

## STUDIES REPORTING HIGHER INCIDENCE RATES AMONG THE MALES

Table XIII summarizes the findings from studies reporting incidence rates of schizophrenia that were higher in males compared to females.

Munk-Jørgensen (1986) selected all the Danish citizens aged 15 years and older that were admitted for the first time in 1972 to a Danish psychiatric institution as in- or day-patients with a diagnosis of schizophrenia according to the ICD-8 criteria. Incidence rates were computed separately in two groups of patients: those receiving a diagnosis of schizophrenia either at their first or at a subsequent admission and those receiving a diagnosis of schizophrenia at their first admission only. In both groups, incidence rates were significantly higher in males compared to females.

Cooper et al. (1987) identified every patient living in the catchment area of a group of psychiatric hospitals and making their first-ever contact during a two-year period because of a potentially schizophrenic illness. Sex-specific rates were provided for a broad definition of schizophrenia, including the diagnostic categories of schizophrenia (ICD-9 295), paranoid states (297) and reactive psychoses (298.2-298.9). Incidence rates were higher in males compared to females, although statistical tests were not performed.

In Canada, Iacono & Beiser (1992) selected individuals aged 15 to 54 years that had lived in the Vancouver metropolitan area for at least 6 months, had no organic cerebral illness, severe mental retardation, chronic physical disorder or chemical dependence, and had not been previously treated with antipsychotic, antimanic or antidepressant drugs. The case-finding network included all the psychiatric hospitals in the area, university and college counselling services, community mental health centers, psychiatrists in private practice, private counselling services, and a random sample of one-sixth of the general practitioners. Incidence rates for schizophrenia were significantly higher in males than in females, irrespective of the diagnostic system used.

Nicole et al. (1992) sampled all the individuals living in the catchment area of Lafontaine Hospital at their first lifetime admission to hospital between 1983 and 1987 with an initial or revised diagnosis of psychotic disorder according to ICD-9 (295, 297, 298, 301.22). For patients with an ICD-9 diagnosis of psychotic disorder, case-notes were reviewed in order to identify those subjects satisfying also the DSM-III-R criteria for schizophrenia at first admission. Incidence rates were higher in males than in females according to both the ICD-9 and the DSM-III-R criteria.

Castle et al. (1993) relied on the Camberwell Cumulative Psychiatric Case Register to select all the individuals having their first contact with psychiatric services between 1965 and 1984 and receiving a diagnosis of schizophrenia. The Operational Criteria Checklist for Psychotic Illness (OPCRIT) (McGuffin et al., 1991) was used to make diagnosis according to a range of different

diagnostic criteria. According to the diagnostic criteria setting no limit to age at onset of schizophrenia (i.e., ICD-9, the Research Diagnostic Criteria, DSM-III-R), there was a slight preponderance of males in overall incidence rates, but a gender difference reaching statistical significance was detected according to the DSM-III-R criteria only. However, when incidence rates were computed separately for two groups of individuals (i.e., those aged less than 45 years and those aged 45 years or older), higher incidence rates among the males were found in the younger age group, whereas a female preponderance was observed in people aged 45 years or older. On the other hand, incidence rates were higher in males compared to females according to the diagnostic criteria setting a limit to age at onset of schizophrenia (i.e., 45 years according to DSM-III and 40 years according to Feighner criteria).

Using the Danish Psychiatric Case Register, Lynge & Jacobsen (1995) identified all the residents in Greenland that were admitted for the first time to a psychiatric hospital or ward in Greenland or Denmark during the period January 1980 to December 1983 and were diagnosed at least once as having schizophrenia either during hospitalization or during outpatient treatment. In the total sample, incidence rates were higher in males compared to females.

Finally, Hickling & Rodgers-Johnson (1995) estimated incidence rates of schizophrenia in Jamaica, sampling patients from medical officers in public and private health sectors. According to the CATEGO class S+, incidence rates were higher in males compared to females and the gender difference was greater among individuals aged 15 to 29 years.

**Table XIII** - Studies reporting higher incidence rates in male compared to female subjects with schizophrenia

Author Country time	Population (N) Age	Diagnostic criteria	Incidence rates (rate/100,000/year)		Male-to-female sex ratio
			Males	Females	
Munk-Jørgensen (1986) Denmark, 1972	3.9 millions (r) > 14	ICD-8 (cl,re)	19.3	10.8	1.79
Cooper et al. (1987) UK, 1978-80	202,214 (r) 15 -54	ICD-9 (cl,br)	28.0	14.0	2.00
Iacono & Beiser (1992) Canada, 1982-84	757,510 (r) 15 - 54	DSM-III (cl,re) ICD-9 (cl,re) RDC (cl,re) Feighner (cl,re) Carpenter (cl,re)	6.8 10.9 7.6 5.6 6.8	2.0 4.1 2.5 1.7 2.5	3.47 2.64 2.98 3.20 2.67
Nicole et al. (1992) Canada, 1983-87	338,300 (t) no age limit	DSM-III-R ICD-9 (br)	12.6 39.8	4.9 22.4	2.57 1.78
Castle et al. (1993) England, 1965 and 1984	171,000 (t) (1965) 118,000 (t) (1984)	ICD-9 (cl,br) <45 years >45 years total RDC (op,re) <45 years >45 years total DSM-III-R (op,re) <45 years >45 years total DSM-III (op,re) <45 years Feighner (op,re) <40 years	25.2 10.4 19.2 16.4 8.7 13.7 11.1 5.2 9.0 13.9 14.8	17.8 17.1 17.6 10.4 14.3 11.9 5.2 9.0 6.7 6.3 6.0	1.41 0.50 1.13 1.58 0.61 1.16 2.14 0.58 1.34 2.20 2.49
Lynge & Jacobsen (1995) Greenland, 1980-83	not reported >14	ICD-8 (cl,re)	40.5	22.5	1.80
Hickling & Rodgers-Johnson (1995) Jamaica, 1992	2.46 millions (t) 15-54	ICD-8 (op,re)	30.4	16.6	1.84

cl=clinical

op=operational

r=risk

re =restrictive

t=total

## **FACTORS THAT MAY INFLUENCE GENDER DIFFERENCES IN INCIDENCE RATES OF SCHIZOPHRENIA**

Incidence rates of schizophrenia vary widely across studies and countries. Moreover, no consistent pattern of gender differences in incidence rates of schizophrenia has been detected. Indeed, most studies have reported that incidence rates are similar in males and females. On the other hand, when gender differences are detected, incidence rates are higher among the males. There is some evidence that higher incidence rates among the males occur especially in the younger age groups, whereas a female preponderance has been reported among individuals with first-onset schizophrenia after age 45.

