# A register based epidemiological description of risk factors and outcomes for major psychiatric disorders, focusing on a comparison between bipolar affective disorder and schizophrenia

**Ph.D. thesis**

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2006

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# 1. List of papers

The thesis is based of the following papers:

Paper I: **Laursen TM**, Labouriau R, Licht RW, Bertelsen A, Munk-Olsen T, Mortensen PB. Family history of psychiatric illness as risk factor for schizoaffective disorder. Arch Gen Psychiatry 2005;62:841-848

Paper II: **Laursen TM**, Munk-Olsen T, Nordentoft M, Mortensen PB. A comparison of selected risk factors for unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia. Submitted 2006.

Paper III: **Laursen TM**, Munk-Olsen T, Nordentoft M, Mortensen PB. Increased mortality amongst patients admitted with major psychiatric disorders. In print The Journal of Clinical Psychiatry 2006.

# 2. Preface

The work on which this thesis is based was carried out at the National Center for Register-based Research in the period 2004-2006. The project was supported by The Stanley Medical Research Institute.

A large number of people have made my Ph.D. study period a pleasant and rewarding experience:

A special thank to my main supervisor Preben B. Mortensen DrMedSc and supervisor Merete Nordentoft MD PhD for their valuable supervision and comments. I am indebted to Trine Munk-Olsen for her never ending support and for the constructive discussions in all parts of the process of writing this Ph.D. thesis.

I would also like to thank Aksel Bertelsen, Rodrigo Labouriau, and Rasmus W. Licht for their significant help and advice, Annette Rand Madsen for her help with the papers and the thesis, and all my colleagues at the National Center for Register-based Research for their valuable support and help.

Thomas Munk Laursen

# 3. Introduction

Schizophrenia and bipolar affective disorders are severe mental disorders characterized by delusions, hallucinations, irrational thoughts and fears (1) and after more than 100 years of research, mechanisms behind the disorders are not fully understood. They are infrequent diseases, but are among the most burdensome and costly illnesses, both on an individual level and in society in general. A total of 21% of the Danish national health expenditures goes to psychiatric treatment (2), and schizophrenia and bipolar affective disorders are considered to be among the most expensive mental disorders in Denmark (3). Schizophrenia and bipolar affective disorders are today placed in two different groups (In Denmark: F2 and F3 chapter in WHO-ICD10 classification (4)), and has historically been dichotomized in two groups, originally proposed by Kraepelin (5):

- Bipolar affective disorder (manic-depressive insanity)
- Schizophrenia (dementia praecox)

It has become clear that neither schizophrenia nor bipolar affective disorders are results of a single cause or single gene. More likely, they are results of the inheritance of a number of genes with relatively small effect compounded by environmental hazards (6). Furthermore, the dichotomization of bipolar affective disorder and schizophrenia, has been questioned, and as a consequence, alternative classifications to replace the Kraepelinian dichotomization have been proposed, especially in Europe (6). These include the developmental theory (7), which suggests a genetic overlap between bipolar affective disorder and schizophrenia, and the continuum theory (5;8-10) which suggests that the major psychiatric disorders constitute a continuum ranging from unipolar depressive disorder, to bipolar affective disorder, to schizoaffective disorder, to schizophrenia, with increasing severity across the spectrum.

A way of elucidating the (possibly overlapping) mechanisms behind bipolar affective disorder and schizophrenia is to examine and compare risk factors, outcomes (as age-specific mortality), and familial aggregation of the two disorders in large population based cohorts. As in all epidemiological studies, no *direct* casual mechanism can be drawn from this approach. However, aggregation of schizophrenia in first degree relatives of a proband suffering from bipolar

affective disorder (and vice versa), overlapping risk factors, and similar outcomes would support an overlap and association between the two disorders. In contrast, no aggregation of schizophrenia in the families of probands suffering from bipolar affective disorder (and vice versa), no overlap in risk factors, and different outcome would support a dichotomization.

# 4. Aim

The overall aim of the thesis was to make a description of the occurrence of bipolar affective disorder and schizophrenia in Denmark, and to examine risk factors for, and outcome of, the two disorders in population based cohorts, using the Danish registers. Furthermore, the aim was to make an evaluation of the results in the context of the classification of bipolar affective disorder and schizophrenia, by examining if the selected risk factors influenced the risk of developing bipolar affective disorder or schizophrenia differently, and by examining if there were differences in the outcome measured as mortality after onset of the disorders. Unipolar depressive disorder and schizoaffective disorder were studied as comparison groups, because unipolar depressive disorder is often closely linked, and precedes, bipolar affective disorder and schizoaffective disorder is defined by having characteristics of both bipolar affective disorder and schizophrenia.

These topics were investigated in 3 register based epidemiologic studies:

- Paper I: The aim of the study was to determine whether a psychiatric history of schizoaffective disorder, bipolar affective disorder or schizophrenia among parents and siblings affected the risk of getting a schizoaffective disorder. Furthermore, to determine, from parallel analyses, if there was a specific pattern of family history of psychiatric illness in persons with schizoaffective disorder compared to persons with bipolar affective disorder or schizophrenia.
- Paper II: The aim of the study was to examine paternal age, place of birth, small for gestational age, and parental loss as risk factors for unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia, focusing on a comparison between schizophrenia and bipolar affective disorder. Furthermore, to examine the incidence of the disorders in a population based setup and evaluate the results in the context of the dichotomization of schizophrenia and bipolar affective disorder.
- Paper III: The aim of the study was to compare mortality rates after admission with major psychiatric disorders, including unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder and schizophrenia, and to examine the impact of family history of psychiatric admission on mortality.

# 5. Background/literature

## 5A. Historical aspects

Schizophrenia and bipolar affective disorder have been separated since Kraepelin introduced a classification of psychotic symptoms more than 100 years ago. When Kraepelin introduced the dichotomization, he was aware of the limitation of the dichotomization, and in 1920 he wrote: "We therefore will have to get used to the fact that the symptoms we have used so far are not sufficient to always reliably distinguish between manic–depressive insanity [bipolar affective disorder] and schizophrenia, but that there are overlaps based on the origin of these symptoms from given preconditions" (11). In 1933, one of the possible limitations of the dichotomization was displayed, as the term schizoaffective disorder was introduced (12). However, the Kraepelinian dichotomization has been the established classification criterion since then, possibly because Kraepelin's terminology was more clear and easy to understand (5). Growing evidence of an overlap between the disorders has since then become increasingly difficult to disregard. Most notably, a genetic overlap and a familial co-aggregation of bipolar affective disorder and schizophrenia has been proposed (13-15).

In summary, three themes have in particular questioned the Kraepelinian dichotomization (5;7):

- The relationship between unipolar and bipolar affective disorder. Today mania and mania/depression are classified as bipolar affective disorder, whereas unipolar depressions have its own categories.
- Schizoaffective disorder, and "in between states". The concept of an illness presenting characteristics from both disorders undermines the dichotomization.
- Alternative models: the continuum concept of psychosis and affective disorders, and recently the developmental model.

## 5B. Risk factors for schizophrenia and bipolar affective disorder

A number of risk factors for bipolar affective disorder and schizophrenia have been studied, with the genetic/familial component as the most pronounced and with the largest impact on the risk. In this section, evidence from the literature of the impact of a number of risk factors is examined. It is not a systematic review of all literature of risk factors, but based on the most important studies (that is, with the best quality of data, large data sets or reviews), emphasizing studies similar to

the studies in this thesis, i.e., Scandinavian (including Finland) population based cohort studies. In general schizophrenia has been studied more intensively than bipolar affective disorder, hence making conclusions more reliable. The effect of each risk factor is summarized in the following way (see Table 1 for overview):

✓ = Evidence suggesting an association

✓̸ = Evidence suggesting an exclusion of association

? = Inconclusive evidence or conflicting evidence for or against an association

BP = bipolar affective disorder

S = schizophrenia

Family history of psychiatric disorder in 1st degree relatives and genetic association (BP = ✓ S = ✓)

Family history of bipolar affective disorder is one of the strongest risk factors for bipolar affective disorder. In the same way, family history of schizophrenia is a very pronounced risk factor for schizophrenia.

However, it is more unclear whether bipolar affective disorder in the family is a risk factor for schizophrenia and vice versa. Recent evidence of such an overlap has surfaced in both genetic and family studies. Berrettini (16) found that there was evidence of 4 susceptibility loci (18p11.2, 22q11-13, 13q32 and 10p14) shared between bipolar affective disorder and schizophrenia, but it should also be noted that evidence of susceptibility loci unique to bipolar affective disorder and unique to schizophrenia was found. Craddock et. al. reviewed the literature and found evidence of an overlap in susceptibility genes DISC1 and NRG1 (17). A Danish study also found a shared susceptibility gene (GRP24) for the two disorders (18) . Bramon & Sham (13) concluded that there was an increased risk of schizophrenia among relatives of probands with bipolar affective disorder and Cardno et al. (19) compared the degree of genetic overlap between schizophrenia, bipolar affective disorder, and schizoaffective disorder and found that there was an overlap in the genes contributing to the three disorders. Maier et al. (20) concluded in a review that schizophrenia and bipolar affective disorder had etiological factors in common. In three Danish

population based register studies by Mortensen et al. and Pedersen et al. (14;21;22), an overlap between bipolar affective disorder in the proband and schizophrenia in the family (and vice versa) was also detected.

Twin-studies, such as, e.g., Cardno et al. (23), calculated heritability estimates of more than 80% in both disorders, but it was not evident whether these high estimates were directly linked to genetic factors, or whether they were also linked to an environmental factor which then had a causal link to the disorder.

*In conclusion*: family history of psychiatric admission (with bipolar affective disorder and schizophrenia, respectively) is by all standards the strongest risk factor for the two disorders. In fact, heritability of major psychiatric disorders are amongst the strongest in human illnesses (1). It is clear that some of the excess risk is genetic, but it is not clear how much of the risk is associated with a direct genetic risk, and how much is associated with environmental factors. Several studies suggest a genetic/environmental overlap and interaction in bipolar affective disorder and schizophrenia.

Small for gestational age (BP = ? S = ✓)

Obstetric complications have mostly been studied in terms of summary scores which summarized several complications in relation to birth. Studies have examined the association with schizophrenia. Weak associations with small for gestational age were found in two studies from Sweden, males only (24;25). However, a meta analysis by Cannon et al (26), examining 5 studies on small for gestational age (including the Swedish studies referred to above) revealed only a non-significantly increased risk in relation to schizophrenia. In a study by Eaton et al (27), small for gestational age was examined while adjusting for urbanization; and they found an increased risk of 'light for age' in schizophrenia and a negative association with affective psychosis, although the results were not statistically significant.

Few studies have examined small for gestational age and the association with bipolar affective disorder. However, a study from Sweden by Hultman et al. (24) examined the whole spectrum of affective psychosis, but no association was found. A Danish study by Osler et al. examined

depression including bipolar affective disorder and found no association with birth weight (28). An Irish case register study by Brown et al. (29) found no association between bipolar affective disorder and obstetric complications in general. A Danish study by Ogendahl et al. (30) found no association between fetal growth and bipolar affective disorder, and suggested a partly different etiology in bipolar affective disorder and schizophrenia. However, in an American case-control study (with non-affected siblings as controls) Kinney et al. (31) found that summary scores of obstetric complications were significantly higher (worse) in cases with bipolar affective disorder, than in controls.

*In conclusion*: different obstetric complications are small, but significant risk factors for schizophrenia. Because of the limited impact of these risk factors they are difficult to measure, unless large cohorts are used. There is limited information on the impact of obstetric complications in general, and small for gestational age in particular, when bipolar affective disorder is the outcome.

Urbanicity of place of birth (BP = ✗ S = ✓)

Place of birth has been shown to be associated with schizophrenia in several studies (22;27;32;33), but no effect was found in bipolar affective disorder or affective disorder (including bipolar affective disorder) in two Danish population based studies by Mortensen et al. and Eaton et al. (14;27). Urbanicity of place of birth has been shown to be a solid proxy variable for urbanicity during upbringing (32), and urbanization has been linked to schizophrenia since the 1930s, but the cause of the increased risk is unclear. Social isolation, nutrition, drift towards the city of individuals who develop schizophrenia, drug abuse, or a higher exposure to influenza, have been proposed explanations (27). An attempt to disentangle the familial part of the excess risk from the individual part has been made, but the study showed that both contributed to the risk (34).

*In conclusion*: urbanicity is strongly associated with schizophrenia, but only to a lesser degree with bipolar affective disorder. No conclusive evidence of an environmental origin or a genetic origin of the excess risk associated with urbanicity has been found.

Early parental loss (BP = ✓ S = ?)

