interviewing the relatives and other informants of the suicide victim.

A fruitful approach for studying suicidal behaviour is that of interviewing and treating those with suicide attempts, or suicidal behaviour in general (Hawton, 1997; Linehan, 1997). Furthermore, use of instruments that measure suicidal ideation and attitudes towards suicide, both in clinical patients (Ahrens & Linden, 1996), and in the general population (Salander Renberg, 1998), are likely to add considerably to our knowledge about suicidal behaviour.

Mental illness in suicide

In Sweden, about 2% of all deaths in men and about 1% of all deaths in women are due to suicide (Official Statistics of Sweden, 1996). About half of all suicide victims have been reported to have had a history of contacts with psychiatric health-care services, varying around 33 – 70% in different studies (Barraclough et al, 1974; Kraft & Babigian, 1976; Beskow, 1979; Sundqvist-Stensman, 1987; Runeson, 1989; Hyden, 1996; Ruschena et al, 1998). Although there is generally an overrepresentation of males in completed suicides (about 2 to 3 times), the male/female ratios for the suicide victims is still larger for those without a history of psychiatric contacts (ranging 2.9-3.2), as compared to those with such a history (ranging 1.3-2.6) (Kraft & Babigian, 1976; Sundqvist-Stensman, 1987; Ruschena et al, 1998). This is likely to be due to some combination between gender differences in the health-care seeking behaviour, gender differences in the diagnostic spectra of psychiatric disorders, and gender differences in the suicidal process.

Information regarding the occurrence and the extent of mental illness in suicide victims, particularly those without any psychiatric contacts, is often obtained by means of psychological autopsy studies (for review see Hawton, Appleby et al, 1998). A variety of sources of information are used in such studies. These include evidence presented at inquest, medical records, information from general practitioners and hospital clinicians, and relatives and friends. Besides assessment of psychiatric disorders and personality characteristics, some information on life events and particular problems faced by the suicide victim prior to death may also be obtained in these studies.

From psychological autopsy studies, including even those with separate analyses for different age and gender groups and urban-rural settings, we have learnt from several international studies that over 90% of suicide victims in general have a diagnosable psychiatric disorder at the time of death. However, most psychiatric patients do not commit suicide. Lifetime mortality due to suicide is approximately 15% in individuals suffering from recurrent depressive episodes, 20% in bipolar patients, 18% in alcoholics, 10% in schizophrenia, and 5-10% in certain types of personality disorders (Mann, 1998). However, Inskip et al (1998) recalculate these risks using contemporary data and modern techniques, and claim that the above quoted lifetime suicide risks are likely to be too high, and they obtain the lifetime risk at 6% for affective disorder, 7% for alcohol dependence and 4% schizophrenia through their models of calculation.

The psychiatric diagnoses in suicide victims comprise a variety of disorders, the main ones being depressive disorders (around 20-30% for males and 40-60% for females), alcohol dependence (around 30-40% for males and 10-18% for females), personality disorders (around 30% including comorbidity), schizophrenia (around 3-6%), as well as anxiety and adjustment disorders (Beskow, 1979; Åsgård, 1990; Henriksson et al, 1993).

The diagnostic spectrum of psychiatric disorders among those with a history of psychiatric contacts is likely to be different when compared to those without such a history, but there are very few studies that enable a reliable evaluation of this issue. Beskow (1979) reported that those with a history of psychiatric contacts had more of affective syndromes and schizophrenia, but less of "crisis reaction" as compared to those without. Similarly, Runeson (1989) and Runeson (1992) reported that those with a history of psychiatric contacts had more of major depression and schizophrenia, but less of adjustment disorders.

Also, the suicidal process as regards inclination, timing and the method of suicide, are likely to be different for those with a history of psychiatric contacts compared to those without. This may be due to a combination of factors like differences in the psychiatric diagnoses, the influence of psychiatric treatment intervention, and differences in personality characteristics including health-care seeking behaviour. Marttunen *et al* (1998) report that the process leading to suicide seems to be relatively short among the male adolescents without any diagnosable psychiatric disorder compared to those with. Runeson (1992) and Runeson *et al* (1996) report that the time interval from the first suicidal

communication to suicide completion in youths was substantially shorter for those with adjustment disorders, and these youths often had a history of recently broken relationships. Moreover, as noted by Palmer et al (1999), we do not know the risk of suicide during the extremely early phases of schizophrenia, such as before an individual receives a formal diagnosis of schizophrenia.

Borderline personality disorder

Research on personality disorders in terms of phenomenology, biological markers, treatment response, family history, and outcome, is steadily increasing. Researchers are faced with the dual task of validating the operational criteria used to diagnose personality disorders as well as validating the different instruments based on these criteria (Zimmerman, 1994). This creates difficulties when comparing different studies on personality disorders with one another.

Historically, the term "borderline" was originally used to diagnose patients who were conceived to be on the border between neurotic and psychotic conditions. Another usage of this term has been to characterize a "borderline personality structure" within the framework of psychodynamically oriented theories (Kernberg, 1967). A semistructured instrument developed in these efforts is the diagnostic instrument for borderline patients (DIB) by Gunderson et al. (1981), and employed in a modified manner (retrospectively from hospital records) in this thesis.

Borderline personality disorder (BPD) is the most intensely studied diagnosis of the "dramatic cluster" of the DSM-III-R axis II diagnoses (American Psychiatric Association, 1987). Central characteristics of this disorder include impulsivity and affective instability, leading to suicide attempts, rage, substance abuse, manipulative responses in relationships, or rapid shifts of emotions. The DSM-III-R axis II diagnosis is often considered as a reference with which the other instruments developed to diagnose borderline personality disorder are compared. Subsequently, various theoretical developments and treatment strategies anchored in the DSM-criteria have been put forward (for review see Beck et al., 1990; Zimmerman, 1994).

Monoamine neurotransmitters

The monoamine neurotransmitters serotonin, dopamine and norepinephrine in the central nervous system are believed to play a role in the etiology, clinical

course and prognosis of several neuropsychiatric disorders. Reduced norepinephrine and serotonin functions have been associated with depressive and anxiety disorders, and high dopamine function has been associated with schizophrenia, although in the light of subsequent developments, these explanations are nowadays considered to be oversimplifications.

Short-term and long-term regulations of monoamine turnover are known to be influenced by both environmental and genetic factors. It has been proposed that substantial changes in their activity could be induced by exposure to psychosocial stressors early in development (Kraemer, 1992; Post, 1992), and studies of nonhuman primates suggest that such changes may be related in part to certain characteristics of the early social rearing environment (Higley et al, 1991; Higley et al, 1993; Clarke et al, 1996).

Genetic influence on the monoamine turnover has been shown in various studies. This has been demonstrated by careful studies on nonhuman primates (Higley et al, 1993). In humans, various genes involved in the synthesis, function and metabolism of the monoamines are studied. Dopamine-related genes studied include the gene for tyrosine hydroxylase (involved in the first step of synthesis of dopamine from tyrosine) and genes for dopamine receptors (Jönsson et al, 1996). Serotonin-related genes studied include the gene for tryptophan hydroxylase (involved in the first step of synthesis of serotonin from L-tryptophan) (Nielsen et al, 1994; Mann, Malone et al, 1997; New et al, 1998), and the gene for serotonin transporter (a protein involved in the reuptake of serotonin from the synaptic cleft into the presynaptic neuron and considered to play a pivotal role in brain serotonin homeostasis; this transporter is also the initial target for several antidepressive drugs) (Lesch, 1998; Lesch & Mössner, 1998; Murphy et al, 1998). By means of targeted disruption of specific genes, genetic investigations are also used to study the adaptive changes occurring in the serotonergic transmission complex when, for example, the genes for the serotonin transporter are lacking in mice (knock-out mice) (Rioux et al, 1999). Similar genetic investigations are also used to study the adaptations in the dopaminergic neurotransmission system in mice lacking the genes for the dopamine transporter (Giros et al, 1996).

Serotonin is receiving an increasing amount of attention in the literature. Brain serotonin neurotransmission is heterogenous and complex in terms of both structure and function, with 15 known receptor types (Murphy et al, 1998). Serotonin has been shown to influence a broad range of physiological systems,

including behavioral functions, for example circadian rhythm, sleep-wake cycle, appetite, aggression, sexual behavior, pain sensitivity, and learning (Lucki, 1998). This diversity is considered to be due to serotonin's orchestrating role in the activity and interaction of several other neurotransmitter systems (Lesch & Mössner, 1998). Serotonin is also considered to be an important regulator of morphogenetic activities during early embryonic development, including cell proliferation, migration, and differentiation, since serotonin shows an early expression in the developing brain prior to synaptogenesis and onset of serotonergic signaling (Lesch & Mössner, 1998).