Several factors may partly account for differences in incidence rates of schizophrenia across studies and countries and influence the male-to-female sex ratios that are detected. These factors include: i) sampling methods; ii) diagnostic criteria; iii) methods used to compute incidence rates; iv) time trends.

### **i) Sampling methods**

The comprehensiveness of the case-finding procedure is of paramount importance in incidence studies of psychiatric disorders. Since annual incidence rates of schizophrenia are expected to be low, prospective follow-up studies assessing the first onset of the disorder in the general population are an expensive and often impracticable endeavour. Indeed, among the studies that have been reviewed, only the WHO Collaborative Study on Determinants of Outcome of Severe Mental Disorders (Sartorius et al., 1986; Jablensky et al., 1992) and Hickling & Rodgers-Johnson's (1995) study have relied on a prospective strategy, whereas the others have used hospital admission statistics or psychiatric case register data.

Several types of criticism can be raised to hospital admission statistics or psychiatric case register data. First, these methods allow for large numbers of patients to be selected with comparatively small effort, but only 'administrative' or 'treated' incidence rates can be derived. It can be expected that 'administrative' or 'treated' incidence rates reflect 'true' incidence rates provided that the lifetime risk for patients with schizophrenia to contact psychiatric services approximates 100%. Actually, this assumption seems questionable. A review of several community studies has reported that the percentage of individuals with schizophrenia that are treated at psychiatric services varies widely, ranging from as low as 50% to 100% (Hambrecht et al., 1994b). Similarly, the data collected during the NIMH-Epidemiologic Catchment Area Study have shown that, among individuals with schizophrenic symptoms during the six months prior to interview, only 57% received some form of outpatient mental health service during that

period or inpatient hospitalization within the prior year (Robins & Regier, 1991). It follows that rates based on contacts with health services should be supplemented with the findings from field studies performed in order to detect subjects with schizophrenia who were never in contact with psychiatric services, to determine the age at onset of the disorder both for these patients and for those who were in contact with psychiatric services, and then to compensate for possible sampling bias (Strömngren, 1987).

Second, studies recording first contacts with psychiatric services sometimes select patients from catchment areas that are very small. It follows that incidence rates may be largely affected by selection artifacts and random influences. Collecting cases over long periods of time may extend the sample, but the stability of social, service or research-related conditions cannot be preserved. For example, Stoll et al. (1993) examined discharge diagnoses from six North American psychiatric teaching hospitals between 1972 and 1988. Beginning in the early 1970s, a gradual increase in the frequency of diagnoses of major affective disorders at all sites was accompanied by a corresponding decrease in diagnoses of schizophrenia at five of the six sites. Overall, diagnoses of schizophrenia showed a threefold decrease and diagnoses of major affective disorders a fourfold increase. Although a true increase in the incidence of affective disorders might be coupled with a real decrease in new cases of schizophrenia, several other forces might influence these changes (e.g., the criteria introduced by DSM-III, which restricted the definition of schizophrenia and broadened the category of major affective disorders; treatment-oriented diagnostic biases associated with the availability of lithium and other mood-altering agents; economic and social forces, including better third-party reimbursement rates and so on). Similarly, Strömngren (1987) examined admissions to the Psychiatric Hospital in Aarhus during the first 100 years of its existence and found that changes in admission rates were correlated primarily to availability of space in the psychiatric institutions, reflecting the natural history of hospital buildings and the political history of Denmark rather than true changes in the incidence of mental disorders. Much the same conclusions were suggested also by Brenner (1973) in his analysis of admissions to New York State Mental Hospital between the mid-nineteenth century and the late 1960s, where admission rates tended to increase during periods of economic decline and this relationship was stronger for patients with diagnoses of functional psychosis.

Third, incidence rates are often based on the annual number of first hospital admissions (or first psychiatric contacts) receiving a diagnosis of schizophrenia. Studies based on local hospital admission statistics can seldom distinguish between first and subsequent admissions for the same disorder; in addition, previous episodes are rarely investigated to control for diagnosis or other relevant clinical features. The resulting distortion can be substantial. Kendell et al. (1993) investigated the methodological problems and sources of bias that may influence the relationship between admission rates and incidence, performing an analysis of inception rates

for schizophrenia and other psychoses in Edinburgh between 1971 and 1989. It was shown that 59% of schizophrenic patients coded as 'first admissions' in 1971 had been in hospital before; even in 1989, 28% of a relatively small number of schizophrenic patients at their 'first admission' were wrongly coded.

Duplication of cases can be eliminated if data are derived from psychiatric case registers, since all the contacts with psychiatric services within a defined catchment area are listed in each individual's data file. However, sufficient provision of care and quality of diagnosis are necessary for the samples drawn from psychiatric case registers to be comprehensive. Although there is evidence that inter-rater agreement on diagnostic codings can be satisfactory, when codings are grouped into a limited number of broad categories (Sytema et al., 1989), diagnoses may be of limited reliability when they are assigned by many different clinicians in very different psychiatric institutions or by clerical staff (Kendell & Kemp, 1989; Sibisi, 1990; Löffler et al., 1994).