Early parental losses have been studied extensively in depression. In the book by Brown and Harris (35), especially maternal loss before the age of 11 was found to be a risk factor for depression. This, has to a much lesser degree, been studied in relation to psychosis in schizophrenia and bipolar affective disorder. A Danish study by Byrne et al. (36) found that parental death by suicide was a risk factor for schizophrenia, whereas no association with parental death by natural causes was found. The same tendency emerged in bipolar affective disorder in a similar Danish population based study by Tsuchiya et al. (37). In a case control study conducted at an Israeli hospital, increased risk of major depression, bipolar affective disorder, and schizophrenia was observed for probands who experienced an early parental loss (not necessarily death of a parent) (38), and by using a structured interview Lewinsohn et al. (39) found that bipolar subjects had a significantly increased risk of not living with both parents compared to persons with no mental disorder.

*In conclusion*: parental loss by suicide is a risk factor for bipolar affective disorder, and to a lesser degree schizophrenia. Parental loss by natural death is a smaller, if any, risk factor for both disorders.

Paternal age (BP = ? S = ✓)

A Danish population based study found an increased risk for schizophrenia associated with advanced paternal age (+50 years old) (36). Two other recent studies found a monotonic linear trend with paternal age as a risk factor for schizophrenia (40;41). A population based study from Sweden also found a linear trend in subjects with no family history of psychiatric admissions, but not in subjects with a family history of mental disorder (42).

*In conclusion*: high age in fathers is an established risk factor for schizophrenia. Most studies suggest that de novo mutations in the oldest fathers' germ cells might lead to the excess risk of schizophrenia. However, underlying selection mechanisms of the old fathers could also be an explanation. Few results on paternal age as a risk factor for bipolar affective disorder are available.

Recent stress especially by loss of child (BP = ✓ S = ✓)

Loss of a child is considered one of the worst stressors a person can experience. In a study by Li et al. (43) (using the same cohort as this thesis), the risk of admission with schizophrenia after loss of a child was significantly higher, especially during the first year after the loss, compared to non-bereaved parents. In general, stress due to loss of a child has not been studied in bipolar affective disorder separately, but in the study by Li et al., the tendency of increased risk was even higher when the whole spectrum of affective disorders was examined. Some studies of stressful life events, as risk factors for bipolar affective disorder/mania, have been performed. In a study by Mathew et al. (44), an association between onset of mania and recent stressful life events was found. This study was, however, made on an Indian population and found some risk factors (e.g., birth of a girl instead of a boy) not normally studied in European/American studies. Bebbington et al. (45) studied life events, and evidence of a link to bipolar (manic/depressive) and schizophrenic psychosis was also found here.

*In conclusion*: recent stressful life events, particularly loss of a child, appear to be risk factors for onset of both bipolar affective disorder and schizophrenia.

Child birth (BP = ✓ S = ✓)

In a Danish population based study, Munk-Olsen et al. (46) (using the same cohort as this thesis) demonstrated that during the first month after birth of the first child, mothers had a 6 times larger risk of admission with schizophrenia (including schizophrenia-like and schizotypal disorders) compared to mothers giving birth a year ago. The risk of bipolar affective disorder was almost 22 times larger during the first month. Becoming a father for the first time was not associated with an increased risk for the two disorders. In an older study by Kendell et al. (47), the same pattern of excess risk of psychosis in women up to 3 month after birth was seen. An association between childbirth in women and excess risk of bipolar affective disorder was present in a study by Hunt & Silverstone (48), and in the period where ICD 8 was used, the different psychiatric diagnoses given shortly after birth of a child were examined by Videbech et al. (49); and both found an aggregation of bipolar (manic/depressive) disorder diagnoses, but not of schizophrenia diagnoses. The same period was examined by Terp & Mortensen (50) who also found the excess risk of psychosis in the period after birth of a child, especially the risk of first admission was elevated.

*In conclusion*: most studies suspect a close link between bipolar affective disorder in women and birth of a child. No excess risk of bipolar affective disorder is likely to be present in relation to fatherhood. The same pattern of association between schizophrenia and childbirth is likely to exist, but to a lesser degree.

Infections during pregnancy (BP = ? S = ✓)

In the literature, prenatal infections such as exposure to influenza have often been associated with schizophrenia (51). A commonly used study design is examination of persons with a prenatal exposure to influenza epidemic. In a Finnish study, Mednick et al. (52) found that persons born during an influenza epidemic more often developed schizophrenia later in life, and especially the second trimester was a vulnerable period. In contrast, a Danish study by Westergaard et al. (53) using a different approach measuring monthly prevalence of influenza in Denmark found no evidence that persons exposed to high prevalence of influenza in the second trimester had an excess risk of developing schizophrenia later in life. Brown et al. (51) used a more direct approach, measuring influenza antibodies in archived maternal serum and a very week association with later schizophrenia arose.

Bipolar affective disorder and exposure to influenza is studied to a lesser degree, and only one study found a tendency (non-significant) towards exposure to influenza in the second trimester and development of bipolar affective disorder later in life (54). Other infections seem to be a risk factor for schizophrenia, e.g. toxoplasma gondii (55), rubella (56), and HSV (57).

*In conclusion*: some evidence suggests that exposure to influenza in, particularly during the second trimester, is a risk factor for schizophrenia. Other maternal infections could be risk factors as well. No association with bipolar affective disorder seems to be present.

Season of birth (BP = ? S = ✓)

In an extensive review by Torrey et al. (58) including more than 250 studies, a consistent winter/spring excess of 5-8 % in persons suffering from schizophrenia and bipolar affective disorder was found. The cause of seasonality was more unclear, but no statistical artifact could

explain the phenomenon. A newer study of mood disorders from Japan by Mino et al. found the same excess in winter/spring births (59), but a recent study from Denmark by Mortensen et al. (14) found no seasonality in bipolar affective disorder. Studies of winter/spring excess in both bipolar affective disorder and schizophrenia often reported excess in different months, which could suggest that results were not very robust. Also, results were affected by confounders and effect modifiers, such as., e.g., gender differences, as the Japanese study (59) suggests.

*In conclusion*: patients suffering from schizophrenia have a clear tendency of being born in winter/spring. It is more unclear whether the same tendency applies to bipolar affective disorder, although several studies suggest more winter/spring births. The cause of the excess birth in spring/winter is far from evident.

Socioeconomic status (BP = ? S = ?)

When socioeconomic status is examined it is difficult to disentangle risk factors from consequences of the disorder in the proband, that is, e.g., having lower income because of the disorder or not the having the disorder because of lower income (or maybe proxy variables). A study by Agerbo et al. (60) showed that socioeconomic factors were affected years before first admission with schizophrenia. Some studies show a small association with parental social class, whereas some show no association (61).

*In conclusion:* numerous studies have examined socioeconomic status using summary scales or methods developed by the authors. But two extensive review studies on schizophrenia (61) and bipolar affective disorder (62) conclude that evidence is indecisive.

Premorbid adjustment (BP = ✗ S = ✓)

Premorbid adjustment (measured by the 'Premorbid adjustment scale' with subscales as social adaptation and academic adaption) was worse in patients suffering from schizophrenia compared to both bipolar affective disorder patients and healthy control, in a study by Cannon et al. (63). In some sub-scores, bipolar affective disorder patients had worse outcomes than healthy controls. Schizophrenic patients showed worse outcome before onset in a number of socioeconomic areas (60), while bipolar affective disorder patients had a much less marked pattern (61). Jones et al.

(64) found in a review that premorbid adjustment problems (precursors) was to a higher degree present in schizophrenia, than in affective disorders.

*In conclusion:* indicators of premorbid adjustment problems are much more prominent in schizophrenia than in bipolar affective disorder.

Cannabis (BP = ? S = ✓)

In a review, Arseneault et al. (65) showed that the use of cannabis was associated with higher risk of developing schizophrenia. One of the first studies to show an association between cannabis use and schizophrenia was a Swedish study by Andreasson et al. (66) where an large excess risk of schizophrenia was present in cannabis users among Swedish conscripts. However, it has since then been debated whether there was a causal effect of cannabis use in the risk of developing schizophrenia (67). Alternative explanations, such as the presence of factors increasing the rates of cannabis use and increasing the risk for schizophrenia, without cannabis being a causal factor for schizophrenia, have been proposed (68). However, Fergusson et al. (69) concluded in a recent review that evidence suggested a causal link between cannabis use and psychosis. The majority of studies examined schizophrenia or did not differentiate between bipolar affective disorder and schizophrenia. However, Henquet et al. (70) examined the risk of expressing manic symptoms (with the subsequence risk of developing bipolar affective disorder) and found that cannabis use was indeed a risk factor.

*In conclusion*: cannabis use is more frequent among persons developing psychosis. Evidence suggests a causal link to be present, although it is still debated.

Ethnicity and migration (BP = ? S = ✓)

A large number of studies, especially in the UK, have examined migration and ethnicity as a risk factor for schizophrenia, e.g. (71;72). They all found an increased risk for schizophrenia in migrants. In a meta analysis Cantor-Graae & Selten (73) found a highly significant relative risk of 2.7 in first-generation migrants for developing schizophrenia. Second-generation migrants had a relative risk of 4.5 (with large confidence limits). They concluded that both a personal and family history of migration was a risk factor for schizophrenia. It was, however, not clear

whether the increased risk was caused by the migration or the ethnicity of the first and second-generation migrants (74). No clear association between bipolar affective disorder and ethnicity was found in a review by Tsuchiya et al. (62) but an association with migration could not be ruled out.

*In conclusion*: persons who migrate have a larger risk of developing schizophrenia. However, the reason for the increased risk is unknown. Ethnicity, selection, or stress from migrating constitute some of the proposed explanations. Few studies of bipolar affective disorder have examined migration, but no evidence of a link has been shown.

**5C. Mortality after psychiatric admission**

The generally increased mortality in patients suffering from a mental disorder was described in an extensive review by Harris & Barraclough (75). They found an increased mortality in schizophrenia and affective disorder, especially by unnatural death. The same tendency was found in a number of register based studies. But, also the mortality from natural causes was higher. In a Swedish study by Ösby et al. (76), an excess mortality of about twice of that of the general population was found in unipolar patients and 2.5 in bipolar patients. Schizophrenia patients had the same tendency in another Swedish study by Ösby et al. (77) (approximately twice the mortality rate from natural death). In a Finnish study by Joukamaa et al. (78), the excess mortality in schizophrenic patients was 3.3 for men and 2.3 for women. In a population based study from Denmark by Mortensen et al. (79), the SMR for patients admitted with schizophrenia was 4.7 for men and 2.3 for women, compared to the general population. The excess mortality from unnatural causes was much higher in the above mentioned studies. Especially the time shortly after discharge from a psychiatric hospital was associated with a high risk of suicide, but the risk remained high (80).

Most studies, including the above mentioned, found an effect modification by age, in the way that younger admitted persons had a relative higher excess risk (compared to persons at the same age, but never admitted to a psychiatric hospital). However, as the listed mortality rates originated from different cohorts and were calculated by different methods a comparison of the excess risk in schizophrenia with the excess risk in bipolar affective disorder was not possible.

Webb and colleagues examined schizophrenia related disorders or affective disorder in the parents as a risk factor for increased mortality in the offspring, in the age group 0-25 years. They found an increased mortality rate in the offspring, if any of the disorders were present in the parents. Especially in the young age groups, a large excess risk of premature death was present (Webb et al., in preparation). In a meta analysis by Webb et al. (81) mortality in offspring of parents with psychotic disorders was examined, but mostly infant death was studied as an outcome and not excess mortality later in life.

*In conclusion*: men and women suffering from bipolar affective disorder or schizophrenia have an excess mortality from both natural and (especially) unnatural causes compared to the general population. However, it is unclear whether patients with schizophrenia have different mortality compared to patients with bipolar affective disorder. Only few studies of mortality in adults with a family history of psychiatric admission in first degree relatives, have been made.

# 6. Material and methods

## 6A. Description of registers

The Danish Psychiatric Central Register:

Data on psychiatric admission in Denmark have been colleted systematically from 1938. From April 1, 1969 these data were computerized and include all admissions to psychiatric hospitals in Denmark, the Faroe Islands, and Greenland. From January 1,1995 outpatient contacts were included (82). There are no private psychiatric in-patient facilities in Denmark, ensuring that all psychiatric admissions are represented in the register. In all, a little less than 2.6 million contacts are recorded in the register and more than 600.000 different patients (July 1, 2005). In the present Ph.D.-thesis information is updated to July 1, 2005, in paper II, and updated to January 1, 2002 in paper I. Paper III was only updated to January 1, 2001, because the cause of death register is not updated beyond 2001.

The diagnostic system used until December 31, 1993 was ICD8 (Danish version) (83), which was introduced in Denmark in 1967, and fully implemented in 1969. When the ICD 9 classification was introduced in other parts of the world in 1978, the psychiatric services in Denmark continued to use the ICD 8 classification system, and on January 1, 1994 the ICD10 (Danish version) (4) classification was introduced in Denmark. All contact diagnoses were used in this thesis. ICD 8 includes main diagnoses (hoveddiagnoser) and auxiliary diagnoses (bidiagnoser). ICD 10 includes basic diagnosis (grundmorbus), main diagnosis (aktionsdiagnoser), and associated diagnosis (tillægsdiagnoser).