A large number of studies use the levels of the metabolites 5-HIAA, HVA and MHPG of the monoamines serotonin, dopamine and norepinephrine, respectively, in the cerebrospinal fluid (CSF) as indicators of the turnover of these monoamines (for review see, among others, Åsberg, 1997). The results obtained from analysing CSF monoamine metabolites are shown to be influenced by several circumstances, although the results on some of them are not consistent enough across the studies (for review see Jönsson et al, 1996). These circumstances include age, gender, height, back length, weight, season or atmospheric pressure at sampling, the subject's position (sitting or recumbent) while sampling, and the spinal level at which the sample is collected. Therefore, adjustment for these circumstances, when possible, need to be done in the analyses.

Although most studies with CSF have measured the metabolites of monoamines, some studies also measure the CSF levels of the transmitters serotonin, dopamine and norepinephrine themselves, and of their precursors tryptophan, tyrosine and phenylalanin (Eklundh et al, 1996; Sjöberg et al, 1998). This is interesting, since CSF is becoming increasingly appreciated as an important physiological channel for "volume transmission" (Zoli et al, 1998), which consists of three-dimensional diffusion of signals in the extracellular fluid for distances larger than the synaptic cleft. Although the exact role of the CSF in such extrasynaptic transmission has yet to be established and elucidated, the existence of volume transmission as such for both dopamine (Garris et al, 1994) and serotonin (Bunin & Wightman, 1998) have already been demonstrated.

Since collection of CSF samples is more cumbersome and invasive than that of peripheral blood samples, serotonin-related measures are also measured in the peripheral blood, in an attempt to associate them with central serotonin measures as well as with impulsivity, aggression, suicide and psychiatric

morbidity (Mann, McBride, Anderson et al, 1992; Mann, McBride, Brown et al, 1992; Moffitt et al, 1998; Pfeffer et al, 1998). These measures include platelet and whole blood serotonin, platelet serotonin transporters and receptors, and whole blood tryptophan.

As reviewed by Hsiao, Potter et al (1993), one of the best replicated findings in biological psychiatry is that monoamine metabolites in the CSF correlate with one another, which reflects complex interactions between the monoamine transmitters. A recent study using continuous CSF sampling over 6 hours found close, sustained positive covariability in concentrations of HVA and 5-HIAA in normal volunteers, suggesting that the balance between dopamine and serotonin is of physiologic importance in the human (Geraciotti et al, 1998). Several studies have presented evidence suggesting that interactions between dopamine and serotonin are of importance in schizophrenia and in its treatment by neuroleptics (Pickar et al, 1992; Hsiao, Colison et al, 1993; Hsiao, Potter, et al, 1993; Kahn et al, 1993; Risch, 1993; Kapur & Remington, 1996).

Some of the inconsistencies observed in various hypotheses generated by studies trying to elucidate the role of each of the monoamines, their receptors, the consequences of pharmacological interventions, and genetic and environmental influences, are expected to become better understood as more progress is made also in the understanding of postreceptor intracellular mechanisms. Stress-induced vulnerability and the therapeutic action of drug treatments are in part likely to occur through these intracellular mechanisms, by increasing or decreasing the neurotrophic factors necessary for the survival and function of particular neurons (Duman et al, 1997).

The neurobiology of suicide

As discussed above, most persons who commit suicide have a diagnosable psychiatric disorder at the time of death, but on the other hand most persons having a psychiatric disorder do not commit suicide. Therefore, some kind of vulnerability to suicidal behaviour independently of psychiatric morbidity is also believed to be present in those who commit suicide.

In fact, several developments suggest an existence of some sort of "suicidality trait" independently of major psychiatric disorders. Ahrens & Linden (1996) could delineate a suicidality syndrome containing hopelessness, ruminative thinking, social withdrawal, and lack of activity independently of the

psychiatric diagnosis, in a large sample of patients comprising schizophrenia and unselected depressive disorders. Also, liability to suicidal behaviour might be familiarly transmitted as a trait independently of psychiatric diagnoses (Brent et al, 1996; Johnson et al, 1998). Based on a twin study, Statham et al (1998) suggest that there may be significant familial variance in suicidality that is not accounted for by the measured psychiatric, personality and sociodemographic variables.

A stress-diathesis or trigger-threshold model of suicidal behaviour, based on considerable amount of work in suicidology, has been developed in the literature (Mann, 1998; Mann, Oquendo et al, 1999; Mann, Waternaux et al, 1999). The following summary of this model is based on the formulations in Mann, Oquendo et al (1999).

According to this model, risk factors are categorized in terms of belonging to one of the two domains of the trigger-threshold construction. The trigger domain comprises most of the clinical features that psychiatrists who evaluate suicidal patients focus on, such as acute psychiatric illness, substance abuse, adverse life events, or a family crisis. In the threshold domain, there are risk factors that receive less attention from psychiatrists, including genetics, personality disorders, and alcoholism. Furthermore, all these risk factors may be interrelated. For example, impulsivity (defined as the rapidity and probability of acting on powerful feelings), suicidal behaviour, and aggression have a well-recognized interrelationship. Within this framework, a patient must have at least one major risk factor from each domain to be at high risk for suicide. Thus, triggers for suicidal acts or aggression interact with the threshold in an individual and result in aggressive or suicidal behaviour.

A large body of studies indicate that the risk of suicide, in terms of a threshold, reflects a trait rather than a state (Mann, Oquendo et al, 1999). Considerable evidence suggests the serotonergic system as a major biochemical trait involved in the regulation of the threshold in suicide, impulsivity and aggression. Genetic factors, a deprived upbringing, low cholesterol, and substance abuse can all be associated with or induce lower serotonergic activity, which in its turn may result in greater impulsivity and aggression that also includes a self-directed aggression in the form of suicidal behaviour (Mann, 1998).

Many clinical studies in support of the above formulation have shown that patients with low CSF levels of 5-HIAA are associated with suicide attempts,

particularly high-lethality or serious suicide attempts, even after controlling for major psychiatric disorders and treatments. A similar relationship exists between CSF 5-HIAA and severity of lifetime aggression. Also, low CSF 5-HIAA levels as compared to high levels, have predicted a higher rate of completed suicides in patients discharged from hospital (Nordström et al, 1994). Åsberg (1997) reports an observation based on unpublished data, that suicide attempters in the study by Träskman et al (1981) who had low levels of CSF 5-HIAA, had planned their attempt during a shorter period of time compared to those with normal levels.

Genetic factors may effect suicide risk by contributing to the threshold for acting on suicidal thoughts, and this may be mediated by genetic modulation of the serotonergic activity (Mann, Malone et al, 1997). Women are at lower risk for suicide than men and have been reported to have higher levels of CSF 5-HIAA or serotonergic activity than men (Bucht et al, 1981; McBride et al, 1990). Furthermore, several postmortem studies give further support for the above model (Mann, Oquendo et al, 1999).

Season of birth in neuropsychiatric disorders

As touched upon in the introduction section above, it has been known for many years that schizophrenia is associated with season of birth, showing an excess of births for winter-spring months and a deficit of births for autumn months in the Northern Hemisphere when compared to the general population (Dalén, 1968; Hare, 1974; Bradbury & Miller, 1985; Torrey et al, 1997). Some studies show season of birth associations for the corresponding winter-spring and autumn months in the Southern Hemisphere, although these are less striking (McGrath et al, 1995; Torrey et al, 1997; McGrath et al, 1999). Several studies have compared schizophrenic patients born during different seasons with each other. Thus, besides a comparison with the birth rates in the general population, several studies investigate differences in the subgroups of schizophrenic patients according to the season of birth as regards clinical features, family history, obstetric complications, and urban-rural differences (Pulver *et al*, 1992; Dassa *et al*, 1996; Franzek & Beckmann, 1996; Verdoux *et al*, 1997; Dalman et al, 1999; Hultman et al, 1999; Mortensen et al, 1999).

Season of birth associations similar to those for schizophrenia have also been found for some affective disorders (Torrey *et al*, 1997; Castrogiovanni, 1998). Several other psychiatric and neurological disorders have also shown

season of birth associations, although no general consistent unifying patterns have emerged (for reviews see Torrey *et al*, 1997; Castrogiovanni *et al*, 1998). These include Alzheimer's disease (Philpot *et al*, 1989; Vezina *et al*, 1996), autism (Bolton *et al*, 1992; Mouridsen *et al*, 1994; Barak *et al*, 1995), Down's syndrome (Puri & Singh, 1995), dyslexia (Livingston *et al*, 1993), eating disorders (Resaul *et al*, 1996), multiple sclerosis (Templer *et al*, 1992), and epilepsy (Procopio *et al*, 1997; Procopio & Marriott, 1998).