Moreover, schizophrenia poses unique difficulties. Munk-Jørgensen (1985) studied a cohort of Danish patients that were admitted to psychiatric institutions for the first time in 1972 and received a diagnosis of schizophrenia either during that year or some time during the following 10 years. Only 50% of the male and 40% of the female patients received a diagnosis of schizophrenia during their first admission. In retrospect, most of the patients later diagnosed as schizophrenics were suffering from the same disease during their first admission and could have received the diagnosis at that time. Nonetheless, an average of 1.7 years for males and 2.2 years for females elapsed between patient's first admission to a psychiatric institution and diagnosis of schizophrenia. Similarly, Hambrecht et al. (1994b) have suggested that there might be a bias against diagnosing schizophrenia. The correspondence between clinical diagnoses and operationalized diagnoses based on the recorded symptomatology was investigated in a random sample of 116 case records drawn from the Danish National Psychiatric Case Register out of all first admissions with a diagnosis of schizophrenia or similar disorders. At first hospital admission, schizophrenia was clearly underdiagnosed clinically and, as a result, was underestimated in the case register, with females being affected more (55.1%) than males (22.4%) by this bias reflecting diagnostic preferences.

## **ii) Diagnostic criteria**

A broad definition of schizophrenia based on clinical criteria is reasonable within the screening process in order to select all probable cases. It is then important to apply operational diagnostic criteria to ensure reliability and validity of diagnosis and comparability of findings across different studies. Kendell et al. (1993) investigated whether the incidence of schizophrenia was falling in the city of Edinburgh between 1971 and 1989, by controlling for possible

confounding factors. Diagnoses of schizophrenia made at first admissions by hospital psychiatrists were checked with those generated by four of the algorithms in the OPCRIT program, namely those simulating the Research Diagnostic Criteria, the criteria of DSM-III-R, the criteria of ICD-10 and Schneiderian first-rank symptoms. Although the proportion of first-admission patients diagnosed as schizophrenics by hospital psychiatrists declined by 22% during the period of study, there was no analogous decline in the proportion so diagnosed by the consistent criteria of a computer algorithm.

A second issue refers to the application of upper age limits to the onset of schizophrenia (i.e., 40 years according to Feighner criteria and 45 years according to DSM-III). Since age at onset of schizophrenia has been reported to be lower in males than in females, this can result in an artifactual excess of males in incidence rates. Using the data from the ABC-Schizophrenia Study, in which subjects aged 12 to 59 years were selected, Hambrecht et al. (1994b) evaluated how the application of an upper age limit of 44 years influenced cumulative incidence rates. As expected, incidence rates based on the population at risk aged 12 to 44 years increased by 31.7% (33.7%) in males and only by 16.0% (21.2%) in females, according to a broad (or restrictive) clinical definition of schizophrenia.

### **iii) Methods used to compute incidence rates**

Estimating the length of time during which an individual is exposed to the risk of becoming a case of the disorder may be difficult, since information about previous episodes of the disorder, the timing of the onset for the new cases, geographical mobility and death is required to compute the total period of exposure. Moreover, incidence rates can be biased by considering in their denominator the total general population instead of the population at risk for developing the disorder. For example, Hambrecht et al. (1994b) estimated that incidence rates provided by the ABC-Schizophrenia Study would have been underestimated by 28% in males and 36% in females if based on the total general population rather than on the individuals at risk. In addition, a clear definition of the population at risk is required to investigate the geographical variation in morbid risk. This might be relevant for studies on gender differences in schizophrenia and associated risk factors. For example, in rural Ireland the distribution of morbid risk for males has shown a random occurrence in space, whereas for females such distribution has revealed very prominent geographical variations (Youssef et al., 1993).

### **iv) Time trends**

Jablensky (1995) has reviewed 13 studies, published between 1985 and 1993, suggesting a significant decline in first admission rates for the diagnosis of schizophrenia over the last three decades. The magnitude of the reported decline is on the order of 40% or more between the

late 1960s and the mid-1980s. Several factors that may influence or partially explain the apparent fall in rates have been considered, including the definitions of 'first admission' or 'first contact', the changes in diagnostic practices and treatment modalities, the changes in the age structure of the population and the inconsistencies in the estimation of rates. All these potential biases considered, the evidence about a decline in incidence rates of schizophrenia is at present unconvincing (Harrison & Mason, 1993; Jablensky, 1995).

Under these limitations, time trends have been reported to differ in males and females, although the findings are not consistent across studies. Using national statistics in Scotland, Eagles & Whalley (1985) has reported that the decline in rates expressed equally in both sexes and in all age groups. On the other hand, Munk-Jørgensen & Mortensen (1992) have shown that first-admission rates in Denmark decreased by approximately 50% in both sexes, irrespective of four alternative ways of calculation, with the exception of males diagnosed as schizophrenic at their latest admission. Finally, case-register data from Oxford have suggested that the decline in incidence rates may be more pronounced in young males (de Alarcon et al., 1992).

## **MORBIDITY RISK FOR SCHIZOPHRENIA**

Only few studies estimated the morbidity risk for schizophrenia. In Fremming's (1951) study, a cohort of 4,130 individuals born on the Danish island of Bornholm during 1883 to 1887 was followed up to the end of 1938. Morbidity risks for schizophrenia were estimated to be 0.75% for males and 1.02% for females, but statistical tests of the difference were not performed.

On the same island, Strömngren and collaborators (Strömngren, 1938; Bøjholm & Strömngren, 1989) performed two census studies in 1935 and 1983, using information from the National Psychiatric Case Register, psychiatric and general hospitals, general practitioners and other key-informants as well as from personal interviews by research psychiatrists. Since the first census was expected to have revealed the vast majority of subjects with first-onset schizophrenia during the preceding 50 years, morbidity risks over this period of time were estimated. They were found to be 0.63% for males and 0.72% for females, but statistical tests of the difference were not performed.

A prospective study was performed by Helgason and collaborators in Iceland (Helgason, 1964; Helgason & Magnusson, 1989), with all the individuals born in Iceland during 1895 to 1897 and still alive in 1910 being traced in 1957 (age 60 to 62 years) and sufficient information on mental health being obtained for 99.4% of them. Those who were alive in 1957 were evaluated again in 1971 (age 74 to 76 years), in 1977 (age 80 to 82 years) and in 1983 (age 86 to 88 years). The

expectancy of developing schizophrenia before the age of 80 to 82 years was 0.7% for males and 1.1% for females (the difference did not reach statistical significance).