The following diagnostic categories were used: unipolar depressive disorder (ICD8: 296.09, 296.29, 296.99, 298.09, 300.49, or 300.19, ICD10: F32 or F33), bipolar affective disorder (ICD8: 296.19 or 296.39, ICD10: F30 or F31), schizoaffective disorder (ICD8: 295.79 or 296.8x, ICD10: F25), schizophrenia (ICD8: 295 [excluding 295.79], ICD10 F20) (Figure1). Number of contacts increased in 1995 because of the inclusion of outpatients contacts (Figure 1). Diagnoses are clinical and not standardized to research diagnostic criteria. See discussion later.

The Danish Civil Registration System (CPR)

The Danish Civil Registration system (84) was established in 1968, where all persons alive and living in Denmark were registered and assigned a 10 digit personal identification number. Furthermore, information on gender, date of birth, place of birth, continuously updated information on vital status (e.g. date of death and migration out of Denmark), and identity of parents/siblings, was recorded. In all, 8.3 million persons are recorded in the register (7.1 mill born in Denmark), and 5.5 million persons (5 million born in Denmark) were alive and present in the register on July 1, 2005. When restricting data from the CPR-register to persons born in Denmark 1955 or later 3.4 million persons were included (Figure 2).

Information on first degree relatives is available in the register, but in the beginning of the coverage-period information is not complete. Completeness of maternal link among persons born in Denmark was 8% in 1950 growing to 98.7% in 1960. Identity of fathers increases from 7.6% for persons born 1950 to 95.7% in 1960. For persons born in 1970 or later, almost 100% has a link to their mother and 99% to their father (85).

The Cause of Death Register

The Cause of Death Register (86) was retrospectively computerized from 1943 (from 1970 by the National Board of Health). The data used in this thesis were updated up to December 31, 2000. In the follow-up period, the register contained causes of death according to the ICD-8 (up to 1994) and ICD-10 (from 1994 to 2000) classification. The underlying cause of death was used when examining cause-specific mortality. Four and a half percent of mortality causes were unknown in the follow-up period (code 780-796 in ICD-8 and R00-R99 in ICD-10), with a tendency to be higher in the later calendar period, probably because the autopsy rate in Denmark declined from 45% in the 1970's, to 30% in 1985, and to 13% in 1996. Most of the unknown causes of death have been shown to be circulatory diseases (86). In the present thesis, cause of death was divided in 14 sub-groups (Table 2) which was further collapsed in unnatural (suicide, homicide, and accidents) and natural causes (remaining causes) of death.

The Danish Medical Birth Register

The Danish Medical Birth Register (87) covers information on all births in Denmark since 1973. It contains information on fetal presentation, earlier pregnancies, delivery, length, birth weight and weeks of gestation. Gestational age and weight at birth were recorded in different ways during the calendar period, but conversions to gestational age in week and birth weight in grams are possible and thus small for gestational age can be calculated. Since the register was established in 1973 the oldest persons recorded in the register are 32 years old (in 2005).

Linkage of registers

All linkage between registers was made by the CPR-number. The CPR-number should, in principle, be unique, but a small percentage of persons changed CPR number, especially in the start of the period where the CPR-number was introduced. These changes were accounted for, in the data used in this thesis, by assigning a truly unique number to each person in the registers, using the information on historical CPR numbers.

## 6B. Statistical methods and epidemiological considerations

Statistical model

Analyses of risk factors were carried out by survival analysis techniques. Cox regression (proportional hazards model) would be the appropriate model to measure the impact of the assumed risk factors while adjusting for potential confounders, but because of the vast number of persons in the cohorts it was not feasible to calculate the estimates of the risk factors from that model. A log-linear model, Poisson regression with the logarithm of time under risk as an offset variable, was used as an approximation to the Cox regression. Using a log linear model in this way (i.e., in a survival analysis with censored observations) was described in the article by Laird and Olivier (88). A thorough description of categorical analysis can be read in the book by Andersen et. al. (89), and the specific association between survival analysis with censored observations and the Poisson regression used in this thesis was described by, e.g., Agresti (90). All three papers used this approximation. The subsequent description was based on Agresti p.189 ff. and Stokes et al.(90;91) and sketches the general association between the likelihood of survival analysis and the Poisson likelihood. In paper III, first admission is replaced by date of death, but the method was the same.

If we assume n independent observations (persons) i = 1,….,n, and follow a person until first admission with a psychiatric disorder (to time $t_i$), or end of study period, and furthermore define a censor variable $w_i$ in the following way (censoring is independent of survival times):

$$w_i = \begin{cases} 1 \; if \;\; onset \;\; of \;\; disorder \\ 0 \; if \;\; censored \end{cases}$$

the general likelihood function in survival analysis has the form:

$$(*) \qquad \prod_{i=1}^{n} [f(t_i)]^{w_i} [1 - F(t_i)]^{1-w_i}$$

Where f (t) is the probability density function for the time T and F(t) the distribution function. That is, the likelihood for one person is f(t) if no censoring has taken place. If the person is censored, the contribution to the likelihood is the probability that the person has not yet been admitted at the time of censoring. The hazard function h(t), is defined in the standard way as the instant rate of admission for a person at time t, given that the person has not yet been admitted:

$$h(t) = \frac{f(t)}{1 - F(t)}$$

Assume furthermore, that T follows an exponential distribution with parameter $\lambda$, that is $T \sim E(\lambda)$ and thereby constant hazard:

$$\left.\begin{array}{l} f(t) = \lambda e^{-\lambda t} \;\; t > 0 \\ F(t) = 1 - e^{-\lambda t} \;\; t > 0 \end{array}\right\} \;\Rightarrow\; h(t) = \lambda$$

Assume the hazard function to have the following standard survival analysis form:

$$h(t; x) = \lambda_k \exp(\beta' x) \quad k = 1, ..., K$$

where x is a set of covariates and $\beta$ is the set of parameters to be estimated and $\lambda_k$ is a (piecewise constant) baseline hazard and K is a division of the time interval.

If these formulas are inserted in (*) and the logarithm applied, the following log-likelihood function will be the result:

$$\sum w_i \log(m_i) - \sum m_i - \sum w_i \log(t_i)$$

where

$$m_i = t_i \lambda_k \exp(\beta x_i)$$

Maximizing this likelihood function is equivalent with maximizing

$$\log(m_i) - \log(t_i) = \log(\lambda_k) + \beta' x_i$$

which is the log-likelihood function for a Poisson log-linear model with offset variable log(total time under risk).

In conclusion, a Poisson log-linear model can be used as an approximation to the survival analysis Cox-regression as long as the hazards rates in the covariates stratums are constant. Because of the large number of cases, the covariates can be divided in to small groups ensuring that this is a reasonable assumption.

Data were analyzed in the SAS GENMOD version 8.2 procedures. P-values were based on likelihood ratio tests and 95 % confidence intervals were calculated by Wald's test. The likelihood ratio method was used in the test of interaction. See the individual papers for further information on statistical methods.

Definition of risk factors and confounders

The statistical models used in this thesis were longitudinal models. By using registers it was possible to monitor the disease status and other vital information on an individual level in time spans of 1 day, and thereby making it possible to use a time-dependent definition of the individual person's status. A person was considered to be disease-free until the day of first admission and afterwards shifting disease status, and considered a patient having a diagnosis of, e.g., schizophrenia. In the same way, a cohort member was defined as having a family history of psychiatric admission from the first day a 1$^{st}$ degree relative (mother, father, or sibling) was admitted to a psychiatric hospital with any psychiatric disorder.

Incidence rate of disorders versus prevalent measurement of disorders

The incidence rate of a disorder is the number of new cases per time unit, whereas the prevalence is the number of cases at a specific time point divided by the number of persons in the cohort (92). In order to ensure that the contacts to the psychiatric hospital were the first contacts, only persons born 1952 (paper I) or 1955 (paper II) were included in the cohorts examined. Cohortees

were at most 17 years old in paper I (14 in paper II) in 1969 when the Psychiatric Central Register was computerized. The risk of being admitted with the disorders examined here before the age of 17 was very small, which ensured true measurement of incidence of first psychiatric contact. Incident psychiatric admission cases are particularly important when the admission is used as the outcome because a mixture of incident and prevalent cases can bias the results in an unknown direction (92). If the admissions are used as covariates in a model with a truly incident outcome, an alternative way of ensuring measurement of incidences is by using a 'washout-period' of e.g. 4 years from 1969 to 1973. This approach was used in paper III.

Relative risk as a measurement of the incidence rate-ratio

All effect measurements between subgroups of the cohort were referred to as relative risks. It was calculated as the incidence rate (new cases per risk time) of a particular outcome in the first subgroup divided by the incidence rate in the second subgroup, taking into account the other covariates. More precisely the measurement was an incidence rate ratio. However, in epidemiological studies, the term relative risk is most commonly used, and hence used in this thesis and the 3 papers.

# 7. Results

This chapter is a summary of the 3 papers with aims and results. A description of the incidence and diagnostic overlaps of the disorders (adapted from Paper II and slightly expanded) is placed in the start of this chapter to give an overview and introduction to the disorders.

## 7A. Incidence and overlap between diagnostic groups

The aim was to describe the incidence of admission with unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia. Furthermore, the aim was to describe the possible overlap between the four diagnostic groups. The results were based on Paper II.

An overlap between the four diagnostic groups was observed. Especially persons admitted with schizoaffective disorder had previously been admitted with schizophrenia (38.0%), bipolar affective disorder (26.2%), and unipolar depressive disorder (35.9%). The listed percentages add up to more than 100 %, because the 3 admission groups are not mutually exclusive (Figure 3). Persons admitted with bipolar affective disorder had often previously been admitted with unipolar depressive disorder (32.5%). Smaller overlaps was observed between the other illnesses, see Table 3.

The incidence of schizophrenia was much higher in the examined age groups than the incidence of bipolar affective disorder. In schizophrenia, the incidence in men from the late teens to the mid 30s was more than double the incidence of women. A peak occurred in the early 20s in men, whereas women had a more flat curve throughout the 20s, indicating a later onset (Figure 4). In contrast to this, women had a higher incidence of bipolar affective disorder in all age groups compared to men. Bipolar affective disorder had a steadily increasing incidence with age in both men and women (Figure 5). Overall, the incidence of schizophrenia peaked at an earlier age than bipolar affective disorder. The incidence according to the age of the proband had a different pattern in bipolar affective disorder when comparing with schizophrenia. It should be noted that the incidence rates displayed in Figure 4-7 were adjusted for calendar time with the year 2000 as a reference, meaning that the incidence rates of schizophrenia and bipolar affective disorder in the year 2000 were chosen to represent the overall rate in the best way. Only persons born in

Denmark after 1955 were included to ensure that the cases were incident. From 1995, outpatient contacts were included.

Bipolar affective disorder had an increasing incidence rate in the age span up to 50 years old, suggesting that some persons with a late first admission with bipolar affective disorder were not included when examining only persons under 50 years old. This has to be kept in mind when interpreting the results. This was of less concern in schizophrenia as the incidence dropped steadily in persons 20 years or older, reaching a low point in the age group 50.

For comparison, women had a much higher incidence of unipolar depressive disorder than men, but a comparable pattern was observed in schizoaffective disorder (Figure 6, Figure 7).

**7B. Paper I: Family history of psychiatric illness as risk factor for schizoaffective disorder**

The aim of the study was to determine whether a psychiatric history of schizoaffective disorder, bipolar affective disorder or schizophrenia among parents and siblings affected the risk of getting a schizoaffective disorder. Furthermore, to determine, from parallel analyses, if there was a specific pattern of family history of psychiatric illness in persons with schizoaffective disorder compared to persons with bipolar affective disorder or schizophrenia.

Family history of admission to a psychiatric hospital is one of the major risk factors for bipolar affective disorder, schizophrenia and also schizoaffective disorder. As pointed out in the introduction, schizoaffective disorders are characterized by including both schizophrenic and affective symptoms, and these characteristics were used when making a comparison of family history of psychiatric admission in bipolar affective disorder and schizophrenia. The paper examined if a specific pattern of family history of psychiatric admission was present in persons admitted with bipolar affective disorder, schizoaffective disorder, and schizophrenia. When bipolar affective disorder was the outcome, bipolar affective disorder in the 1$^{st}$ degree relatives was by far the strongest risk factor; however, schizophrenia among first degree relatives was a small, but significant risk factor. When schizophrenia was the outcome, the strongest risk factor was schizophrenia among 1$^{st}$ degree relatives, but still with bipolar affective disorder as a smaller, but significant risk factor. When schizoaffective disorder in the proband was examined,

bipolar affective disorders and schizophrenia in the 1st degree relatives were risk factors of the same magnitude (not significantly different). The main results are presented in Table 4.