A few earlier studies have investigated a possible relationship between the month of birth and suicides in the population. Ellsworth (1938) noted that the distribution of the birth months for those who committed suicide was different from those who did not, and Pokorny (1960) found an overrepresentation of suicide cases born in the month of July in a case-control study. However, three subsequent studies could not replicate any association between the month of birth and completed suicides (Lester, Reeve, & Priebe, 1970; Sanborn & Sanborn, 1974; Lester, 1987). A recent study, however, showed small variations in the season of birth for suicides among Alaska Natives, with summer births showing more suicides (Kettl *et al.*, 1997).

As regards suicide in relation to birth conditions, Salk *et al* (1985) found that compared to controls, those committing suicide in young adulthood had a significantly higher frequency of maternal, antenatal and perinatal complications, a result that could not be replicated by Neugebauer & Reuss (1998). These two papers did not investigate any possible relationships between conditions around birth and the types of suicide methods. Jacobson *et al* (1987) reported an association between the type of birth trauma and the subsequent method of suicide in adulthood. Jacobson & Bygdeman (1998) conducted a case-control study and found a significant association between traumatic birth and "violent" suicide as adults. Appleby (1998) suggests that the link between conditions around birth and violent suicide is more likely to occur through mental illness rather than by an imprinting hypothesis proposed by Jacobson *et al* (1987) and Jacobson & Bygdeman (1998).

AIMS OF THE THESIS

- To conduct a multivariate study on a register of completed suicides, investigating the methods of suicide in relation to sociodemographic variables including season of birth, gender, age, place of residence, marital status, year of suicide, and season of suicide.
- To study the season of birth variations in the cerebrospinal fluid levels of the metabolites of the monoamines serotonin, dopamine, and norepinephrine, the first two of which are known to be related to suicidal behaviour.
- To investigate the relationship between the five section scores of the diagnostic interview for borderline patients (DIB) and the cerebrospinal fluid levels of the monoamine metabolites, and to study the season of birth variations in the DIB.
- For the birth seasons showing a variation in the CSF levels of the monoamine metabolites, to investigate the season of birth variations in the age at suicide and the method of suicide used in the register of completed suicides.
- To investigate further the mechanisms behind the season of birth variations in suicidal behaviour by studying these in relation to mental illness and to any history of psychiatric contacts, in the register of completed suicides.

MATERIAL AND METHODS

Register of completed suicides in Västerbotten

As a part of the ongoing efforts to study the epidemiology of suicide and develop suicide preventive strategies in the county of Västerbotten in northern Sweden, information has been collected from the Cause of Death Registrar, Statistics Sweden, for all suicides from 1952 onwards. The information includes the method of suicide, gender, age, place of residence, marital status, the date of suicide, and the date of birth. Some studies based on these data have been reported in different phases (Jacobsson & Renberg, 1986; Salander Renberg & Jacobsson, 1999).

Västerbotten as a whole is a sparsely populated region with about 260 000 inhabitants and an area of about 55 500 km². It offers different kinds of human milieus and life-styles - mountainous areas, forestal areas with the traditional farming occupation, a few technically developed industries in the forestry and mining sectors, the growing university town of Umeå, and some other small towns. The region has experienced emigration from the inner rural areas to the coastal urban area (particularly Umeå), as well as to the south of Sweden. Also, immigration into the region from the south has occurred for persons (and their families) with academic and health care professions, and those with particular skills in the technical and industrial fields.

Västerbotten had traditionally low suicide rates compared to the national suicide rates of Sweden. Whereas suicide rates in Sweden have been decreasing steadily during the last decades, the rates of suicide in Västerbotten increased in the 1970s and the 1980s so that an equalizing trend towards the national rates has occurred (Jacobsson & Renberg, 1986; Salander Renberg & Jacobsson, 1999).

The studies of Paper I and Paper V employ the above suicide register for the period 1952 – 1993 (1466 cases). The study of Paper VI employs the period 1961 – 1980 (693 cases), for which all the in-patient and out-patient psychiatric registers and archives in the county were also examined to find out whether the suicide victims had ever been in any contact with (in-patient or out-patient) psychiatric care, and the psychiatric diagnosis they had obtained in that case.

With the arrival of ICD-8, the registration system was changed in 1969 to include also “undetermined manner of death” (E980 – E989). Therefore, 223

(20%) of the 1102 cases pertaining to the period 1969 – 1993, and 96 (19%) of the 496 cases pertaining to the period 1969 – 1980, thus constitute undetermined suicides, the remaining being determined suicides (E950 – E959).

CSF monoamine metabolites in clinical sample in Stockholm

Patients

The patients in the studies of Paper II, Paper III, partly of Paper IV, were obtained from those who had participated in different psychobiological research programs on mood disorders during 1973 to 1987 of the Psychiatry Department of the Karolinska Institute in Stockholm. One requirement for admission was that there should be no evidence of physical illness, schizophrenia, organic brain syndrome, or substance abuse. Another requirement was that the patients had not received adequate antidepressant or neuroleptic treatment prior to admission (small or occasional doses were allowed, provided there were no clinical contraindications to a wash-out period).

The DSM-III-R criteria (American Psychiatric Association, 1987) had not been published when these research programs were initiated, but these criteria were used retrospectively on the basis of psychiatric records, inventories, and clinical ratings.

The total number of patients available comprised 261 subjects. Most of the analyses of Paper II concern 241 of these, who had the diagnoses of mood, anxiety, and adjustment disorders, the remaining diagnoses being excluded to reduce the problem of diagnostic heterogeneity. The inclusion criteria for the study of Paper III, where also evaluations according to the DIB retrospectively from hospital records were made, are described in the section on DIB below.

Lumbar puncture

Informed consent was obtained from all patients prior to lumbar puncture. The lumbar puncture was preceded by a wash-out period of varying duration, with a minimum of 4 days (usually longer) (Åsberg et al., 1984). During this period no psychotropic drugs were given, with the exception of benzodiazepines for sedation when needed. Lumbar punctures were performed in a standardized manner at the LIV-LV level. The CSF was collected in the early morning between 8 and 9 a.m., before the patients had risen and after at least 8 hours of fasting and strict bed rest since midnight. With the patient in the sitting position,

the first 12 ml of CSF were collected as a pool with a fine, disposable needle. After centrifugation, the samples were immediately frozen in aliquots in silanized glass tubes and stored at -20°C until analysed. Except for occasional headache, there were no complications from the lumbar punctures.

Determinations of monoamine metabolites

The CSF monoamine metabolites HVA, 5-HIAA, and MHPG were assayed by using mass fragmentographic methods developed by Bertilsson (1981). All CSF samples were analysed with the same technique and by the same laboratory at the Department of Clinical Pharmacology at Huddinge Hospital. The CSF metabolite concentrations are given as nanomoles per liter (nM: for 5-HIAA, $1\text{ng/mL} = 5.23\text{ nM}$; for HVA, $1\text{ ng/mL} = 5.49\text{ nM}$; and for MHPG, $1\text{ ng/mL} = 5.43\text{ nM}$).

In the melancholic patients, the MHPG levels determined from the introduction of the method in 1973 until April 1975 were much higher and had a larger standard deviation (mean 76.4, SD 23.7 mmol/l). The concentrations of 5-HIAA and HVA do not show any such tendencies to shift over the years. Since the same patient selection criteria were used during the period, this difference for MHPG is probably due to an error of unknown origin in the analytical method. All MHPG values determined before mid 1975 have therefore been discarded. Thus, the total number of individuals in the statistical analyses where MHPG is involved is smaller than in the remaining analyses.

Diagnostic interview for borderline patients (DIB)

The DIB is a semistructured interview developed by Gunderson, Kolb and Austin (1981), containing totally 29 items, as follows. Each item evaluates the presence of specific symptoms or behavior and obtains an item score of either 0 (no), 1 (probable), or 2 (yes). Two specified items have been given the possibility to obtain an item score of 4 if the symptoms/behavior are substantial. Based on theoretical and empirical considerations, the items are grouped into five areas of functioning: Section I (4 items) for social adaptation, Section II (5 items) for impulse action patterns, Section III (5 items) for affects, Section IV (8 items) for psychosis, and Section V (7 items) for interpersonal relations. For each section, two cut-off points are applied to the sum of its item scores to obtain a section score of 0 (low), 1 (intermediate), or 2 (high). The section

scores are then summed numerically to obtain the total DIB score (0 to 10). Individuals having a total DIB score of 7 or more are diagnosed as having a borderline personality disorder.