In the Lundby Study (Hagnell, 1966; 1989) the population of two parishes nearby Lund, in Sweden, was repeatedly assessed during the 25 years between 1947 and 1972. The cumulative risk of developing schizophrenia up to the age of 60 years was 2.1% for males and 0.7% for females, but statistical tests of the difference were not performed.

More recently, Newman et al. (1988) have estimated the morbidity risk for schizophrenia, using cross-sectional data collected in Edmonton, Canada, as part of a general population survey and a statistical procedure based on recall. The morbidity risk for the disorder was 1.2% for males and 1.0% for females (the difference did not reach statistical significance).

In conclusion, these findings suggest that the morbidity risk for schizophrenia over the life span is around 1%, with little difference between the two sexes after statistical variation is taken into account.

## **PREVALENCE OF SCHIZOPHRENIA**

Since prevalence of schizophrenia is expected to be low in the general population, only lifetime prevalence rates by sex of respondents are reported in Table XIV. The lifetime prevalence rates reported here include those subjects who ever met the criteria for schizophrenia during the entire lifespan prior to examination.

Eight studies were based on the Diagnostic Interview Schedule and DSM-III criteria. The NIMH-Epidemiologic Catchment Area Study in the United States (Robins & Regier, 1991) as well as the surveys carried out in Puerto Rico (Canino et al., 1987), Edmonton (Bland et al., 1988b), Christchurch (Wells et al., 1989), Korea (Lee et al., 1990a, b) and Hong Kong (Chen et al., 1993) were based on household probability samples of the general population. The Taiwan Psychiatric Epidemiology Project was carried out in three distinct populations in metropolitan, township and rural areas (Hwu et al., 1989). Finally, the study carried out in Iceland (Stefansson et al., 1991) included half of the population born in Iceland in 1931 and living there in December 1986. The lifetime rates of schizophrenia were generally low, although wide variation in rates was apparent across studies and ranged between 0.1% and 3.0%. The correspondent female-to-male sex ratios ranged between 0.2 and 1.5.

On the other hand, Levav et al. (1993) assessed a sample of first generation Jewish Israelis, using the Schedule for Affective Disorders and Schizophrenia-Research Diagnostic Criteria. Rates

of schizophrenia were less than 1% according to both the definite and probable levels of diagnostic confidence and tended to be higher among the males.

**Table XIV** - Lifetime prevalence rates of schizophrenia from general population studies

Author Country, time	Sample (N)	Age range (years)	Instruments Diagnostic Criteria	Rates (%)			Female-to-Male Sex Ratio
				Males	Females	Total	
Canino et al. (1987) Puerto Rico, 1984	1,513	18 - 64	DIS DSM-III	1.9	1.2	1.6	0.6 : 1
Bland et al. (1988b) Canada, 1983-86	3,258	18 and over	DIS DSM-III	0.5	0.6	0.6	1.2 : 1
Wells et al. (1989) New Zealand, 1986	1,498	18 - 64	DIS DSM-III	0.3	0.4	0.3	1.3 : 1
Lee et al. (1990a,b) Korea, n.r.	3,134 1,966	18 - 65	DIS DSM-III	0.4 <sup>a</sup> 0.7 <sup>b</sup>	0.2 <sup>a</sup> 0.4 <sup>b</sup>	0.3 <sup>a</sup> 0.5 <sup>b</sup>	0.5 : 1 0.6 : 1
Robins & Regier (1991) USA, 1980-83	18,571	18 and over	DIS DSM-III	1.2	1.7	1.5	1.4 : 1
Chen et al. (1993) Hong Kong, 1984-86	7,229	18 - 64	DIS DSM-III	0.1	0.1	0.1	1.0 : 1
Hwu et al. (1989) Taiwan, 1982-85	11,004	18 and over	DIS DSM-III	2.8 <sup>c</sup> 1.9 <sup>d</sup> 3.7 <sup>e</sup>	3.2 <sup>c</sup> 2.8 <sup>d</sup> 0.7 <sup>e</sup>	3.0 <sup>c</sup> 2.3 <sup>d</sup> 2.3 <sup>e</sup>	1.1 : 1 1.5 : 1 0.2 : 1
Stefansson et al. (1991) Iceland, 1987-88	862	55 - 57	DIS DSM-III	0.7	0.0	0.3	—
Levav et al. (1993) Israel, 1982-88	2,741	24 - 33	SADS RDC	1.0* 1.0**	0.4* 0.4**	0.7* 0.5*	0.4 : 1 0.4 : 1

\* Either probable or definite level of diagnostic confidence

\*\* Only definite level of diagnostic confidence

<sup>a</sup> Urban area <sup>b</sup>Rural area <sup>c</sup>Metropolitan Taipei <sup>d</sup>Small towns <sup>e</sup>Rural villages

n.r.= not reported

In addition, three studies provided one-year prevalence rates of 'treated' schizophrenia, using data from psychiatric case registers. In South-Verona, Italy, Tansella et al. (1982) reported rates per 1,000 population at risk of 1.3 for males and 1.1 for females in 1979 (male-to-female sex ratio = 1.2); the corresponding figures in 1980 were 1.5 and 1.1 (male-to-female sex ratio = 1.4). In Portogruaro, Italy, De Salvia (1993) reported rates per 1,000 population at risk of 0.6 in males and

0.5 in females (male-to-female sex ratio = 1.2). Finally, in England Freeman & Alpert (1986) found rates per 1,000 population at risk of 7.0 in males and 6.6 in females (male-to-female sex ratio = 1.1).

## **FACTORS THAT MAY INFLUENCE PREVALENCE RATES OF SCHIZOPHRENIA**

Prevalence rates of schizophrenia that have been reported in the literature vary widely across sites and no consistent gender differences are found. Torrey (1987) has reviewed over 70 published studies on prevalence of schizophrenia and suggested that a large proportion of variation across populations cannot be explained in terms of diagnostic inconsistencies or differences in study design. For example, Kendler & Eaton (1988) examined the potential bias introduced by the proband method in epidemiologic investigations. Using this method, the probability of ascertainment for an individual depends on the number of available relatives. It follows that for psychiatric disorders which are associated with decreased family size (e.g., schizophrenia), the underestimation of prevalence by the proband method may be non-trivial.