There was an equal aggregation of bipolar affective disorder and schizophrenia in families of persons admitted with schizoaffective disorder, and schizoaffective disorder may be genetically linked to both. Furthermore, bipolar affective disorder in the 1st degree relatives was a risk factor for schizophrenia in the proband and vice versa, suggesting genetic and/or environmental overlap between the etiologies of the two disorders.

### 7C. Paper II: A comparison of selected risk factors for unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia

The aim of the study was to examine paternal age, place of birth, small for gestational age, and parental loss as risk factors for unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia, focusing on a comparison between schizophrenia and bipolar affective disorder. Furthermore, to examine the incidence of the disorders in a population based setup and evaluate the results in the context of the dichotomization.

Results showed that high paternal age had a tendency to be a risk factor for all disorders, but most pronounced in schizophrenia. Examination of unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia showed that urbanization became increasingly strongly associated with outcome, from virtually no difference in unipolar depressive disorder to a twofold risk of schizophrenia associated with birth in Copenhagen (compared to a rural area). In children born at term, small for gestational age was only significantly associated with higher risk of schizophrenia. Loss of a parent was a risk factor for all 4 disorders, especially after unnatural death of a parent, but with the same pattern of excess risk. An overlap in the risk factors examined in this study was found, and the differences in terms of risk factor were quantitative rather than qualitative; that is only the magnitude, and not the direction of the risk factors, differed. This could suggest a genetic and environmental overlap between the disorders. Results were not conflicting when they were held up against other models, but the huge differences in incidence and gender composition could indicate that the Kraepelinian dichotomization could be upheld, not only in the clinical context, but also when studying the

causes of schizophrenia and bipolar affective disorder, respectively. The main results are presented in Table 5.

### 7D. Paper III: Increased mortality amongst patients admitted with major psychiatric disorders.

The aim of the study was to compare mortality rates after admission with major psychiatric disorders, including unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder and schizophrenia, and to examine the impact of family history of psychiatric admission on mortality.

Results showed that cohort members who had been admitted with unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, or schizophrenia had an increased mortality by every cause of death, except for cancer in schizoaffective disorder and bipolar affective disorder. Women with a psychiatric admission had a higher relative excess mortality than men. Men and women, who had been admitted with a diagnosis of schizophrenia, had a higher mortality from natural death, than after an admission with schizoaffective disorder, bipolar affective disorder or unipolar depressive disorder. On the other hand, schizophrenia was associated with a lower mortality from unnatural death compared to schizoaffective disorder, bipolar affective disorder or unipolar depressive disorder. Especially, cohortees suffering from schizoaffective disorder had a higher mortality rate ratio from unnatural death than those suffering from schizophrenia. See Figure 8-11. Theses figures also suggests that comparison between the groups are not easily summarized in one number.

Persons never admitted to a psychiatric hospital, had an excess mortality if a first degree relative had had a psychiatric admission. This excess mortality was highest if a family member had a unipolar depressive disorder. If a person had been admitted, the impact of admission in the family was not as large, although persons admitted with unipolar depressive disorder had a small but significant excess mortality if a family member had a mental disorder.

# 8. Strengths and limitations of the cohort design and the register based clinical diagnosis

The main advantage of using the Danish registers is that results are truly population based and free of selection bias (with respect to identifying the persons admitted) and interpretation of results can be made accordingly. Other advantages include:

- Large statistical power, because of large data sources. Especially an advantage in relatively rare diseases as examined in this thesis
- Calculation of true admission-incidence is possible, because the entire population is included
- Low cost
- No attrition. No loss to follow-up, except from person migrating out of Denmark
- Data already exist
- No recall bias. (Especially important in family history of psychiatric admission)
- Data not collected for particular purpose
- Non-differential misclassification, if any; that is, equal distribution of information in cases and controls

The main disadvantages of using registers include:

- Documentation of variables often of poor standard
- Difficult to validate data
- Quality of data, risk factors and confounding factors limited to basic information
- Clinical diagnoses and not research criteria diagnoses
- Not possible to draw causal inference, but only associations

Clinical register based diagnosis

Two studies have validated the clinical diagnoses of schizophrenia and bipolar affective disorder, in the Psychiatric Central Register against research criteria diagnoses. They showed high agreement between the register diagnoses and the research criteria diagnoses (93;94). The diagnosis of schizoaffective disorder might be associated with poor validity as Figure 3 also suggests, but no validation studies exist.

If misclassification was present in the studies we assume it to be non-differential, i.e., measurement error in exposed and unexposed persons is the same. Family members of a person admitted with, e.g., a diagnosis of schizophrenia do not have a higher degree of measurement error than family members of non-Schizophrenic persons. Because of that, relative risks would be biased towards the null hypothesis (RR = 1.00) (95).

Only the most severe cases of the psychiatric diseases were included in this study, as we only investigated persons in contact with the psychiatric system in Denmark. From 1995 information on outpatient status was recorded and as treatment of psychiatric illness in Denmark today tends towards outpatient treatment instead of inpatient treatment we included these patients (paper I and II). We thereby introduced a measurement error in terms of incidence versus prevalence of the persons categorized as outpatients. We have no indication of whether a person was an outpatient before 1995. We believe, however, that this problem is of less concern, because during the early follow up period, persons with these severe illnesses were seldom outpatients only.

# 9. Discussion

## 9A. Key findings

- Paper I
  - Bipolar affective disorder in a first degree relative was a large risk factor for bipolar affective disorder
  - Schizophrenia in a first degree relative was a large risk factor for schizophrenia
  - There was an equal aggregation of bipolar affective disorder and schizophrenia in families of persons admitted with schizoaffective disorder
  - Bipolar affective disorder in a first degree relative was a risk factor for schizophrenia and vice versa
- Paper II
  - Gender differences between bipolar affective disorder and schizophrenia were present in age-specific incidences
  - A large overlap between the diagnostic groups was present, i.e. persons admitted with schizophrenia had previously been admitted with bipolar affective disorder and vice versa.
  - Advanced paternal age was a small risk factor, most pronounced for schizophrenia
  - Place of birth was a risk factor for schizophrenia, but not for bipolar affective disorder
  - Small for gestational age was a risk factor for persons born preterm, but in schizophrenia also a small risk factor for persons born at term
  - Loss of a parent was a risk factor for both disorders
- Paper III
  - There was an excess mortality from all causes of death in patients suffering from schizophrenia and bipolar affective disorder, but schizophrenia patients had an even larger excess mortality from natural death than bipolar affective disorder patients, whereas the opposite applied to unnatural death

## 9B. Discussion of risk factors and mortality in the separate disorders from paper I, II, III

The risk factors and outcomes studied in the three papers and the risk factors described in Table 1 seemed to be operating in different stages of the life span.

- **Risk factors operating before birth**

- **Risk factors operating around birth**
- **Stressful events later in life**
- **Behavioral markers as risk factors**
- **Outcome measured as mortality**

**Risk factors operating before birth**

Paper I demonstrated a very strong hereditary component in the etiology of the disorders, especially in bipolar affective disorder, and the impact of heredity was even larger than in schizophrenia. This is in line with other studies (8;14;21-23) and family history is widely accepted as the strongest risk factor. Paper II showed that urbanicity at birth was the risk factor with the most pronounced discrepancy between bipolar affective disorder and schizophrenia. There was a dose-response like curve of urbanicity, starting with almost no impact on unipolar depressive disorder, over small impact on bipolar affective disorder, larger impact on schizoaffective disorder, ending with a large impact on schizophrenia, irrespective of psychiatric admission status of the first degree relatives. Whether urbanicity at birth is a genetic factor and thereby acting before birth or an environmental factor, is still debated (14;22;27;32-34). Here it was categorized as a risk factor acting before birth, but it may well be a proxy variable for both genetic and later environmental risk factors. Paper II found that paternal age was a small risk factor for both bipolar affective disorder and schizophrenia. A dose-response like pattern was found in relation to the risk of schizophrenia and, de novo mutations in the paternal germ cells could be an explanation for the excess risk of the disorders in persons with an old father (36;40-42). However, a selection of the old fathers could also explain the observed excess risk, as men becoming fathers for the first time at an old age tend to have a larger risk of admission with a psychiatric disorder (46).

Ethnicity/migration was not examined in this thesis, as only persons born i Denmark were included and the vast majority of the cohort members are ethnic Danes. Evidence from the literature suggests a genetic link, either because of a different genetic background of immigrants or a selection (which could be genetic) of persons who migrate (73;74), and thus here placed under the heading; operating before birth.

**Risk factors operating around birth**

Paper II suggested that persons born small for gestational age had an increased risk of schizophrenia and bipolar affective disorder. Many risk factors seemed to operate in the childhood and during pregnancy (26;96). An estimation by Kim-Cohen et al (97) suggested that 32% of the manic cases and 25% of schizophrenia cases could be prevented if successful treatment was conducted in the childhood of later patients. However, this was extrapolated from a small number of cases. In Paper II, it was only possible to follow persons born 1973 or later, thus limiting the opportunity to find strong evidence of a link between small for gestational age and bipolar affective disorder and schizophrenia. However, persons born preterm and small for gestational age showed an excess risk for both disorders. Evidence seems to suggest that stressors in early life trigger bipolar affective disorder and schizophrenia, and one of the alternative models to the Kraepelinian dichotomization originates from the hypothesis (see paragraph 9C).

Season of birth was not examined in this thesis, but in the literature it is suggested to be a risk factor for bipolar affective disorder and schizophrenia. Infections during pregnancy are risk factor for schizophrenia and psychosis, but studies of an association with bipolar affective disorder as a separate disorder have not been conducted. These observations suggest that early stressors influence highly on the risk of the two disorders (51-55).

**Stressful events later in life**

Paper II suggested that loss of a parent was a risk factor for both disorders; even loss of a parent from natural causes seemed to be a risk factor. It could be argued that loss of a parent should not be allocated in this group and with equal right could be placed in the previous group as the stressor took place in early life (or even, that it is due to genes in the parents), and no immediate symptoms or signs suggesting bipolar affective disorder or schizophrenia were observed. The risk of admission was almost the same, irrespective of age of the proband at the time of loss, but with a tendency to be larger if the loss was before the age of 5. In the literature, loss of a parent has also been suspected to be a risk factor, but mostly after suicide (36;98). This thesis suggests that loss of a parent after natural death is a risk factor as well.

Childbirth was not examined in this thesis, but has recently been examined (in the same cohort as paper II) as a risk factor for bipolar affective disorder and schizophrenia. Results showed that it was a risk factor for onset of both disorders, but only in women (46). The use of cannabis has not been examined in population based cohorts, but much evidence (65) seems to suggest it to be a risk factor for both disorders.

It can be concluded that evidence suggests that stressors in adult life can activate the onset of the two disorders.

**Behavioral markers as risk factors**

Premorbid adjustments have been shown in patients suffering from bipolar affective disorder and schizophrenia (64) but they are difficult to disentangling from consequences of the disorders.

**Mortality**

Paper III demonstrated that large excess mortality from all causes was present in unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia emphasizing, the severity of the disorders. Focusing on bipolar affective disorder and schizophrenia, high excess mortality rates were found, especially in the younger age groups. Schizophrenic patients have by definition a poor outcome as Kraepelin defined schizophrenia by a worse outcome, persistency and severity compared with bipolar affective disorder. Mortality was especially high for suicide compared to persons never admitted, but also mortality from natural death was high, irrespective of which cause of death was studied. Explanations of this could be side-effects of pharmacological treatment (99), unbalanced diets (100), rate of cigarette smoking (101;102), lesser use of medical services (103), or negative social consequences (60). A review by Tsuchiya et al. (62) concluded that bipolar affective disorder patients tended to be associated with unemployment, lower income and single marital status, all closely associated with increased mortality (104).

**In summary on the separate disorders**

The results from this thesis as well as evidence from the literature (6;96;105) suggest that the liability to schizophrenia and bipolar affective disorder is transmitted through a number of genes

with relative small effects. In the context of this genetic risk, or predisposition, numerous environmental factors operate as risk factors. Moreover, this thesis demonstrates that the environmental risk factors act in different stages of the life span. Stressors before, during, and after birth can trigger the disorders later in life, but also stressors later in adolescence and adult life can cause the onset of the disorder. However, it is difficult to pinpoint the exact timing of the risk factors, because some of the risk factors are possibly only proxy variables for the real risk factor or in some cases even only selection mechanisms. Furthermore, the risk factors, both environmental and genetic, interact with both known and unknown risk factors. None of the risk factors examined in this thesis (at least in the way they were defined here) or among the reviewed literature have been demonstrated to be a necessary cause for developing bipolar affective disorder or schizophrenia. In the same way none of the risk factors or combinations of them was sufficient causes of the disorders. The risk factors examined in this thesis is probably only a part of many risk factors for the disorders. The excess mortality is probably a combination of several 'life style' factors.