Although the DIB is constructed for a semistructured interview, it is applicable to scoring from hospital records retrospectively with minor modifications limited mainly to the time frame, using a more extensive frame when scoring from records. This possibility was suggested by Gunderson (1982) based on then unpublished studies. Using the DIB retrospectively on hospital records, McGlashan (1983) found a high degree of concordance between the retrospective DIB and the borderline criteria of DSM-III. To compare the scores obtained from the actual interview of the DIB with those obtained by retrospective ratings from hospital records, Armelius et al (1985) conducted a study where two trained, experienced clinical psychologists and two nontrained students rated the sections of the DIB from hospital records of 16 patients. The total DIB scores thus obtained had high correlations (around 0.80 for the trained judges and around 0.55 for the nontrained judges) with those obtained by the actual DIB interview.

In Paper III and Paper IV, we scored the DIB retrospectively from hospital records as discussed above. From earlier experience on using hospital records in DIB, it was decided to include subjects who were at most 60 years old. Also, subjects who had insufficient information in the hospital records or had organic mental disorders, were excluded.

Thus, from the 261 subjects in the Stockholm data, we excluded 22 cases over 60 years, 1 case with organic mental disorder, and 36 cases with insufficient information in the hospital records, yielding totally 202 cases for the study of Paper III.

The above selection criteria were also applied to all those who had committed suicide in Västerbotten during the period 1961 – 1980 either during in-patient or out-patient care in psychiatry, or within one year after the last contact with psychiatric care. This selected a group of 130 subjects, which partly includes those of Kullgren et al. (1986). For the study of Paper IV, data on both the groups of subjects, 202 from Stockholm and 130 from Västerbotten, were analysed, thus containing totally 332 persons in this sample.

Statistical methods

For all the statistical analyses, we employed the statistical software package SPSS (SPSS Base System, 1996). All the statistical tests of significance were two tailed.

Nonparametric methods were preferred. Thus, comparisons between pairs of groups were made by the Mann-Whitney U test (Wilcoxon), and comparisons among three or more groups were made by the Kruskal-Wallis one-way ANOVA. When adjustments for covariates were required in the comparisons, the nonparametric analyses were complemented by multivariate parametric ANOVA models. Correlations were evaluated by the nonparametric Spearman correlation coefficients. Correlations when controlling for covariates were evaluated by standard parametric partial correlation coefficients.

A statistical approach that was employed repeatedly in the thesis (Papers I, IV, V, and VI), is that of logistic regression (Kahn, 1983; Hosmer & Lemeshow, 1989; Kleinbaum, 1994; SPSS Base System, 1996). Logistic regression is a statistically powerful multivariate approach to discriminate between two nominal categories or groups with regards to a set of pertinent variables (called covariates).

For example, in Paper V we were interested in comparing the birth season February-April with the remaining year in relation to the covariates method of suicide, gender, age at suicide, place of residence, etc., in the register of all completed suicides during a specified period. For a covariate that consists of a set of categories (for example, method consists of the six categories hanging, poisoning, firearms, petrol gases, drowning, and remaining.), one category serves as a reference and each of the other categories of that covariate is compared to this reference by evaluating the odds ratio for that category. The reference category obtains an odds ratio of 1.00. As an example, if hanging is chosen as the reference category, then it obtains an odds ratio of 1.00. If poisoning obtains an odds ratio of 0.66, then the interpretation is that persons committing suicide using poisoning are 0.66 times less likely than those using hanging, to have the birth season February-April rather than the rest of the year. For an odds ratio greater than 1.00, for example 1.50, we would say "1.50 times more likely than hanging". The p-value of the statistical test attached to the odds ratio refers to testing whether this odds ratio is significantly different from 1.00. The calculation and interpretation of odds ratio just described consists of a

coding system for the covariates that is called the "indicator coding system", and this is employed in Papers IV, V, and VI.

In the logistic regressions of Paper I, however, we employ a coding system for the covariates that is known as the "deviation from means coding system". Here, the value of the calculated odds ratio for a category is not directly related to any reference category, but it is rather compared to the overall or average effect of all the categories. If the category 'poisoning' of the covariate called 'method of suicide' obtains an odds ratio of 0.72 in the comparison of the birth season May-August with the birth season January-April, then persons committing suicide with poisoning are 0.72 times less likely than an overall effect of all the suicide methods to have the birth season May-August.

RESULTS AND COMMENTS

Suicide methods and sociodemographic variables (Paper I)

In this epidemiological study with the register of all completed suicides during 1952-1993 in Västerbotten, it was discovered for the first time that suicide methods were associated with the season of birth. Table 1 summarizes the results of multivariate statistical analyses (logistic regressions) relating the methods of suicide with gender, age at suicide, place of residence, marital status, year of suicide, season of suicide, and season of birth.

In the literature, suicide methods are often classified into a non-violent group comprising poisoning and petrol gases and a violent group comprising the other methods like hanging, firearms, drowning, jumping and cutting (Åsberg et al, 1976; Träskman et al, 1981; Mann & Malone, 1997). In some studies, they are classified into an active group and a passive group. Such classifications are not always defined in the same way in the studies. In our study, examination of table 1 does not reveal any obvious grouping of the methods which would be valid across the sociodemographic variables.

On the whole, we found clear associations between the preferred method of suicide and its availability. We also found that preference for particular methods, which in part reflects their degree of acceptability, vary according to the individual's sociodemographic and temporal circumstances. We further found some evidence pointing towards compensatory changes in the remaining methods when the availability of one method is changed, at least in some sociodemographic strata.

Table 1: Methods of suicide in relation to sociodemographic variables obtained by multiple logistic regressions in the register of all completed suicides 1952 – 1993.

	<u><i>Preferred significantly more by left category</i></u>	<u><i>No significant difference</i></u>	<u><i>Preferred significantly more by right category</i></u>	
Female	Drowning Poisoning	Hanging	Firearms Petrol gases	Male
Age under 45 years	Petrol gases	Hanging Poisoning Firearms	Drowning	Age 45 and over
Residence urban	Poisoning Drowning Petrol gases	Hanging	Firearms	Residence rural
Non- married	Drowning Poisoning	Firearms	Petrol gases Hanging	Married
In recent years	Petrol gases Poisoning	Drowning	Firearms Hanging	In the past
Suicide around summer	Drowning	Hanging Poisoning Firearms Petrol gases		Suicide remaining year
Birth season Sep-Dec	Poisoning Petrol gases	Firearms Drowning	Hanging	Birth season Jan-Apr

Season of birth in CSF monoamine metabolites (Paper II)

This study demonstrates, for the first time, that CSF monoamine metabolites show a statistically significant variation according to the season of birth. Figure 1 gives the variation of the metabolites according to the month of birth for the sample of patients with mood, anxiety and adjustment disorders.

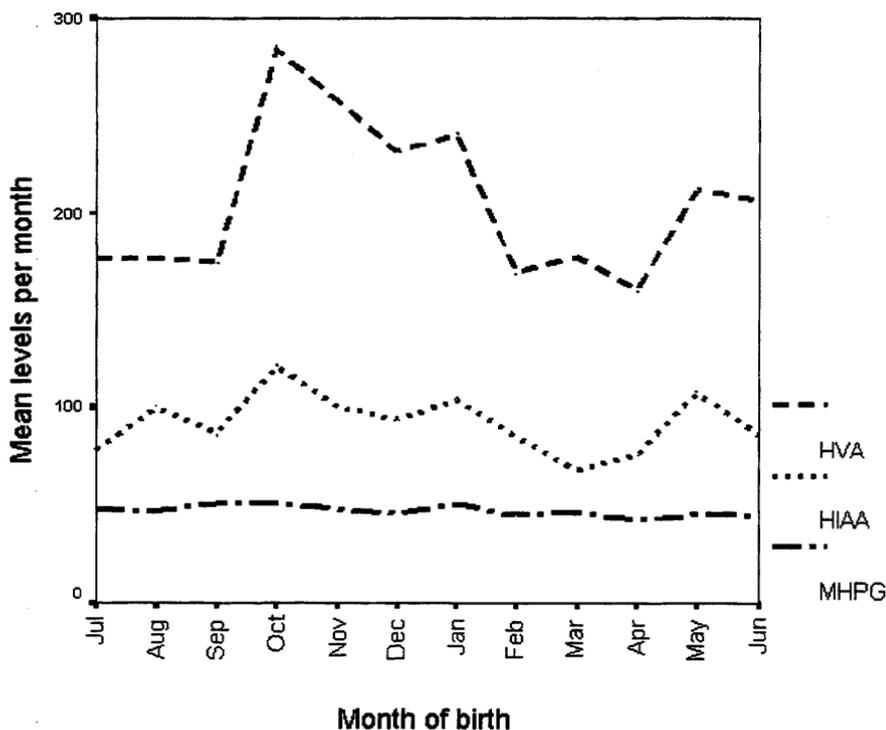


Figure 1. Mean levels of CSF monoamine metabolites (nmol/l) according to the month of birth for 241 patients with mood, anxiety and adjustment disorders.