Although prevalence rates can yield an estimate of the burden of a disorder in a given population and provide indirect evidence of incidence variation and concomitant risk factors, they should be interpreted with caution in etiologic research since demographic and clinical variables may greatly influence them. It follows that it is unclear whether schizophrenia is equally uncommon in males and females or whether the reported gender differences are 'real' and not simply the result of selection artifacts or random influences. In the light of these considerations, Jablensky (1995) has suggested that "new prevalence surveys employing refined sampling and diagnostic techniques in populations selected for consistent previous reports of 'outliers' or contrasting findings...should be seriously considered for international funding and administrative coordination by the World Health Organization".

## **NATURALISTIC OUTCOME OF SCHIZOPHRENIA**

The issue of gender differences in naturalistic course and outcome of schizophrenia is complex and problematic, since different diagnostic standards, research instruments and outcome criteria hamper direct cross-study comparison. Recently, Hegarty et al. (1994) have reviewed the twentieth-century literature on outcome in schizophrenia to elicit historical trends that might be associated with changes in diagnostic and therapeutic practices. Three hundred and twenty studies on outcome in dementia praecox or schizophrenia, published between 1895 and 1992, were included in the analyses. Overall, 40.2% of the patients were considered improved at follow-ups lasting, on average, 5.6 years (range between 1 and 40 years). Outcome was significantly better when patients

were diagnosed according to systems with broad criteria (46.5% of the patients were improved) or undefined criteria (41.0% of the patients were improved) rather than narrow criteria (27.3% of the patients were improved). The proportion of patients who were rated as improved increased substantially after mid-century as a probable result of changes in intervention strategies, a broadened concept of schizophrenia or a selection bias related to changes in health care. Unfortunately, possible gender differences in outcome were not investigated.

Here we have reviewed the studies that investigated the naturalistic course and outcome of schizophrenia and provided separate data for males and females. Four broad domains have been considered separately: clinical status at follow-up; social adjustment at follow-up; inpatient treatment during follow-up; mortality.

## **CLINICAL STATUS AT FOLLOW-UP**

Table XV sets out the studies, ordered by length of follow-up, that investigated the clinical outcome of male and female patients with schizophrenia. The studies showed marked differences in the diagnostic criteria and instruments used, in sample selection, in the definition of good or poor clinical outcome as well as in statistical analyses performed to assess gender differences in outcome. In general, females have been reported to show a better clinical outcome than males in the short term (i.e., over the first five years of follow-up), whereas gender differences tend to disappear over longer periods.

**Table XV - Clinical outcome of male and female patients with schizophrenia**

Author Country	Sample (N)		Diagnostic criteria (years)	Length of follow-up	Outcome criteria	Findings
	Males	Females				
Jablensky et al. (1986) Colombia, Czechoslovakia Denmark, India, Ireland Japan, Nigeria, UK, USA, USSR	1,078 (total) first-ever contacts		ICD-9 CATEGO	2	- Number of discrete psychotic and non psychotic episodes/number and clinical quality of remissions - Proportion of follow-up period: i) in psychotic episodes; ii) in complete remission; iii) on anti-psychotic medications iv) in psychiatric hospital.	F better than M
Hambrecht et al. (1992a) Bulgaria, Croatia, Germany, Netherlands, Sudan, Switzerland, Turkey	277 onset	233 within 24 months	ICD-9	2	Mental, working and treatment status were rated jointly to assign each patient to a single outcome category	F better than M
Scottish Schizophrenia Research Group (1989; 1992) Scotland	49 (total) first admissions		Clinical	2	Readmissions and/or positive/negative symptom,	F better than M
	44 (total) first admissions		Clinical	5	Readmissions and/or positive/negative symptom,	F equal to M
Watt et al. (1983) Shepherd et al. (1989) UK	61 48 first admissions	60	PSE/ICD-8	5	Clinical outcome according to PSE	F better than M
WHO (1979) China, Colombia, Czecho- slovakia, Denmark, India, Nigeria, UK, USA, USSR	543 (total) consecutive admissions or referrals		ICD-9 CATEGO	2	Time spent in psychotic episode	F better than M
Leff et al. (1992) Colombia, Czechoslovakia, Denmark, India, Nigeria, UK, USA, USSR	270 consecutive admissions or referrals	261	ICD-9 CATEGO	5	Time spent in psychotic episode	F better than M
Thara & Rajkumar (1992) India	36 first admissions	31	Feighner	5	Time spent in psychotic state and pattern of course as classified in the Psychiatric and Personal History Schedule	F better than M
Breier et al. (1992) U.S.A	30 chronic patients	28	not specified	6 (mean)	Positive/negative symptoms, neuroleptic exposure, suicide attempt, disorders as major depression, alcoholism, substance abuse	F equal to M
Lynge & Jacobsen (1995) Greenland	24 first admissions	13	ICD-8	7	Presence and severity of mental symptoms, neurotic or personality disfunction	F equal to M
Salokangas (1983) Finland	39 first admissions	61	Clinical	7.5	Neurotic and psychotic symptoms	F equal to M
	53 first admissions	31	Clinical	8	Neurotic and psychotic symptoms	F equal to M