## 9C. Discussion of overlap between bipolar affective disorder and schizophrenia from paper I, II, III

There was an overlap in the disorders, since excess mortality was observed in both disorders, and risk factors were shared between the disorders. A familial aggregation of bipolar affective disorder in schizophrenic probands, and vice versa, was also present. Furthermore, patients suffering from schizoaffective disorder had a tendency to have previous admissions with bipolar affective disorder and schizophrenia (Table 3, Figure 3), indicating a phenotype difficult to classify for the clinicians, thereby emphasizing that persons with traits of both disorders existed. Moreover, schizoaffective disorder patients had an equal aggregation of schizophrenia and bipolar affective disorder in the first degree relatives. Risk factors for schizoaffective disorder, as, e.g., urbanicity at birth, presented size and characteristics that was a mixture of the risk factors for bipolar affective disorder and schizophrenia. The huge overlap between the diagnostic groups was a dilemma in it self. In most studies, the issue of persons having several different diagnoses over time was solved by assigning one lifetime diagnosis to a person, using a hierarchy with schizophrenia at the top. However, this approach had a tendency to underestimate the differences

between the diagnostic groups (106). In this thesis a non-hierarchic approached was used and large overlap between the disorders was found.

The risk factors presented in Table 1, but not tested in this thesis, showed the same tendency with an overlap of the risk factors between the disorders. However, some risk factors seemed to operate solely on one of the disorders, e.g., infections, urbanicity at birth, and developmental precursors, as risk factor for schizophrenia, but not for bipolar affective disorder. In the same way, there were differences in the excess mortality.

How does these results consent with the dichotomization versus the developmental model (7) or the continuum model (5;8), having in mind that causal inference, as pointed out, should be made with caution?

**If the Kraepelinian dichotomization** is assumed to be correct, one would expect some risk factors to have a different impact on the two disorders. But, the differences between the risk factors for bipolar affective disorder and schizophrenia were quantitative rather than qualitative, that is, only the magnitude, and not the direction of the risk factors, differed.
In opposition to the dichotomization schizoaffective disorder and the above described characteristics of persons suffering from this disorder also exist. In favor of a dichotomization is that gender composition and age at onset differed. Schizophrenia patients had a higher excess mortality from natural causes, which is in line with a worse outcome than bipolar affective disorder. The worse outcome of schizophrenia was one of the main reasons for Kraepelin's dichotomization.

**The developmental model** (7) suggests that certain susceptibility genes are shared between bipolar affective disorder and schizophrenia, and these genes predispose an individual to psychosis in general, and that other genes/environmental factors may act on this background resulting in schizophrenia, but in the absence of these additional gene/environmental factors, a pathway towards bipolar affective disorder is the result (Figure 12). The results presented in this thesis and the literature examined, where not in conflict with this hypothesis. The susceptibility genes should result in some common genetic risk factors (e.g., family history of bipolar affective

disorder and schizophrenia, age of the father by de novo mutations) and some acting only on the risk of schizophrenia (e.g., place of birth). Some environmental factors during pregnancy and childhood should only be risk factors for schizophrenia (e.g., small for gestational age for children born at term) and some for both disorders (e.g., parental loss). Other results from Table 1, not tested in the thesis, fitted well into the model as some risk factors were shared between the disorders and some unique to the disorders.

**The continuum model** (5;8) assumes the major psychiatric disorders to be a continuum from unipolar depressive disorder, to bipolar affective disorder, to schizoaffective disorder, to schizophrenia, with increasing severity, and worse outcome, across the spectrum (Figure 13). When considering this model we would expect some risk factors to show the same dose-response characteristic, and results from study II suggested that urbanicity, age of the father, and, to a lesser degree, small for gestational age had that dose response characteristics across the diagnostic groups. Study I also suggested schizoaffective disorder as an intermediate state between bipolar affective disorder and schizophrenia. However, gene-environment interaction was not examined.

It was clear from Paper I that bipolar affective disorder in a first degree relative is a much stronger risk factor for bipolar affective disorder than schizophrenia in a first degree relative, and vice versa for schizophrenia. It is not possible, from epidemiological studies of this type, to conclude on the degree of overlap between the disorders. However, all evidence suggests that an overlap is present. Whether the continuum model, taking all the major psychiatric disorders into account, or whether the developmental model is the correct one, can be difficult to disentangle from the studies in this thesis.

### 9D. Can the disorders be prevented?

Can schizophrenia and bipolar affective disorder be prevented and do epidemiological studies contribute to that? Many risk factors are merely statistical assertions and have no predictive value at individual level (58). However, some conclusions can be drawn from this thesis. The thesis demonstrates that several genetic and environmental risk factors operate on the individual risk for the disorders. In the search for susceptibility genes, the best way to elucidate the mechanism

behind the disorders would therefore be to take into account the environmental factors and the way they affect the risk of disorders. By doing that, it may be possible, through identification of ‘at risk’ individuals and appropriate interventions, ultimately to prevent the psychotic illness from developing (107). A gene-environment interaction has been shown between stressful life events and a functional polymorphism in the gene 5-HHT as risk factors for depression, and a gene-environment interaction between the COMT gene and cannabis use as a risk factor for psychosis (108;109). Other examples will probably arise in bipolar affective disorder and schizophrenia.

If schizophrenia and bipolar affective disorder, as this thesis suggest, at least in part has a common etiologic background, new studies must take that into account. Genetic studies have recently turned in the direction of examining susceptibility genes for both disorders, e.g., (17;18;110). By recognizing the possible overlap between the disorders, as well as taking gene-environment interactions into account, it may be possible to close in on the ultimate objective: to prevent bipolar affective disorder and schizophrenia.

# 10. Future studies

Future studies should:

- Focus on both bipolar affective disorders and schizophrenia and not only one of the disorders
- Focus on linkage of population based registers and bio-banks (with a larger degree of information on, e.g., a genetic level) which would make it possible to examine environmental and genetic factors and their interactions
- Use registers to locate differences and similarities between bipolar affective disorder and schizophrenia
- Use registers to describe the pattern of psychiatric patients shifting from one diagnostic category to another, and thereby clarify the relationship between the disorders

# 11. Conclusion

An aggregation of schizophrenia in families of probands suffering from schizophrenia was present in the cohort examined in this thesis, and bipolar affective disorder aggregated in families of probands suffering from bipolar affective disorder. Furthermore, probands suffering from schizophrenia had a smaller, but significant aggregation of bipolar affective disorder in the family, and vice versa. Paternal age, urbanicity at birth, being born small for gestational age, and loss of a parent, were all risk factors for both schizophrenia and bipolar affective disorder. However, differences were also present between bipolar affective disorder and schizophrenia, in particular in the impact of urbanicity at birth. Schizophrenic patients had an even larger excess mortality from natural death than bipolar affective disorder patients, whereas the opposite applied to unnatural death.

The results demonstrated an overlap in the risk factors, and outcome, for the two disorders. There were also differences between the phenotypes, but they were quantitative rather than qualitative, that is, only the magnitude, and not the direction of the risk factors, differed. Excess mortality was present in both disorders, and only the magnitude of the excess mortality differed. This could suggest a genetic and environmental overlap between the disorders, and results were not conflicting when they were held up against other models than the traditional Kraepelinian dichotomization of psychosis. However, a substantial difference in incidence rate and gender distribution, and the larger aggregation of bipolar affective disorder in the families of bipolar affective disorder patients (compared to schizophrenia, and vice versa) could indicate that the Kraepelinian dichotomization continues to be useful and warranted for the time being, not only in the clinical context, but also when studying the causes of schizophrenia and bipolar affective disorder, respectively. However, more attention should be paid to the possible overlap between bipolar affective disorder and schizophrenia.

Previous evidence and results from this thesis suggest that patients suffering from schizophrenia and bipolar affective disorder have a genetic vulnerability or predisposition towards the disorder (possibly at least overlapping) but environmental factors interact with this predisposition. Therefore, the results call for further research examining multiple risk factors at the same time, as well as incorporating individual genetic markers (and other individual samples, e.g., blood

samples) in population based cohorts, and comparing bipolar affective disorder and schizophrenia in the same setup, before or if the Kraepelinian dichotomization should be disregarded.

# 12. Summary

This Ph.D. thesis summarizes the results from 3 cohort studies describing risk factors for and mortality of major psychiatric disorders with focus on comparison between schizophrenia and bipolar affective disorder. Furthermore, the results are evaluated in the context of the dichotomization of schizophrenia and bipolar affective disorder.

The studies were based on four Danish registers: the Psychiatric Central Register, the Danish Civil Registration System, the Cause of Death Register, and the Danish Medical Birth Register. From the registers, large population based cohorts were identified and followed over several decades. Survival analysis techniques were applied to identify risk factors and mortality rates.

The results demonstrated an overlap in risk factors for schizophrenia and bipolar affective disorder. Excess mortality (compared to persons never admitted with a psychiatric disorder) was present in persons suffering from the two disorders. Differences were also found between the phenotypes, but they were quantitative rather than qualitative, that is, only magnitude, and not direction of the risk factors (and the excess mortality), differed. Results were not conflicting when they were held up against other models than the traditional Kraepelinian dichotomization of the disorders.

In conclusion, the results suggest that schizophrenia and bipolar affective disorder patients have a genetic vulnerability or predisposition towards the disorders (possibly at least overlapping), and environmental factors act (or interact) with this predisposition. However, large differences in gender distribution and age at onset are present, and differences and similarities between the disorders should be further examined before the Kraepelinian dichotomization can be disregarded.

# 13. Danish summary

Denne ph.d. afhandling sammenfatter resultaterne af 3 kohortestudier, som beskriver risikofaktorer for, og dødelighed efter, alvorlige psykiske sygdomme. En sammenligning af bipolar affektiv lidelse (tidligere benævnt maniodepressiv lidelse) og skizofreni er især i fokus. Resultaterne bliver evalueret med henblik på at undersøge, om den traditionelle tvedeling af bipolar affektiv lidelse og skizofreni skal tages op til overvejelse.

Kohortestudierne baserer sig på fire danske registre: Det Psykiatriske Centralregister, CPR Registret, Dødsårsagsregistret og Det Medicinske Fødselsregister. Store populationsbaserede kohorter blev identificeret og fulgt gennem flere årtier. Risikofaktorer og dødelighedsrater blev udregnet ved hjælp af statistiske overlevelsesanalyser.

Studierne viste et overlap mellem risikofaktorerne for skizofreni og bipolar affektiv sindslidelse. Patienter indlagt med de to psykiske lidelser havde efterfølgende en overdødelighed i forhold til personer uden psykisk sygdom. Der var også nogle forskelle i risikofaktorerne for de to psykiske sygdomme, men det var mere forskelle i størrelsen af risikofaktorerne og ikke retningen af dem. På samme måde var der små forskelle i dødelighedsraterne, men det overordnede billede var en stor overdødelighed. Resultaterne stemte overens med alternative forklaringer til den traditionelle Kraepelinske dikotomisering.

Konklusionen på afhandlingen er, at det tyder på, at personer, der får skizofreni eller bipolar affektiv sindslidelse, har en fælles genetisk sårbarhed, eller prædisponering, for de to sygdomme, som bliver påvirket af forskellige miljøbestemte risikofaktorer. Der er dog store forskelle på køns- og aldersfordelingerne i de to grupper af sygdomme, og yderligere analyser af forskelle og ligheder mellem skizofreni og bipolar affektiv lidelse skal udføres inden den Kraepelinske dikotomisering af sygdommene kan forlades.

# 14. Figures and tables

**Table 1**

**Risk factors for bipolar affective disorder and schizophrenia**

| | Bipolar affective disorder | Schizophrenia |
|---|---|---|
| **Family history of psych. adm.*** | ✓ | ✓ |
| **Small for gestational age*** | ? | ✓ |
| **Urbanicity of place of birth*** | ✓/ | ✓ |
| **Early parental loss*** | ✓ | ? |
| **Paternal/maternal age*** | ? | ✓ |
| Recent stress espec. by loss of child | ✓ | ✓ |
| Child birth | ✓ | ? |
| Infections | ? | ✓ |
| Season of birth | ? | ✓ |
| Socioeconomic status | ? | ? |
| Developmental precursors | ✓/ | ✓ |
| Cannabis | ? | ✓ |
| Ethnicity and migration | ? | ✓ |

* Risk factors examined in this thesis.