The statistical evaluation was done by stratifying the year into three 4-month seasons of birth beginning February in a first analysis, and into four 3-month seasons of birth beginning February in a second analysis. Statistical adjustments were made for gender, age, height, the diagnostic category, and the month of lumbar puncture. Significant season of birth variations were found in HVA, HVA/5-HIAA and HVA/MHPG, with high values of these for the birth

season October to January. We further found a significant season of birth variation in 5-HIAA, with low values for the birth season February to April and a tendency for high values for the birth period covering October to January. Season of birth variations were also found in correlations between the monoamine metabolites.

The DIB versus CSF monoamine metabolites (Paper III)

Of the five section scores of the DIB, only section II (impulse action patterns) showed an association with the CSF monoamine metabolites in a group of 202 patients containing 92% with mood, anxiety and adjustment disorders, and 8% with other diagnoses (Paper III). The group with an intermediate value 1 of this section score, depicting a tendency for impulsivity without being predominantly so, had significantly higher levels of 5-HIAA, HVA, HVA/MHPG, and 5-HIAA/MHPG than the groups with values 0 or 2, even after controlling statistically for sex, age, height and presence of mood disorder. In fact, these levels for score value 1 were higher than in any other subgroup obtained by stratifying the whole material according to any other pertinent variables like sex, age, height, presence of mood disorder, or the total DIB score.

Otherwise, we did not find any significant differences in the CSF levels of the monoamine metabolites and their ratios when comparing those with borderline personality disorder diagnosed by a high value of the total DIB score (cutoff values 7 or 6, respectively) with the remaining. These results are in line with those in the literature indicating that biological markers may be associated with certain aspects of the borderline personality disorder rather than the disorder as a whole (Lahmeyer et al, 1988; Gardner et al, 1990; Ogiso et al, 1993; Hollander et al, 1994).

The DIB versus season of birth (Paper IV)

In the pooled data, those with the intermediate score of section II (impulse action patterns) were significantly more likely to have been born during the birth season October to January, and those with the high score of section IV (psychosis) were significantly more likely born during the birth season February to April. Separate analyses for the two samples, and for the two diagnostic groups mood disorders and schizophrenia, gave associations in the same direction for section II (impulse action patterns). For the birth season February

to April, those with schizophrenia had significantly high scores on section III (affects), and those in the non-schizophrenic group had significantly high scores on section IV (psychosis). Those with mood disorders had furthermore high section III (affects) scores for the birth season October to January. These results are compared with earlier results on interrelationships between season of birth, CSF monoamine metabolites, and suicidal behaviour.

Season of birth in method of suicide and age at suicide (Paper V)

Those with suicide age under 45 years were more likely than older suicides to have been born during February to April, significantly so compared to October to January. This was more pronounced for the later birth-year cohort (born in 1931 or later). Those who preferred hanging rather than poisoning or petrol gases were significantly more likely born during February to April. Those who preferred poisoning rather than hanging were significantly more likely born during October to January, particularly for the later birth-year cohort. The results regarding suicide method were somewhat more pronounced for males. The results of the study are compatible with a hypothesis of season of birth variation in CSF monoamine metabolites. Figures 2a, 2b and 2c below show the percentages for all, for males, and for females, respectively, for suicide by hanging in one curve and the by the pooled category of poisoning and petrol gases in the other curve, in relation to the month of birth. These complement the results of Figure 1.

Figure 2a (Both genders combined):

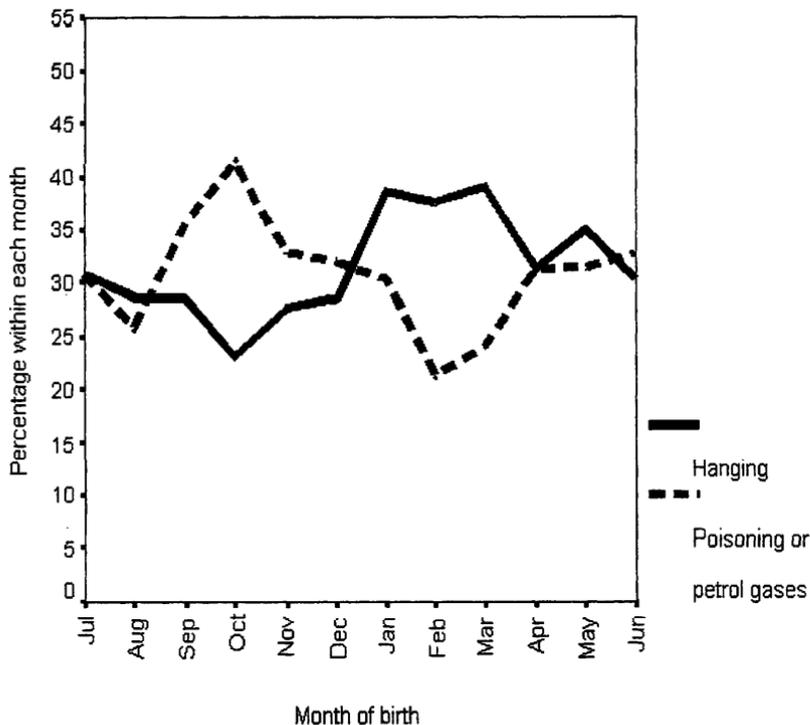


Figure 2b (Males):

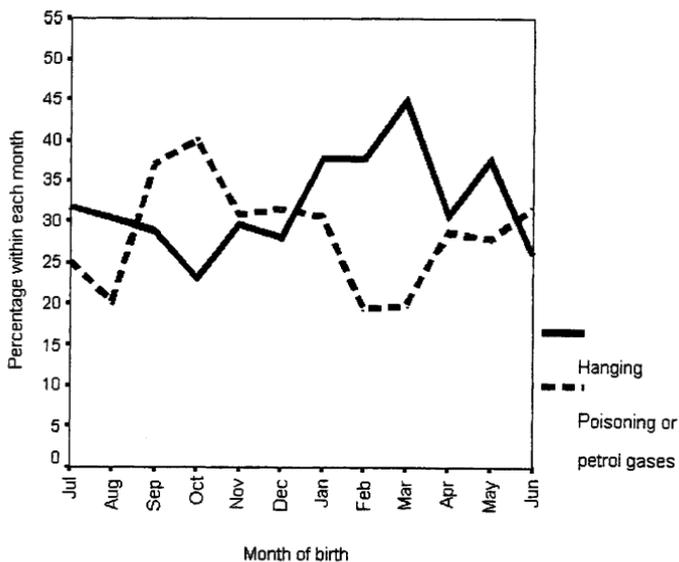
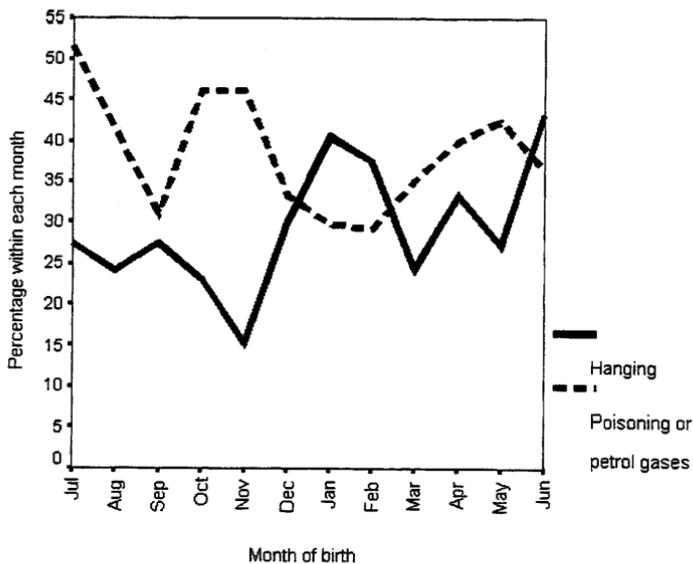


Figure 2c (Females):



Psychiatric contacts, suicide methods, and season of birth (Paper VI)

Age did not show any season of birth variation in this register for a shorter period of 20 years (included among the 42 years of Paper V). Suicide victims without a psychiatric history, but not those with a psychiatric history, showed similar season of birth variations for suicide methods as found earlier. Those born during February – April were significantly more likely, and those born during October – January significantly less likely, to have preferred hanging rather than poisoning or petrol gases. These associations were stronger for the determined cases, for males, and for urban residence. The group with a psychiatric history were significantly younger at suicide and contained significantly more births during February – April, largely due to the schizophrenia cases. Thus, season of birth association in suicidal behaviour is found for those with clinically less severe forms of psychiatric disorder rather than with serious mental illness. This may be mediated by a variation in vulnerability to suicide based on the serotonergic system, independently of major psychiatric disorders.