Tsoi & Kua (1992) China	234 first admissions	172	Clinical	10	Psychiatric symptoms (mood, thought processes, delusions, hallucinations, cognitive functions)	F equal to M
Thara et al. (1994) India	40 first admissions	36	ICD-9	10	PSE symptoms, percentage of time spent in psychotic state	F equal to M
Tsoi & Wong (1991) China	189 first admissions	141	ICD-9	5 10 15	Psychiatric symptoms (thought disorder, affective blunting, depression, delusions, hallucinations)	F equal to M F equal to M F equal to M
Affleck (1976) Scotland	86 chronic patients	67	Clinical	12 (mean)	Clinical status and drug regime	F equal to M
Bland & Orn (1978) Canada	22 first admissions	21	ICD-9	14	Psychiatric condition and intellectual deficit	F equal to M
Schmid et al. (1991) Germany	209 consecutive admissions	293	Clinical	22.4 (mean)	Psychopathological remission	F equal to M
Harding et al. (1987a,b) USA	81 chronic patients	87	DSM-III	32 (mean)	Clinical status according to the Global Assessment Scale	F equal to M
Ciampi (1980) Switzerland	92 chronic patients	197	Clinical	39.6 (median)	Clinical 'end state' (indifference, motor stereotypes, affective withdrawal, thought disturbances, abulia, hypochondria, mutism, negativism)	F equal to M
Loyd et al. (1985) USA	103 consecutive admissions	97	Feighner	2-4 35-40	Psychiatric symptoms	F equal to M F equal to M

Note. Only statistically significant differences were considered.  
F = Females  
M = Males

## SOCIAL ADJUSTMENT AT FOLLOW-UP

Table XVI summarizes the findings from follow-up studies investigating social adjustment of male and female patients with schizophrenia. Direct comparison across studies is difficult due to differences in the criteria and dimensions used to evaluate social adjustment, including marital status, occupational status and working ability, social contacts and social interaction, living arrangements or maladaptive behaviours. Moreover, some studies combined ratings from different dimensions to obtain a single outcome measure. Despite these limitations, most of the studies have reported a better social adjustment for females compared to males. This finding is in agreement with the frequent observation that females have a better premorbid functioning than males.

**Table XVI - Social outcome of male and female patients with schizophrenia**

Author Country	Sample (N)		Diagnostic criteria	Length of follow-up (years)	Outcome criteria	Findings
	Males Sample	Females selection				
Beiser et al.(1994) Canada	33 (total) first episode		DSM-III	1.5	Quantitative and qualitative aspects of work performance	F better than M
Jablensky et al. (1986) Colombia, Czechoslovakia Denmark, India, Ireland Japan, Nigeria, UK, USA, USSR	1,078 (total) first-ever contacts		ICD-9 CATEGO		Proportion of follow-up period during which the social functioning of the patient was impaired	F better than M
Test et al. (1990) U.S.A	82	40 <12 months in psychiatric and penal institutions	RDC DSM-III	2	Work functioning; number of contacts or friends; social and sociosexual lives; substance abuse; arrests; community residential settings	F equal to M
Watt et al. (1983) Shepherd et al. (1989) UK	61	60 48 first admissions	PSE/ ICD-8	5	Employment; household activities; child rearing; sociability; heterosexual adjustment; intimate relationships; leisure activities	F better than M
WHO (1979) China, Colombia, Czecho- slovakia, Denmark, India Nigeria, UK, USA, USSR	585 (total) consecutive admissions or referrals		ICD-9 CATEGO	2	Occupational adjustment; relationship with friends; degree of social interaction	F equal to M
Leff et al. (1992) Colombia, Czechoslovakia, Denmark, India, Nigeria, UK, USA, USSR	270	261 consecutive admissions or referrals	ICD-9 CATEGO		Occupational adjustment; relationship with friends; degree of social interaction	F better than M
Thara & Rajkumar (1992) India	36	31 first admissions	Feighner	5	Occupational adjustment and social interactions	F better than M
Breier et al. (1992) U.S.A	30	28 chronic patients	not specified	6 (mean)	Quantity of work and number of social relations	F better than M
Salokangas (1983) Finland	39	61 first admissions	Clinical	7.5	Percent of follow-up to period unable assistance received; on pension; difficulty in social adjustment; living arrangements	F better than M work; social
	53	31	Clinical	8		F better than M
Tsoi & Wong (1991) China	189	141 first admissions	ICD-9	5 10 15	Work status	F equal to M F equal to M F equal to M
Affleck (1976) Scotland	86	67 chronic patients	Clinical	12 (mean)	Occupational status, living arrangements	F better than M
Bland & Orn (1978) Canada	22	21 first admissions	ICD-9	14	Relationships with named persons; economic productivity; loss of productive time	F better than M

Schmid et al. (1991) Germany	209 consecutive admissions	293	Clinical	22.4 (mean)	Employment status	F better than M
Ciampi (1980) Switzerland	92 chronic patients	197	Clinical	39.6 (median)	Quantity and quality of relationships living arrangements; time in employment; marital status	F equal to M
Loyd et al. (1985) USA	103 consecutive admissions	97	Feighner	2-4  35-40	Occupational status  Occupational status; residence; marital status	F equal to M  F equal to M

Note. Only statistically significant differences were considered.  
F = Females M = Males

## INPATIENT TREATMENT DURING FOLLOW-UP

Table XVII shows the findings from follow-up studies reporting inpatient care provided to subjects with schizophrenia after discharge from psychiatric hospital. Most studies have reported no gender differences in number of re-admissions or length of hospital stay during follow-up. When gender differences are reported, females tend to receive less inpatient care compared to males.

**Table XVII - Inpatient treatment during follow-up for male and female patients with schizophrenia**

Author Country	Sample (N)		Diagnostic criteria	Length of follow-up (years)	Outcome criteria	Findings
	Males	Females Sample selection				
Jablensky et al. (1986) Colombia, Czechoslovakia Denmark, India, Ireland Japan, Nigeria, UK, USA, USSR	1,078 (total) First-ever contacts		ICD-9 CATEGO	2	Time in hospital	F equal to M
Test et al. (1990) U.S.A	82 < 12 months in psychiatric and penal institutions	40	RDC DSM-III	2	Time in inpatient settings	F equal to M
Watt et al. (1983) UK	61 48 first admissions	60	PSE/ICD-8	5	Time without readmissions	F better than M
Breier et al. (1992) U.S.A	30 chronic patients	28	not specified	6	Time in hospital	F equal to M (mean)
Lynge & Jacobsen (1995) Greenland	24 first admissions	13	ICD-8	7	Time in hospital Number of admissions	F worse than M F equal to M
Salokangas (1983) Finland	39 first admissions	61	Clinical	7.5	Time in hospital	F equal to M
	53 first admissions	31	Clinical	8	Time in hospital	F better than M
Angermeyer et al. (1990) Germany	137 first admissions	141	DSM-III-R	6-11	Number of hospitalizations Duration of hospitalization	F equal to M F equal to M