✓ = Evidence suggesting a positive or negative association

✓/ = Evidence suggesting an exclusion of association

? = Inconclusive evidence or conflicting evidence for or against an association

**Table 2**

**Cause of death. N = 1 749 417**

| | Cause of death* | ICD10 | ICD8 | N | Percent |
|---|---|---|---|---|---|
| 01 | Tuberculosis | A15-A19, B90 | 010-019 | 2 180 | 0.12 % |
| 02 | Infection | A00-A09, A20-A99, B00-B89, B91-B99 | 000-009,020-136 | 14 541 | 0.83 % |
| 03 | Malignant neoplasm | C00-D09 | 140-209 | 433 711 | 24.79 % |
| 04 | Old age including apoplexy | F03.9, I60-I72, R54 | 430-438, 794-794, 290-315, 440-448 | 241 518 | 13.81 % |
| 05 | Cardiovascular diseases | I00-I25,I27,I30-I52 | 390-429 | 549 131 | 31.39 % |
| 06 | Respiratory diseases | J00-J99 | 460-519 | 132 274 | 7.56 % |
| 07 | Digestive diseases | K00-K93 | 520-577 | 61 837 | 3.53 % |
| 08 | Genito-urinary diseases | N00-N99 | 580-629 | 23 825 | 1.36 % |
| 09 | Malform. and chr. anomalies | Q00-Q99 | 740-759 | 8 825 | 0.50 % |
| 10 | Illness in the perinat. Per. | P00-P96 | 760-779 | 7 261 | 0.42 % |
| 11 | Suicide | X60-X84, Y87.0 | 950-959 | 37 264 | 2.13 % |
| 12 | Homicide | X85-Y09, Y87.l | 960-978 | 1 660 | 0.09 % |
| 13 | Accidents | V01-X59, Y10-Y86, Y87.2, Y88-Y89 | 810-823, 800-807, 825-949 | 70 397 | 4.02 % |
| 14 | All other | Rest | 210-289, 320-389, 450-458, 630-738, 780-793, 795-796, 979-999 | 164 993 | 9.43 % |

* Cause 01-10, 14 = natural cause of death. Cause 11, 12, 13 = unnatural cause of death. Updated to 2000.

**Table 3**

**Overlap between diagnostic groups, paper II***

| Current admission | Previous admission | | | |
|---|---|---|---|---|
| | Unipolar | Bipolar | Schizoaff. | Schizophr |
| Unipolar<br>N = 31,752 | ---<br>--- | 2.2%<br>N = 699 | 0.6%<br>N = 188 | 2.5%<br>N = 809 |
| Bipolar<br>N = 4,490 | 33.5%<br>N = 1459 | ---<br>--- | 4.9%<br>N = 221 | 9.15%<br>N = 411 |
| Schizoaff<br>N = 2,115 | 35.9%<br>N = 759 | 26.2%<br>N = 553 | ---<br>--- | 38.0%<br>N = 803 |
| Schizophr<br>N = 13,297 | 12.5%<br>N = 1665 | 3.3%<br>N = 441 | 3.4%<br>N = 457 | ---<br>--- |

Note: Previous admissions not mutually exclusive. Previous admission defined as admission on the same day or before.

**Table 4**

**Adjusted relative risk (RR) for developing schizoaffective disorder, bipolar affective disorder and schizophrenia, associated with family history of psychiatric illness, paper I ***

| Family history of psychiatric diseases | Schizoaffective disorder RR (95 % conf. Int.) | Bipolar affective disorder RR (95 % conf. Int.) | Schizophrenia RR (95 % conf. Int.) |
|---|---|---|---|
| Not admitted (ref) | 1.00 - | 1.00 - | 1.00 - |
| Any contact | 2.76 (2.49, 3.06) | 2.39 (2.21, 2.58) | 2.41 (2.31, 2.51) |
| Additional effect of: | | | |
| Bipolar aff disorder | 3.23 (2.63, 3.95) | 5.19 (4.52, 5.95) | 1.44 (1.27, 1.63) |
| Schizophrenia | 2.57 (2.11, 3.13) | 1.69 (1.42, 2.01) | 3.22 (2.96, 3.50) |
| Schizoaffective dis. | 1.92 (1.43, 2.57) | 1.34 (1.05, 1.71) | 1.20 (1.01, 1.44) |

* Relative risk, mutually adjusted for family history of psychiatric illness, birth order, paternal/maternal age at birth, place of birth, number of siblings, calendar year and gender-age interactions.

**Table 5**

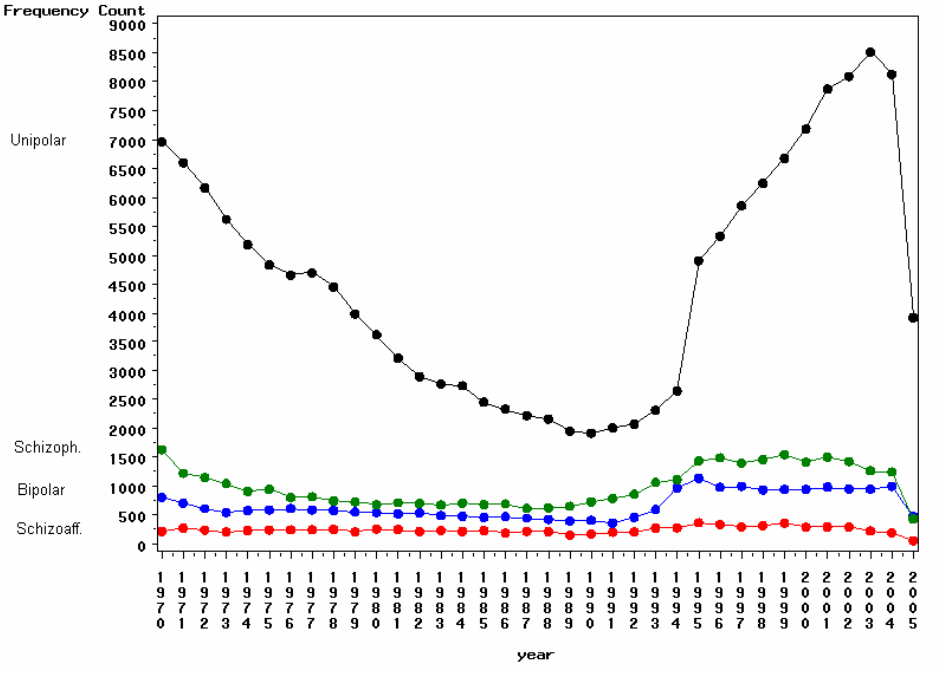
**Association between selected risk factors and mental disorder, paper II ***

| | **Unipolar** | **Bipolar** | **Schizoaff** | **Schizophr.** |
|---|---|---|---|---|
| **Loss of a parent, natural** | + | + | + | + |
| **Loss of a parent, unnatural** | ++ | ++ | ++ | ++ |
| **Paternal age** | + | + | + | ++ |
| **Place of birth** | + | + | ++ | +++ |
| **S. f. ges. age 37-** | ++ | ++ | ++ | + |
| **S. f. ges. age 37+** | - | - | - | + |

* Association indicated by:
- : no association.
+: weak association.
++: some association.
+++: strong association.

## Figure 1

**Number of incident inpatient/outpatient stays in the Danish Psychiatric Central Register, from 1970 to July, 2005**




## Figure 2

**Number of births in Denmark from 1955 to 2004**

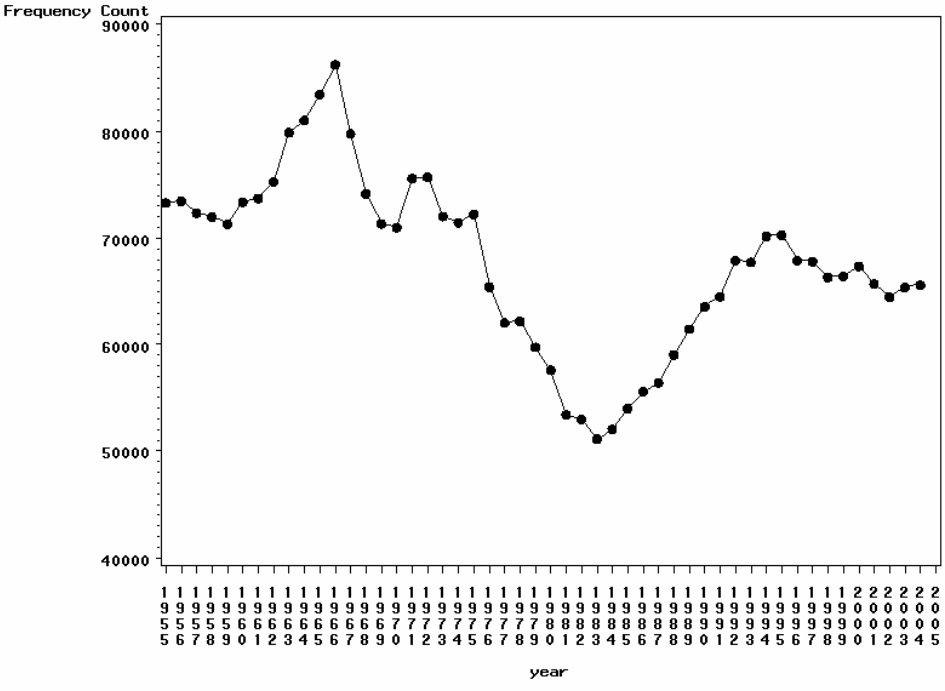
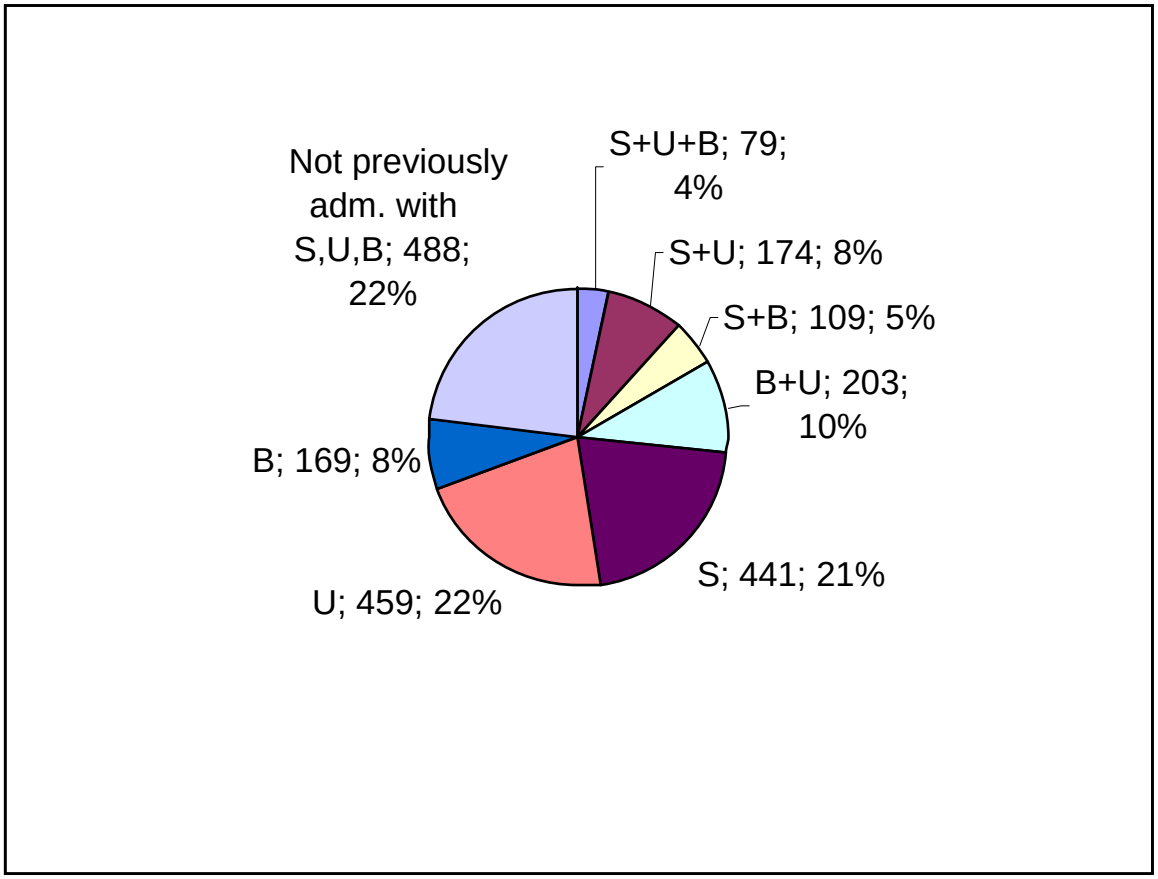


**Figure 3**

**Patients previous admission before being diagnosed with schizoaffective disorder, paper II**

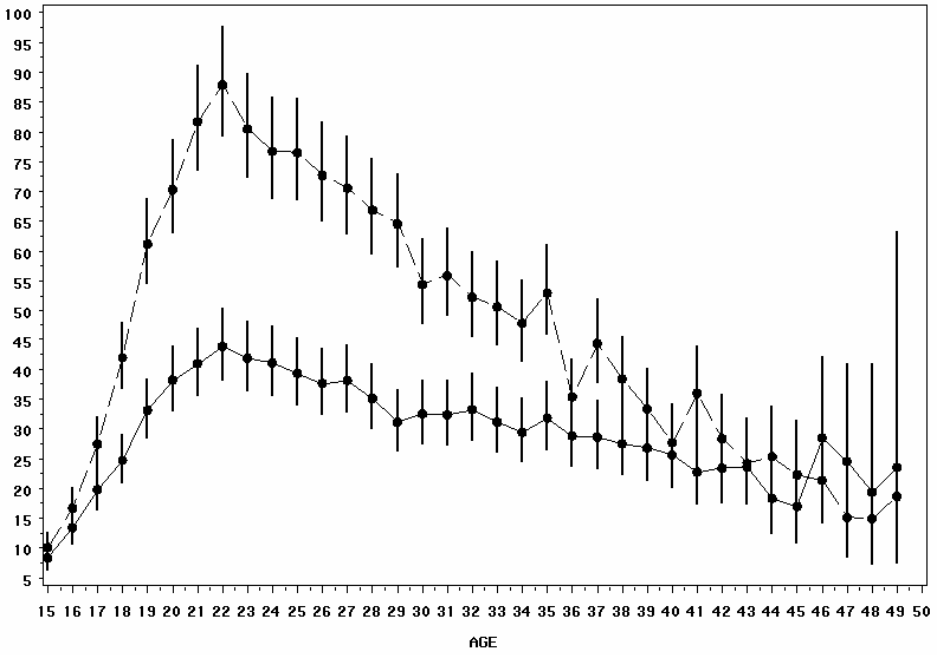



*

* Cohort members born in Denmark 1955 or later. Percent rounded. S = schizophrenia, B = bipolar affective disorder, U = unipolar depressive disorder.