GENERAL DISCUSSION

In the exploratory analysis of completed suicides of Paper I, we had categorized the year into three birth seasons, and found that those born during the first birth season (January-April) were significantly more likely to have chosen the suicide method hanging rather than poisoning or petrol gases. We found the opposite relationship for the third birth season (September-December).

In an independent clinical study with data from Stockholm of Paper II, we chose to analyse the season of birth variations in CSF monoamine metabolites by selecting the divisions into birth seasons that were most likely to detect the variation with respect to the curve for the mean monthly values. We therefore chose three equal birth seasons beginning February in one analysis, and four equal birth seasons beginning February in a second analysis. This gave us the birth season February-April from the first analysis showing significantly low 5-HIAA levels, and the birth season October-January from the second analysis showing significantly high values of HVA (and nonsignificantly high 5-HIAA) and metabolite ratios.

From this point onwards, we focussed the analysis regarding the season of birth by considering only the two main birth seasons obtained above, namely February-April and October-January. We did this to reduce the problem of obtaining spurious season of birth associations, the risk for which would have been greater if we in each application had scrutinized the months of birth in order to get the most significant divisions of birth seasons. In Paper V we found a significant season of birth association even with the age at suicide, although this was not striking and could not be replicated in the smaller subsample of Paper VI.

Thus, in future attempts to replicate our results, one should not strictly adhere to exactly the birth seasons considered by us. Some studies on season of birth association for schizophrenia have found that the peak month of excess or deficit compared to controls, shifted between different decades (or other periods) of birth (Torrey et al, 1997). Also, some shifting between countries is expected to be found.

Parallel to the above results, we found that the *intermediate* score 1 of section II (impulse action patterns) of the DIB showed a significant association with high monoamine metabolite values (Paper III), as well as with the birth

season October-January. The latter result was obtained in two independent samples, a clinical sample from Stockholm and a sample containing completed suicides in Västerbotten (Paper IV). Although an interpretation of these results is not straightforward, we believe that they point towards a potential protective role of higher than normal levels of 5-HIAA (or perhaps HVA). In terms of the trigger-threshold (or stress-diathesis) model discussed in "Background" above, we believe that these results suggest that higher than normal levels of the serotonergic activity yield higher than normal thresholds, thus attenuating the suicidal behaviour generated by powerful triggers.

Further support for this hypothesis may be obtained by scrutinizing the CSF 5-HIAA levels in published papers. Gardner et al (1990) report higher concentrations of CSF 5-HIAA in the subgroup of borderline personality disorder patients with no serious suicide attempts as compared to both normal controls and those with serious suicide attempts. Virkkunen et al (1994) report higher mean CSF concentrations of 5-HIAA and HVA in nonimpulsive offenders as compared to both healthy volunteers and those with antisocial personality disorder or intermittent explosive disorder. Mann & Malone (1997) report that higher levels of CSF 5-HIAA were associated with a history of suicide attempts resulting in less medical damage, and they suggest that this observation is consistent with a potential protective effect of higher levels of CSF 5-HIAA. However, since they do not report levels on relevant controls, we do not know if they obtained higher levels only in comparison within the two subgroups or also in comparison with controls.

In the study on the DIB in Paper IV, we also found that for those born during February-April, schizophrenic patients had high scores of section III (affects) and non-schizophrenic patients had high scores of section IV (psychosis). A possible interpretation of this result is that this birth season, combined with psychiatric morbidity, is likely to elevate both affects and psychosis sections, but that this elevation becomes obvious when the basic level of the psychiatric morbidity involved is not excessively high in the corresponding section. In terms of the model of a psychopathological continuum with schizophrenia at one end and affective psychosis at the other, this interpretation implies an addition of features also from the other end of the spectrum for this birth season.

An interesting link between affective and psychotic disorders through obstetric complications was reported by Marcelis et al (1998). They found, in

comparing patients having psychotic symptoms with controls, that familial morbid risk of psychotic disorders was not associated with the individual's exposure to obstetric complications, but on the other hand familial morbid risk of affective disorders was. They suggest that the factors that contribute to familial aggregation of affective symptoms in psychotic patients also influence the likelihood to experience obstetric complications, so that part of the relationship between family history of affective disorder and psychosis in the individual may be mediated by obstetric complications.

An association of suicidal behaviour with season of birth is, to a large extent, a reflection of its association with conditions related to pregnancy and delivery (if we disregard the "procreational habits hypothesis" depending on seasonal conception proclivities, see Torrey et al, 1997). A reasonable thought linking birth conditions with suicidal behaviour, which has also appeared in the literature (Appleby, 1998), would be to link it through mental illness, since an association between birth conditions and mental illness (particularly schizophrenia) has been reported in several studies. However, we found in Paper VI that the season of birth association with suicidal behaviour in completed suicides was not seen in those with a history of psychiatric contacts, but seen in those without. This suggests, to the extent that we may extrapolate the association with season of birth to association with pregnancy and birth conditions, that this association is likely to exist at least in part independently of major mental disorders. Further support in favour of this suggestion is given by the season of birth variations in monoamine metabolites found in Paper II.

As regards research in neurobiology, the results of our thesis on the whole point towards a greater need to put emphasis on the neurodevelopmental aspects concerning the monoamine neurotransmitter systems, particularly serotonin. The role of neurodevelopment and neurodevelopmental impairment in psychiatric disorders is increasingly recognised (Van Os et al, 1997; Green, 1998). The neurodevelopmental aspects of the monoamine neurotransmitters are likely to contribute further to an understanding of the season of birth associations found in neuropsychiatric disorders.

Also, it is important to bear in mind that the ongoing research in the broad field of neurobiology is yielding information and insight on the role of neurotransmitters not only from the perspective of pathogenesis, but also from the perspective of salutogenesis.

CONCLUSIONS

- Several significant differences in preference for suicide methods were found among the various categories of the variables gender, age, place of residence, marital status and year of suicide. In particular, those born around winter-spring (January-April) were significantly more likely to have chosen the suicide method hanging rather than poisoning or petrol gases, whereas those born around autumn (September-December) were significantly more likely to have chosen poisoning or petrol gases rather than hanging.
- For the clinical subjects from Stockholm with mood, anxiety and adjustment disorders, those born during February to April had significantly lower levels of 5-HIAA, whereas those born during October to January had significantly higher levels of HVA, HVA/5-HIAA, and HVA/MHPG, and there was a tendency for these to have higher levels of 5-HIAA.
- Those with an intermediate score of section II (impulse action patterns) (depicting only a tendency for impulsivity) of the DIB, had significantly higher levels of 5-HIAA, HVA, HVA/MHPG and 5-HIAA/MHPG, and they were significantly more often born during October-January. Those born during February-April had significantly high affects scores if they had schizophrenia, and significantly high psychosis scores if they were non-schizophrenic. This is interpreted as that they have an addition of features from the other end of the spectrum of the psychopathological continuum with schizophrenia at one end and affective disorders at the other end.
- For the birth season February-April that had shown low levels of 5-HIAA in Stockholm, we found preference for hanging rather than poisoning or petrol gases in the register of completed suicides in Västerbotten. On the other hand, for the birth season October-January that had shown high levels, we found preference for poisoning or petrol gases rather than hanging.
- Season of birth association in suicidal behaviour is found for those with clinically less severe forms of psychiatric disorder rather than those with serious mental illness. This may be mediated by a variation in vulnerability to suicide based on the serotonergic system, independently of major psychiatric disorders.

Chotai J (1999). Självmordsbeteende i relation till födelseårstiden: neurobiologiska och epidemiologiska studier (Season of birth in suicidology: neurobiological and epidemiological studies). Doktorsavhandling. Sektionen för psykiatri, Institutionen för klinisk vetenskap, Umeå universitet, 901 85 Umeå.