Goldstein (1988) USA	58 early phase of the disorder	32	DSM-III	10	Number of hospitalizations Length of hospital stay	F better than M F better than M
Riecher et al. (1990) Denmark	527 first admissions	642	ICD-8	10	Number of readmissions	F equal to M
Tsoi & Kua (1992) China	234 first admissions	172	Clinical	10	Number of readmissions	F equal to M
Munk-Jorgensen (1986) Denmark	370 first admissions	217	ICD-8	10.7-11.7	Time spent in in- or day- patient settings	F better than M
Tsoi & Wong (1991) China	189 first admissions	141	ICD-9	5 10	Number of rehospitalizations Number of rehospitalizations Number of rehospitalizations	F equal to M F equal to M F equal to M
Affleck (1976) Scotland	86 chronic patients	67	Clinical	12 (mean)	Number of rehospitalizations	F equal to M
Eaton et al. (1992) Australia	7,271 (total)		ICD-8	20	Risk of rehospitalization	F equal to M
USA	13,870 (total)		DSM-	7.5	Risk of rehospitalization	F equal to M
Denmark	9,250 (total)		ICD-8	20	Risk of rehospitalization	F equal to M
UK	532 (total) first admissions		ICD-8	20	Risk of rehospitalization	F equal to M

Note. Only statistically significant differences were considered.

F = Females

M = Males

## MORTALITY

Mortality has been reported to be higher among schizophrenic patients compared to the general population (Ciompi, 1980; Amadeo et al., 1995). The relative risk seems to be considerably increased in the first few years following discharge from psychiatric hospital and tends to decrease thereafter (Munk-Jørgensen & Mortensen, 1992; Goldstein et al., 1993). As to diagnostic subtypes, Ciompi (1980) has reported that mortality rates were relatively high for catatonic schizophrenia and somewhat low for paranoid schizophrenia. This finding was not confirmed by Munk-Jørgensen & Mortensen (1992), who showed that, in both sexes, mortality rates were higher for hebephrenic and unspecified schizophrenia and relatively low for catatonic schizophrenia.

Mortensen & Juel (1993) have reported that, although absolute mortality rates were usually higher in males than in females, age-specific relative risk was generally higher in females, particularly in the younger age groups. For both sexes, the relative risk tended to decrease with increasing age and was significantly increased in all age groups except for the eldest. Suicides and other violent causes of death were increased in both sexes. Relative risk for suicide was higher among patients aged less than 30 years and among females compared to males until the age of 60 years. In both sexes, the suicide risk was especially pronounced in the first year of follow-up and remained

high throughout the five-year follow-up in the youngest patients. Among the natural causes of death, mortality from heart diseases and diseases of the respiratory system was significantly increased in both males and females.

## **FACTORS THAT MAY INFLUENCE GENDER DIFFERENCES IN NATURALISTIC OUTCOME OF SCHIZOPHRENIA**

Follow-up studies of patients with schizophrenia have devoted increasing attention to methodological issues and recent advances have involved the conceptual framework, the design, the representativeness of the sample and its description, the source and quality of the data, the development of reliable and valid outcome measures, the selection of proper comparison groups and the statistical techniques (McGlashan et al., 1988). Here some of the factors are discussed that may influence gender differences in the course and outcome of schizophrenia, including: i) diagnostic criteria; ii) outcome criteria; iii) sample selection; iv) length of follow-up.

### **i) Diagnostic criteria**

The concept of dementia praecox and, later, of schizophrenia has been a disputed entity in modern medicine. Schizophrenia is still defined by its clinical picture and the evolution of symptoms over time, since no external validating criteria for the diagnosis have been established in spite of several suggestive genetic, biological and environmental findings (Jablensky, 1986).

Although we can now define a particular construct of schizophrenia with reasonable agreement, the construct itself should be considered as provisional and based on a need to achieve consensus about definitions. Early attempts to explore and validate the construct of schizophrenia were mainly based on descriptive and epidemiological techniques, with the validity of a given construct being determined by the evaluation of the clinical picture, the course and outcome of the disorder, the response to treatment, the laboratory tests and/or the familial aggregation. This earlier approach has been complemented by techniques drawn from neurosciences and attempts have been made to understand schizophrenia in terms of underlying neural mechanisms. While the earlier approach conceptualized schizophrenia primarily in terms of a single disease entity, the second approach is particularly useful for the exploration of subtypes or dimensions of the disorder (Andreasen & Carpenter, 1993).

It remains a topic of continuing dialogue how best to characterize patients suffering from schizophrenia and, at the same time, arrive at a diagnosis that has specific clinical utility and can be

reliably assessed (Keith & Matthews, 1991). The difficulties confronting both the researcher and the clinician have been exemplified by Endicott et al. (1986). When seven systems for the diagnosis of schizophrenia were tested for their ability to predict short-term outcome at follow-up and compared with each other, with selected specific symptoms and with a simple additive symptom score, none of the systems nor the symptoms had strong predictive value, although DSM-III, Schneiderian First Rank Symptoms and the additive symptom score performed somewhat better than the other predictors.

These findings suggest that doubts still remain as to how the boundaries of schizophrenia should be defined. Using a computer pattern-recognition program of patient's initial characteristics, Kazanetz (1989) has provided evidence in support of the distinction between schizophrenia and borderline states. Indeed, good correlation was observed between computer diagnosis and follow-up data, analysed according to Kraepelin's model of schizophrenia and its course.

On the other hand, if exclusion criteria restrict selection to subjects with clearly established symptoms and signs of schizophrenia (as stipulated by current operational criteria), the sample would consist predominantly of subjects with severe and long-lasting disorders. Such a sample would be perfectly adequate for assessing the effects of a given treatment, but would not advance research into risk factors and mechanisms underlying the course of the disorder, since the less severe and typical forms, which are a natural part of the clinical spectrum of the disorder, as well as the early stages of illness would be missed (Jablensky et al., 1986).