**Figure 4**

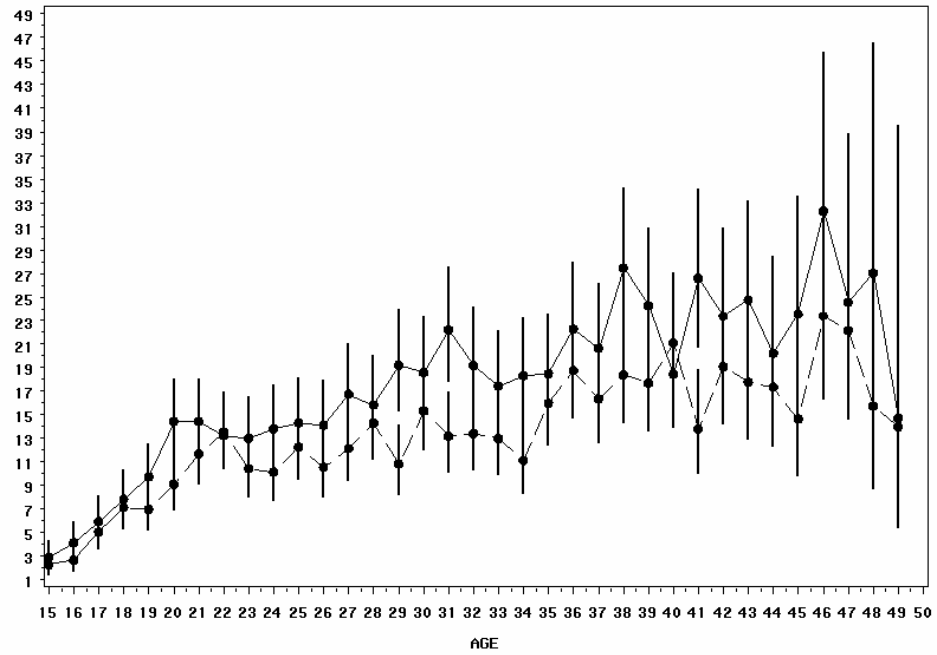
**Age specific incidence of admission with schizophrenia, paper II**




Incidence per 100.000 person years. Adjusted for calendar time. Ref. cat. = 2000. Vertical lines represent 95% conf. int. Dotted line = Men. Full line = Women.

**Figure 5**

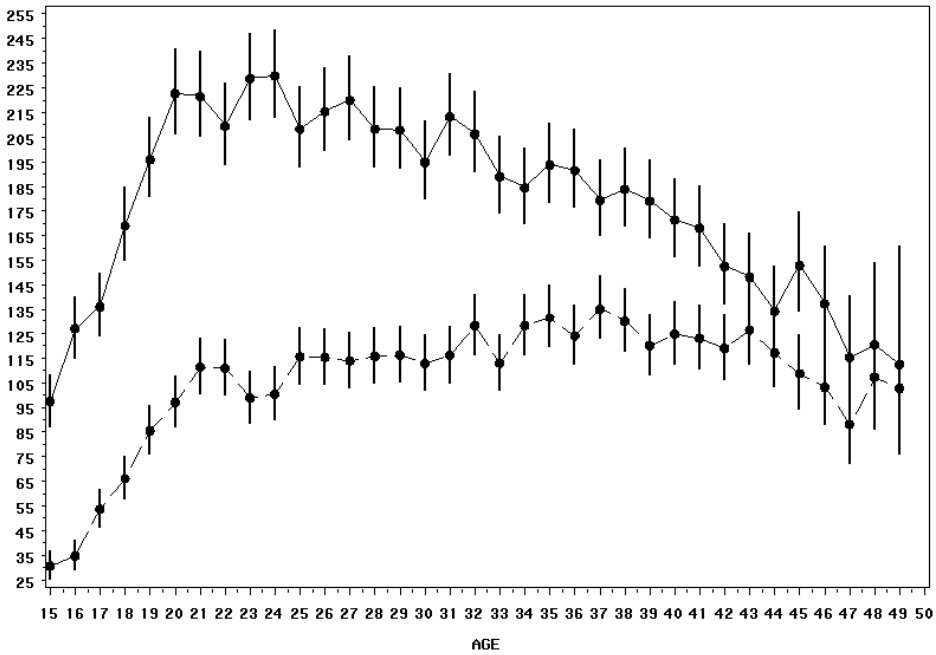
**Age specific incidence of adm. with bipolar affective disorder, paper II**




Incidence per 100.000 person years. Adjusted for calendar time. Ref. cat. = 2000. Vertical lines represent 95% conf. int. Dotted line = Men. Full line = Women.

**Figure 6**

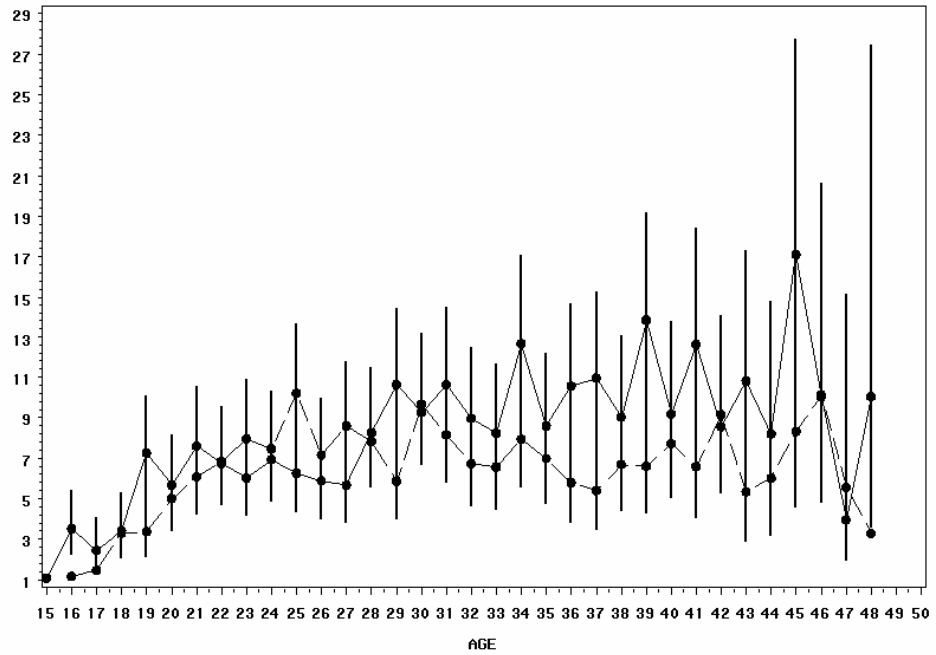
**Age specific incidence of admission with unipolar depressive disorder, paper II**




Incidence per 100.000 person years. Adjusted for calendar time. Ref. cat. = 2000. Vertical lines represent 95% conf. intervals. Dotted line = Men. Full line = Women.

**Figure 7**

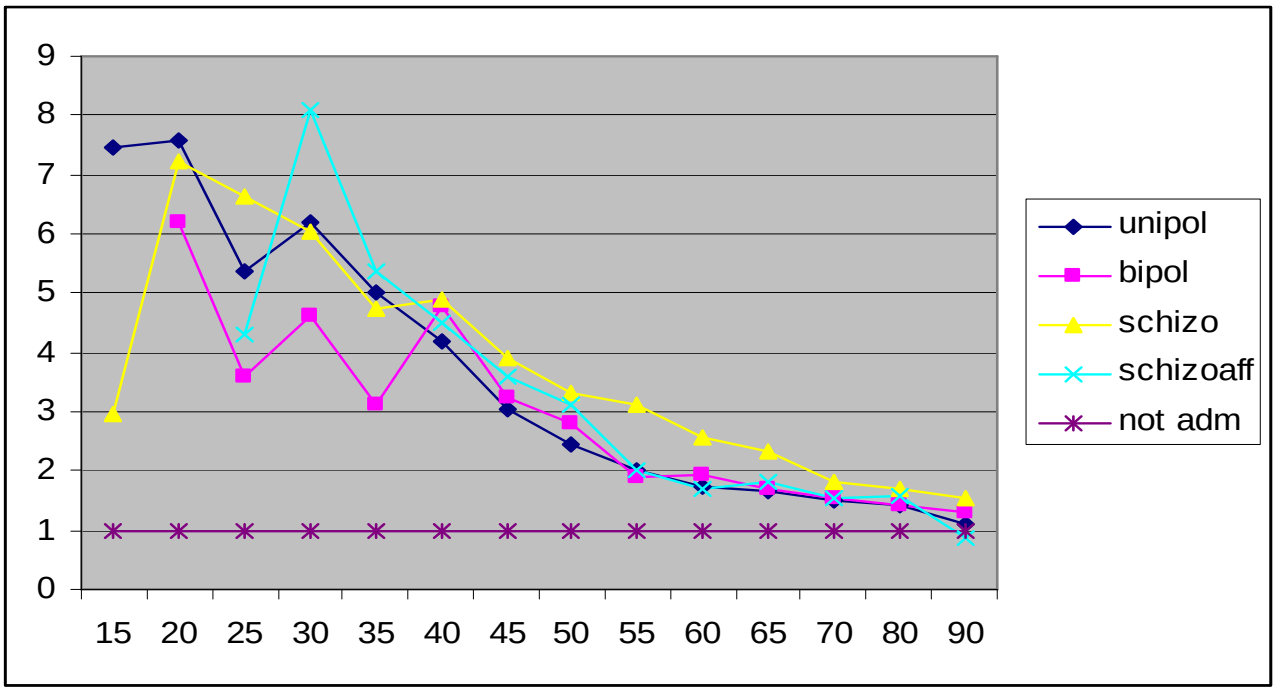
**Age specific incidence of admission with schizoaffective disorder, paper II**




Incidence per 100.000 person years. Adjusted for calendar time. Ref. cat. = 2000. represent 95% conf. int. Dotted line = Men. Full line = Women.

**Figure 8**

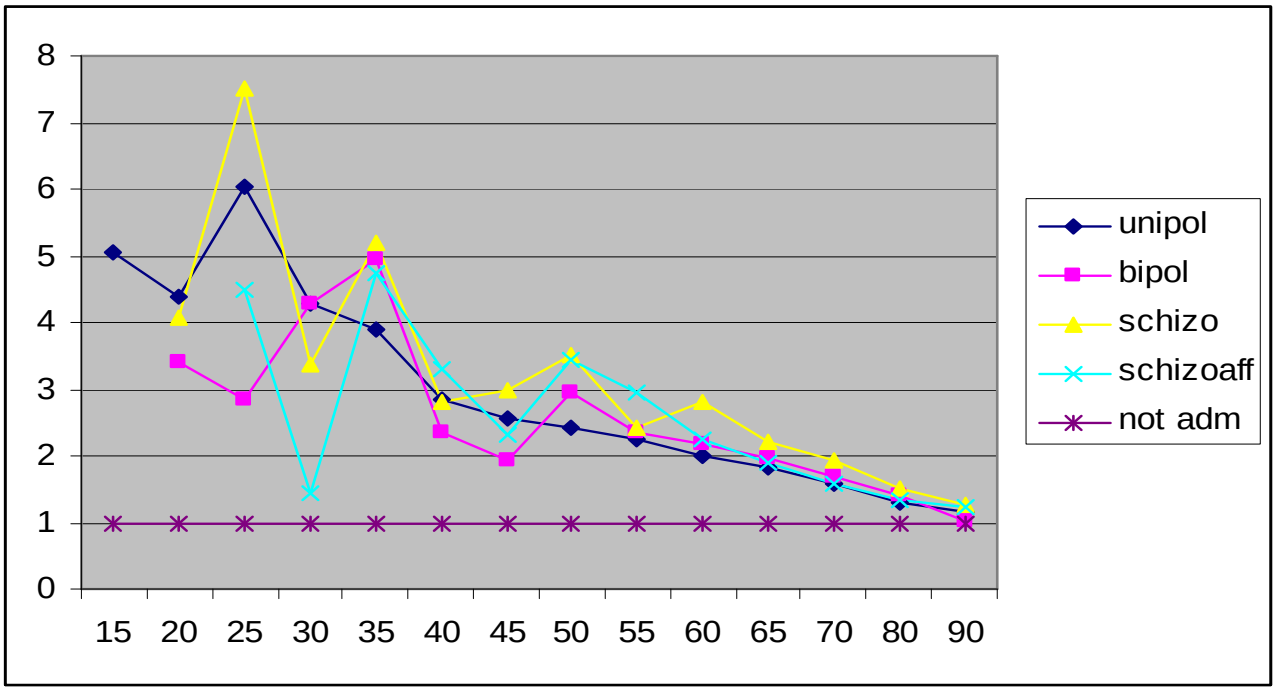
**Mortality rate ratio according to admission status, natural death, men, stratified by age, paper III ***




* Adjusted for calendar-time. Reference = never admitted to a psychiatric hospital.