Inledning

Avhandlingen är en sammanläggningsavhandling som består av sex arbeten och en ramberättelse.

Sedan många år är det känt att patienter med schizofreni uppvisar en association med födelseårstiden ("season of birth", födelsesäsong), så att för gruppen av personer som har schizofreni, finns ett 5-8% överskott på vår-vinter månaderna vad gäller födelseårstiden, och ett underskott på höstmånaderna, jämfört med normalbefolkningen. För södra hemisfären har man funnit motsvarande samband för södra hemisfärens årstider, även om dessa är mindre påfallande (McGrath et al, 1995; McGrath et al, 1999). Vidare finns det ett flertal rapporter om en association med födelseårstiden även för andra psykiatriska och neurologiska åkommor, exempelvis bipolär (manodepressiv) sjukdom, autism, Alzheimers sjukdom, ätstörningar och epilepsi, för att nämna några, men dessa studier har inte gett samstämmiga resultat. Flera hypoteser finns för att förklara associationer med födelseårstiden, men inga har visat sig vara tillräckligt allmängiltiga vid upprepningsförsök. Dessa omfattar hypoteser om subtila graviditets och obstetriska komplikationer och infektioner, ljusets betydelse, variationer i nutrition, meteorologiska förhållanden, och variationer i genetiska faktorer. Sannolikt är det så att flera av dessa faktorer samverkar, och dessa är verksamma på olika sätt i olika miljöer och under olika omständigheter (Torrey et al, 1997; Castrogiovanni et al, 1998).

Avhandlingen utgör ett bidrag till självmordsforskning. En särskild tonvikt läggs på att studera associationer med födelseårstiden, dels vad gäller självmordsbeteenden (ålder vid självmord och självmordsmetoden), och dels vad gäller variabler och aspekter som är kända för att vara relevanta i självmordsforskning. I avhandlingen studeras problemkomplexet både från ett

neurobiologiskt perspektiv och från ett epidemiologiskt perspektiv. Vi visar för första gången att de födda under olika årstider visar olikheter vad gäller även självmordsbeteenden och besläktade variabler.

Ett område som undersöks här och som är relevant vid självmord, är nivåerna av metaboliterna (5-HIAA, HVA respektive MHPG) till monoaminerna serotonin, dopamin och noradrenalin i hjärnans cerebrospinal vätska. Dessa monoaminer utgör viktiga signalsubstanser (neurotransmittorer) som har visat sig ha en särskild betydelse inom psykiatin. Traditionellt har ett överskott på dopamin varit kopplat till schizofreni, medan ett underskott eller dåligt nyttjande av serotonin och noradrenalin varit kopplade till depression. Serotonin anses vara involverad i ett flertal viktiga kroppsfunktioner såsom sömn-vakenhet, aptit, aggression, sexuella funktioner, smärta, inläring, och andra funktioner (Lucki, 1998). Uppbyggnaden av det serotoninerga systemet har visat sig vara mycket komplext med ett 15-tal olika serotoninreceptorer, och kan delas upp i flera delsystem (Murphy et al, 1998). Ett växande antal studier har visat ett samband mellan en låg omsättning av det serotoninerga systemet och impulsivitet, aggressivitet och självmord (Mann & Malone, 1997; Åsberg, 1997; Mann, 1998).

Man har dock blivit alltmer medveten om dels att det föreligger ett invecklat samspel mellan dessa monoaminer (och troligen med även andra neurotransmittorer), och dels att omsättningen av dessa monoaminer hela tiden påverkas av individens samspel med den rådande miljön, även om genetiska faktorer spelar en viktig roll för monoaminernas omsättning (Higley et al, 1991; Higley et al, 1993; Hsiao et al, 1993; Clarke et al, 1996; Jönsson et al, 1996).

Ett annat område av betydelse inom självmordsforskning och som studeras i avhandlingen är kring den psykiatriska diagnosen 'borderline personlighetsstörning'. Idag är denna diagnos välkänd inom ramen för det diagnostiska DSM-systemet. Utmärkande drag hos patienter med denna diagnos innefattar impulsivitet och känslomässig instabilitet som ofta leder till självmordsförsök, raseri, drogmissbruk, manipulativa drag i relationer och humörsvängningar.

Historiskt sett användes begreppet "borderline" för att beteckna ett psykiatriskt tillstånd som var på gränsen (eng. border) mellan 'neuros' och 'psykos'. Ett annat sätt att använda begreppet utvecklades av psykodynamiskt orienterade forskare för att beteckna en "borderline personlighetsstruktur" (Kernberg, 1967). I denna veva utvecklades ett instrument av Gunderson et al.

(1981) under benämningen 'the diagnostic interview for borderline patients' (DIB). Instrumentet består av ett antal utvärderingar uppdelade i fem sektioner som kallas social anpassning, impulsivt beteende, affekter, psykos respektive interpersonella relationer. Vi tillämpar en modifierad användning av DIB i avhandlingen där informationen inhämtas från journalhandlingarna snarare än genom intervjuer med patienterna.

En beskrivning av de enskilda arbeten.

- (I) *Chotai J, Salander Renberg E, Jacobsson L: Method of suicide in relation to some sociodemographic variables in northern Sweden. (Archives of Suicide Research, in press).*

I denna epidemiologiska studie analyseras det totala registret av alla fullbordade självmord i Västerbotten under de 42 åren 1952 – 1993 (1466 fall) med hjälp av multivariata statistiska metoder (multiple logistisk regression). Vi undersöker relationen mellan självmordsmetoder och diverse sociodemografiska variabler som kön, ålder, boende som tätort eller landsbygd, civilstånd, år för självmord, årstid för självmord och årstid för födelse. Här upptäcker vi för första gången att självmordsmetoden är associerad till födelseårstiden. Vi finner statistiskt signifikanta samband så att de som var födda under vår-vinter månaderna oftare använde hängning som självmordsmetod snarare än förgiftning eller bilavgaser, och de som var födda under höst månaderna visade det omvända sambandet. Här diskuteras även sambanden mellan självmordsmetoder och de övriga sociodemografiska variablerna. En förståelse av det komplexa samspelet - mellan vilken självmordsmetod som är tillgänglig, vilken metod individen föredrar eller accepterar, och metodens farlighet - är nödvändig för att kunna genomföra effektiva förebyggande strategier. Detta arbete innehåller ett bidrag även inom detta område.

- (II) *Chotai J, Åsberg M: Variations in CSF monoamine metabolites according to the season of birth. (Neuropsychobiology 1999, 39, 57-62).*

I denna neurobiologiska studie studeras, för första gången, relationen mellan födelseårstiden och CSF nivåerna för 5-HIAA, HVA och MHPG i en grupp av 241 patienter med de psykiatriska diagnoserna förstämningssyndrom, ångestsyndrom och anpassningsstörningar. Vi finner ett signifikant samband så att de födda under perioden februari till april hade lägre 5-HIAA nivåer och de födda under perioden oktober till januari hade bland annat höga HVA nivåer

och även höga (men icke-signifikanta) nivåer på 5-HIAA. Med hänsyn till det som är känt om relationen mellan självmordsbeteende och nivåerna av 5-HIAA och HVA, så pekar dessa resultat i samma riktning som de epidemiologiska resultaten i arbetet (I) ovan.

(III) Chotai J, Kullgren G, Åsberg M: *CSF monoamine metabolites in relation to the diagnostic interview for borderline patients (DIB).*

(Neuropsychobiology, 1998, 38, 207-212).

Utmärkande drag hos patienter med borderline personlighetsstörning är bland annat suicidalt beteende och impulsivitet, vilka i sin tur har visat ett samband med låga värden på CSF nivåerna av 5-HIAA och HVA. I detta arbete undersöks relationen mellan CSF monoamin metaboliterna och de fem sektionerna i ett diagnostiskt instrument (DIB) för borderline personlighetsstörning genom en granskning av journalerna för en grupp av 202 patienter överlappande med gruppen i arbetet (II). Med förvåning finner vi att höga värden på 5-HIAA och HVA uppvisar ett samband med *mellanskalan* på impulsivitet. Med stöd av några andra studier i litteraturen tolkas dessa fynd som att högre än normala värden på 5-HIAA och HVA skulle vara skyddande mot ett utpräglat impulsivt och våldsamt självmordsbeteende, hos de som är belastade med andra riskfaktorer som framkallar ett självmordsbeteende.

(IV) Chotai J, Salander Renberg E, Kullgren G, Åsberg M: *Season of birth variations in dimensions of functioning evaluated by the diagnostic interview for borderline patients (Manuskript).*

Här undersöks sambandet mellan de olika sektionerna för DIB och födelseårstiden i två sinsemellan helt oberoende stickprov, det första bestående av 130 fullbordade självmord i Västerbotten och det andra bestående av 202 patienter i Stockholm från arbete (III) ovan. Vi finner att *mellanskalan* för impulsivitet uppvisar ett samband, återigen pekande i samma riktning och förenlig med ovanstående arbeten. Vidare finner vi att för de som var födda under perioden februari – april, de schizofrena patienterna fick höga värden på "affects"-skalan av DIB och de övriga patienterna fick höga värden på "psychosis"-skalan på DIB.

(V) *Chotai J, Salander Renberg E, Jacobsson L: Season of birth associated with the age and method of suicide. (Archives of Suicide Research 1999, in press).*

I denna studie genomförs närmare undersökningar av sambandet mellan å ena sidan födelseårstiden och å andra sidan självmordsmetoder och andra sociodemografiska variabler. Detta görs för olika grupper av födelseår (födelsekohorter) bland de fullbordade självmorden i Västerbotten under 1952 - 1993. Vi finner att även åldern vid självmord visar ett visst statistiskt samband med födelseårstiden, pekande i samma riktning som ovanstående arbeten, och sambandet är starkare för män. Den teoretiska kopplingen mellan ovanstående neurobiologiska och epidemiologiska studierna diskuteras ingående.

(VI) *Chotai J, Salander Renberg E: Season of birth variations in suicide methods with or without any history of psychiatric contacts. (Manuskript).*

I detta epidemiologiska arbete undersöks alla de 693 fullbordade självmord i Västerbotten under de 20 åren 1961–1980. Förutom information om självmordsmetoden och sociodemografiska variabler inhämtas även information om eventuell kontakt med psykiatri genom en granskning av alla psykiatriska journaler. Här finner vi att sambandet mellan födelseårstiden och självmordsbeteenden gäller för de som inte hade haft någon kontakt med psykiatri, men inte för de som hade haft psykiatriska kontakter. Flertalet av de som är kända inom psykiatri ofta har en svårare och mera kronisk psykisk sjukdom än de som inte har etablerad kontakt med psykiatri. Därför tyder våra resultat på att sambandet mellan födelseårstiden och självmordsbeteenden tycks vara oberoende av psykisk sjukdom. Behandling inom psykiatri tycks snarare sätta ut en eventuell relation med födelseårstiden. Det tycks finnas en oberoende sårbarhet för särskilda självmordsbeteenden, sannolikt förmedlad genom graden av omsättningen av monoaminerna i hjärnan, framförallt det serotoninerga systemet.

Sammanfattande slutsatser

I avhandlingen visas (i epidemiologiska studier) att det finns ett statistiskt samband mellan födelseårstiden och självmordsbeteende, framförallt självmordsmetoden hos fullbordade självmord i Västerbotten 1952-1993. De som var födda kring vinter-vår månaderna februari-april var mera sannolika, och

de som var födda kring höstmånaderna oktober-januari var mindre sannolika, att välja hängning som självmordsmetod hellre än förgiftning eller bilavgaser. Detta samband var statistiskt signifikant även efter justering för andra förklarande variabler i multivariata analyser.

Samtidigt visas i avhandlingen (i neurobiologiska studier), hos en helt annan grupp av individer i Stockholm, att nivåerna (eller deras inbördes relationer) i cerebrospinal vätskan av nedbrytningsprodukter (metaboliter) till signalsubstanserna serotonin, dopamin och noradrenalin visar ett statistiskt signifikant variation med födelseårstiden. De som var födda kring vinter-vår månaderna februari-april hade signifikant lägre nivåer av serotonin metaboliten och de som var födda kring höstmånaderna hade högre nivåer av serotonin och dopamin metaboliter. Låga nivåer av serotonin metaboliten är kända för att vara relaterade till impulsivitet och användandet av våldsammare självmordsmetoder, och det finns studier som tyder på att individer med högre värden på metaboliterna skulle vara något mindre impulsiva (Higley et al., 1996) och använda mindre våldsamma självmordsmetoder (Mann & Malone, 1997). Sektionen för impulsivitet i instrumentet DIB visar ett samband med metabolitnivåerna som kan tolkas som att höga nivåerna utgör ett visst skydd mot impulsivitet som har sitt upphov i andra riskfaktorer (Arbete III).

Således är resultaten i de epidemiologiska studierna och de neurobiologiska studierna i avhandlingen förenliga med varandra. De ger stöd åt en hypotes att födelseårstiden skulle ha ett visst samband med vilken sorts självmordsbeteende individen uppvisar. Arbete VI visar vidare att detta samband inte var beroende av någon samtidig förekomst av allvarlig psykisk sjukdom som skulle ha föranlett behandling inom psykiatri. Sambandet mellan självmordsbeteende och födelseårstiden tycks bero, åtminstone delvis, på en variation i funktionerna hos de monoaminerga neurotransmittorererna (framförallt det serotoninerga systemet) i relation till födelseårstiden.

Avhandlingens begränsningar

- I avhandlingen finns inga undersökningar som skulle belysa huruvida benägenheten att begå självmord som sådan varierar med födelseårstiden – så denna fråga är obesvarad. Av de som redan begått självmord har vi däremot funnit att födelseårstiden har ett visst samband med vilken självmordsmetod de använde och vid vilken ålder de begick självmord.

- Vi har funnit att CSF nivåerna av 5-HIAA och HVA visar ett samband med födelseårstiden för en grupp patienter med vissa psykiska sjukdomar (förstämningssyndrom, ångestsyndrom och anpassningsstörningar). Vi vet dock inte hur detta förhåller sig för normalbefolkningen eller för personer med andra tillstånd.
- För registret över fullbordade självmord i Västerbotten under 1961 –1980 har vi granskat de psykiatriska journalerna. Vi vet dock inte i vilken utsträckning dessa självmordsoffer hade haft någon kontakt med primärvård eller med övrig sjukvård.
- Vi vet de psykiatriska diagnoserna för de självmordsoffer under 1961 – 1980 som hade haft någon kontakt med psykiatri. Vi har dock inte någon information angående omfattningen av psykisk sjukdom hos de övriga självmordsoffren, eftersom vi har inte genomfört någon ”psykologisk obduktion” för dessa.
- Vi har inte gett några slutgiltiga förklaringar för varför det skulle föreligga samband mellan å ena sidan födelseårstiden och å andra sidan självmordsbeteende, neurotransmittorer och diagnostiska instrumentet för borderline personlighetsstörningar. Flera tänkbara förklaringar eller hypoteser finns, och dessa kan beröra någon punkt i individens hela förlopp, från befruktningen till uppväxttiden, enligt följande:
 - (a) om föräldrarna har några egenskaper som kan påverka barnets självmordsbeteende genom ett socialt, psykologiskt eller genetiskt arv, och om samma egenskaper på något sätt också påverkar föräldrarnas sexuella mönster så att befruktningen oftare äger rum under särskilda årtider, så föds följaktligen barnen till dessa oftare under särskilda årtider (“the procreational habits hypothesis”).
 - (b) den gravida kvinnan, och därmed fostret, utsätts för miljöpåverkan olika under olika årtider. Vissa infektioner är vanligare under våren än under hösten (“the viral hypothesis”). Moderns näringsintag, tillgång till solljus, vanor såsom rökning, samt stressframkallande omständigheter, kan vara olika under olika årtider.
 - (c) omständigheter kring förlossning eller perioden kort därefter kan variera med födelseårstiden.

- (d) det kan finnas genetiska egenskaper hos fostret som är relevanta för det studerade tillståndet (exempelvis självmordsbeteende), gener som samtidigt kan tänkas göra fostret mer eller mindre motståndskraftig mot graviditetsrisker under årstider med hög risk.
- (e) det första levnadsåret, då individen och individens hjärna utvecklas avsevärt, innehåller olika erfarenheter beroende på om man är född under hösten eller under våren. Detta gäller solljus och övriga meteorologiska förhållanden såväl som den sociala rytmen.
- (f) vid skolstarten på hösten så är de som är födda under vårmånaderna något äldre än de som är födda under hösten samma år. Känslan av grupptillhörighet och rangordningen i gruppen kan därmed upplevas olika beroende av födelseårstiden.

Det finns en hel del forskning kring somliga av ovanstående hypoteser i samband med andra neuropsykiatriska tillstånd (Torrey et al, 1997; Castrogiovanni et al, 1998). Dock kommer ytterligare forskning att behövas för att få en närmare förståelse.

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