**Figure 9**

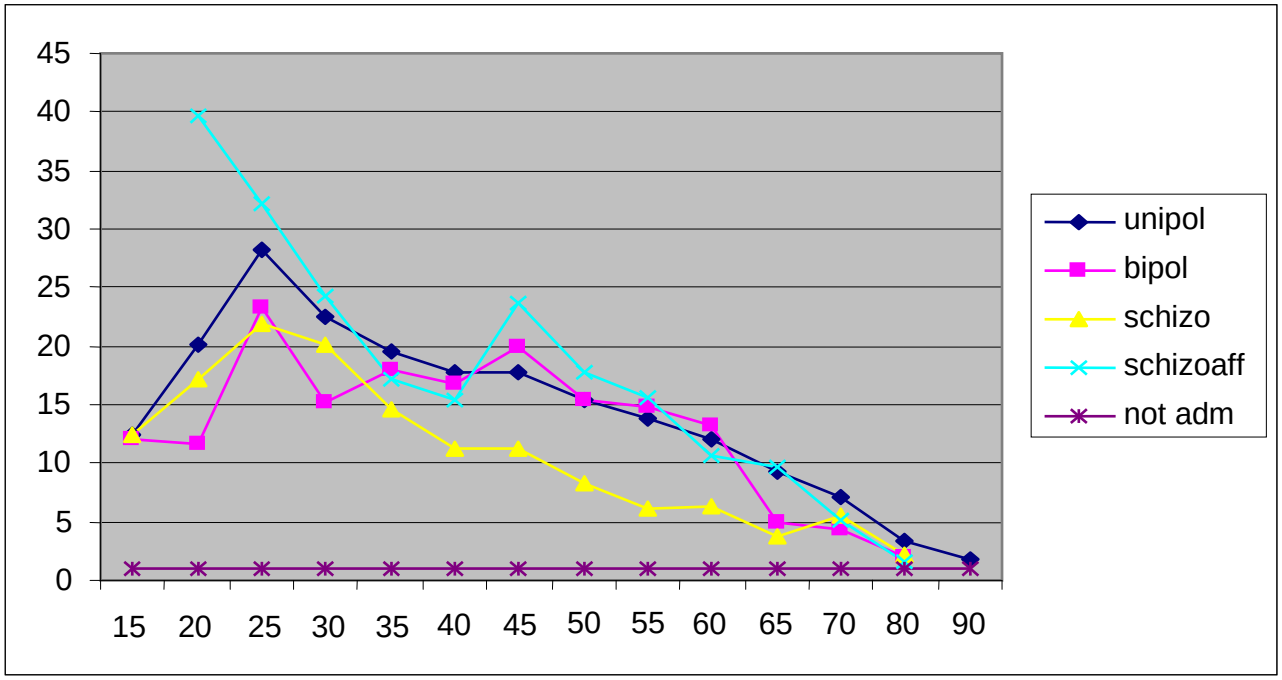
**Mortality rate ratio according to admission status, natural death, women, stratified by age, paper III ***




* Adjusted for calendar-time. Reference = never admitted to a psychiatric hospital.

**Figure 10**

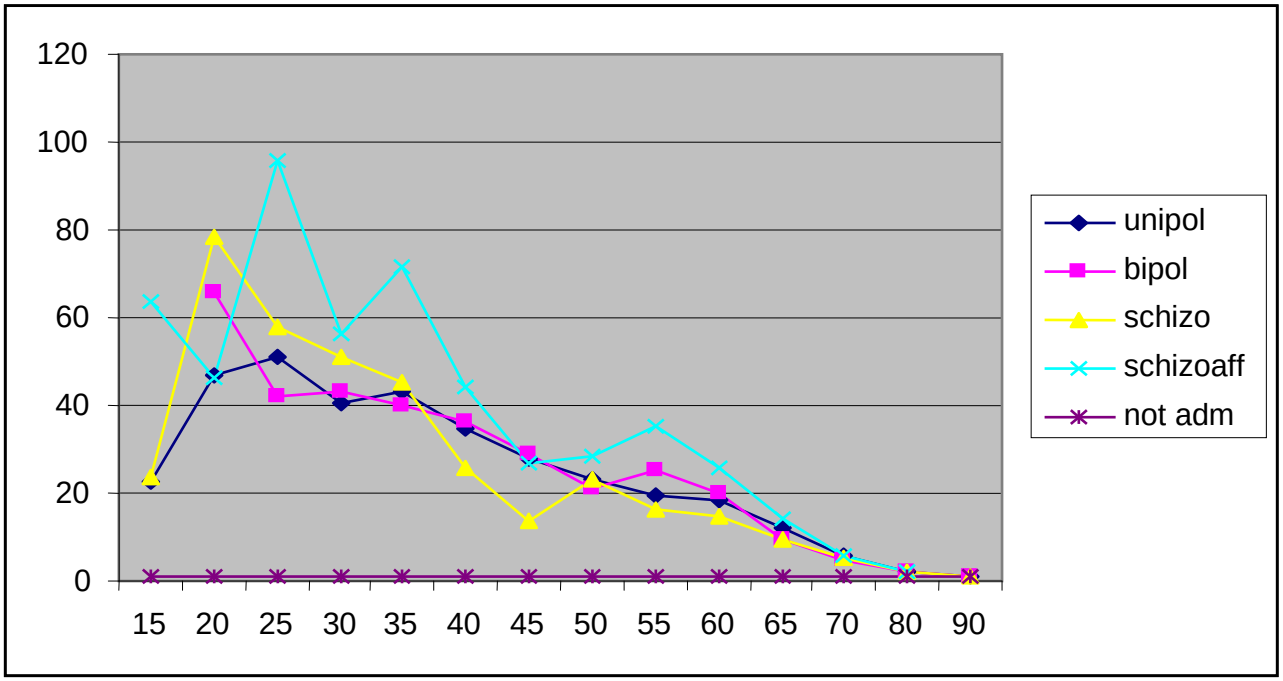
**Mortality rate ratio according to admission status, unnatural death, men, stratified by age, paper III ***




* Adjusted for calendar-time. Reference group = never admitted to a psychiatric hospital.

**Figure 11**

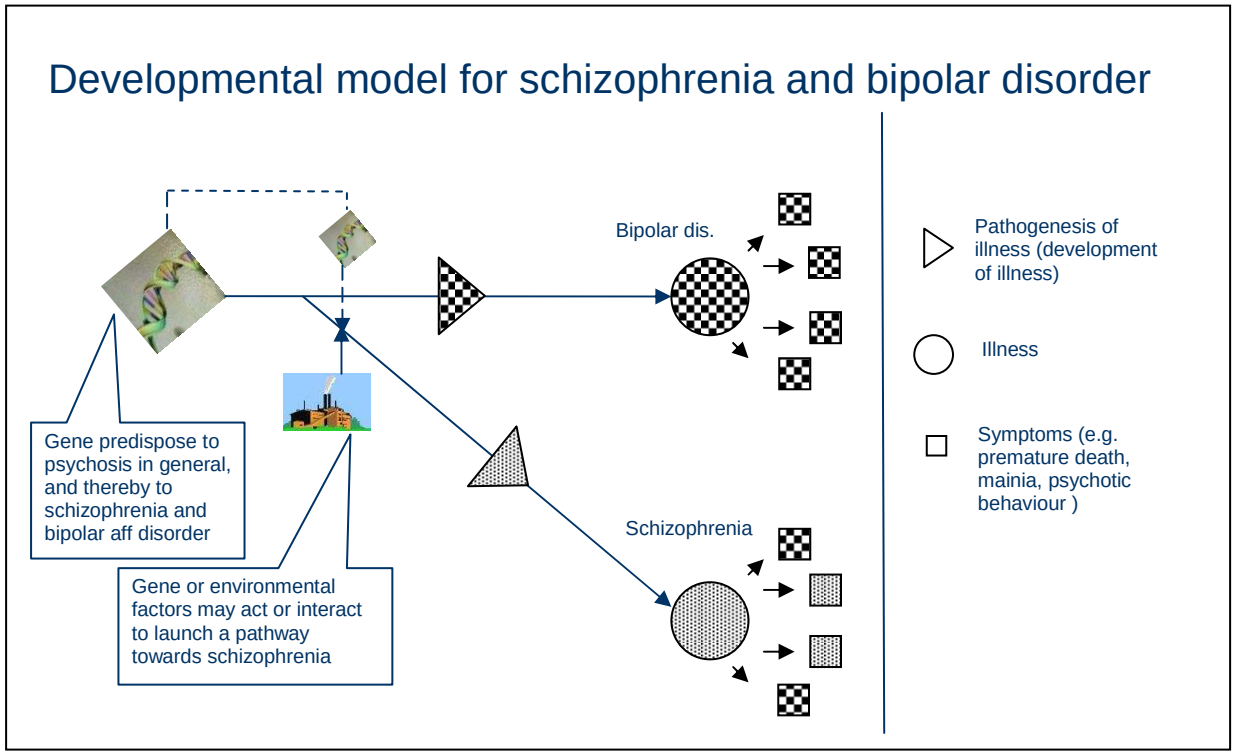
**Mortality rate ratio according to admission status, unnatural death, woman, stratified by age, paper III ***




*: Adjusted for calendar-time. Reference group = never admitted to a psychiatric hospital.

**Figure 12**

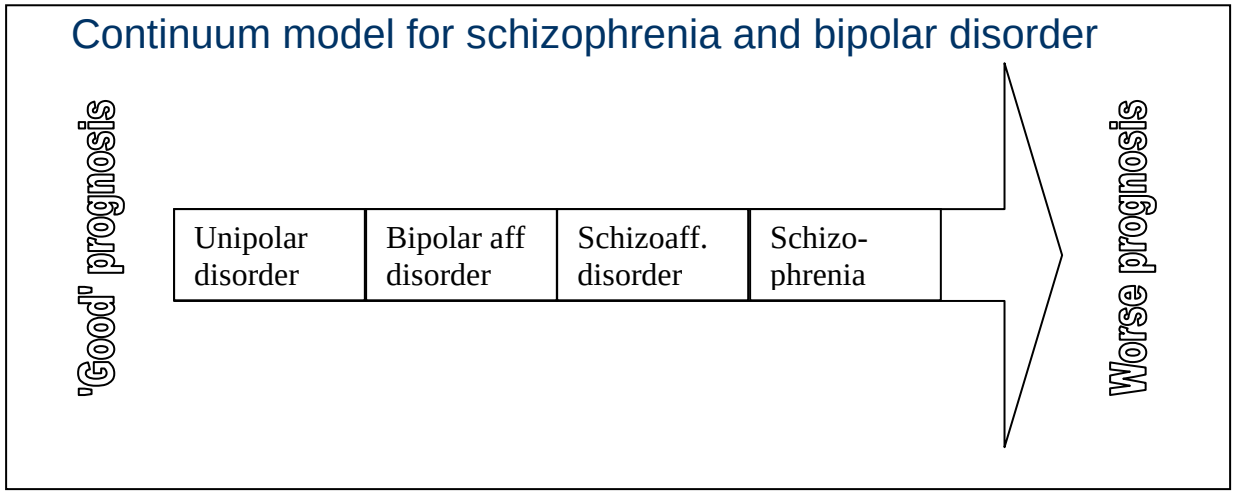
**The developmental model for the association between bipolar affective disorder and schizophrenia**




Inspired by Murray et al. (7).

**Figure 13**

**The continuum model for the association between bipolar affective disorder and schizophrenia**




Inspired by Angst and Moller (5;8) and others.

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