In addition, there is evidence that the use of restrictive diagnostic criteria may increase a gender effect in favour of females, since more females compared to males tend to be excluded from the selection procedure (Lewine et al. 1984; Westermeyer & Harrow, 1984). For example, Castle et al. (1993) examined all first-contact patients with non-affective functional psychoses from a defined geographical area, using operational criteria of varying stringency in setting age at onset of the disorder. The overall first-contact incidence rates of non-affective functional psychoses were approximately equal in males and females; however, the ratio of male-to-female incidence rates rose progressively when Research Diagnostic Criteria (male-to-female ratio=1.2), DSM-III-R (1.3), DSM-III (2.2) and Feighner (2.5) criteria for schizophrenia were applied.

Given these limitations, it has been suggested that a multidimensional approach to the pathogenesis of schizophrenia and related disorders may provide important clues as to the genetic and pathophysiology of schizophrenia as well as of other disorders that may be part of a continuum of schizophrenia-related disorders. For example, the study of patients with schizotypal personality disorder suggests that a dimension of deficit-like or 'negative' symptoms of asociality and interpersonal impairment may be associated with neuropsychological and psychophysi-

ologic correlates of altered frontal function, whereas the psychotic-like or 'positive' symptoms seem to be more related to an increase in dopaminergic activity. It is conceivable that these two dimensions may represent partially distinct but potentially interactive pathophysiologic processes that may converge and interact to result in schizophrenia (Siever et al., 1993).

In conclusion, the generalizability of the results from outcome studies is expected to depend largely on the extent to which the diagnostic and outcome criteria are independent to each other and reproducible. Although several standardized diagnostic systems are now available, different sets of rules are often recommended. It follows that, at present, it is not possible to speak of a 'natural' long-term course of schizophrenia, since research findings are influenced to a large extent by diagnostic criteria (Wing, 1988).

## **ii) Outcome criteria**

The measurement of outcome is a complex task and outcome information is often hard to be obtained. At present, health indicators that have been used as outcome measures include mortality, morbidity (e.g., disability days, bed days or restricted activity days, hospital admission figures), direct measures of health and social functioning, subjective health indicators, and measures of unmet needs. However, differences in strategies, in research instruments and in completeness of data collection have often prevented direct comparison across studies (Jenkins, 1990).

It is a common finding that different outcome indicators generally intercorrelate to a modest degree and this observation limits the validity of any study using a single dimension as the sole outcome criterion. It is recommended that multiple criteria are applied in order to provide a comprehensive and articulated picture of the natural course of a disorder. Furthermore, since the judgment assigning a rating to outcome may vary according to the beholder (i.e., the investigator, the patient, a patient's relative, the mental health professional), it may be useful to collect more than one perspective (Ruggeri & Tansella, 1995).

Despite recent improvements in systems for classifying mental disorders, the issue of course description has not been fully addressed. A review of the current strategies used to classify the courses of schizophrenia has shown several differences in the number of courses described, in the structure of the course categories, in the relative emphasis on syndrome symptoms versus syndrome change and in documenting specific course features (i.e., illness onset, illness outcome and types of symptoms). Thus, cross-study comparisons of long-term illness patterns are limited and cumulative statements on prognosis are expected to remain problematic until some standardization is introduced (Marengo, 1994).

Moreover, when hospital records are used to assess the course of schizophrenia, the criteria that are adopted to count hospital admissions should be clearly stated, since the number of episodes during follow-up depends on whether all hospital admissions are counted irrespective of the diagnosis given on each occasion or only those admissions are selected in which patients receive a diagnosis of schizophrenia. Changing the selection criteria may modify the effect of gender on outcome of schizophrenia. For example, Häfner et al. (1991b) have shown that, among patients satisfying broad diagnostic criteria for schizophrenia, the trend towards a more favourable course in females became increasingly evident the more restrictive the diagnosis was at each admission. Instead, among patients satisfying restrictive diagnostic criteria for schizophrenia, no gender differences in outcome were detected irrespective of type of readmissions (i.e., all hospital admissions during follow-up; admissions with a broad diagnosis of schizophrenia; admissions with a restrictive diagnosis of schizophrenia).

Finally, numerical ratings of outcome are often reductionistic and global and make it difficult to place results into a meaningful perspective. Thus, a certain amount of narrative case material from follow-up assessments should be reported for a meaningful 'anchoring' of the scale values. In this regard, Breier (1988) has suggested that many important issues that may be relevant to the course and outcome of chronic psychiatric disorders are not readily amenable to investigation with existing large samples and quantitative methodologies. For example, complex interactive phenomena that change over time, such as the longitudinal impact of changes in social role and work function on levels of symptomatology, are particularly difficult to be quantified and assessed in studies based on large samples. Thus, small sample studies based on a 'qualitative' methodology may be useful because they offer the possibility for examining the longitudinal interplay of a wide range of variables in individual patients, delineating new course variables, developing models of course change and generating unique research hypotheses for consideration in future large sample 'quantitative' studies.

### **iii) Sample selection**

The clear characterization of the sample under investigation in terms of demographic and other predictor variables is essential for adequate comparison, replication and generalization of results. For example, Walker & Lewine (1993) have provided a model to explain how gender differences and sampling methods might interact to influence research findings. Under the assumption that the mean level of illness severity is greater in one sex, an explanation has been offered of how gender differences might be attenuated or even reversed as a function of sampling procedure. Indeed, both patients' self-perceptions and perceptions of others partially determine whether a patient is in treatment, with voluntary treatment resulting primarily from the patients' subjective feelings of distress and involuntary treatment occurring especially when

others perceive the patient as unmanageable or dangerous. The Authors suggest that the severity of illness threshold for involuntary treatment is lower for male schizophrenics than for female ones as a function of gender differences in behavioural and social characteristics. On the other hand, the severity of illness threshold for voluntary treatment is expected to be lower for female schizophrenics than for male ones, since females are more likely to acknowledge and report their psychological distress and to seek treatment. It follows that, as the proportion of patients under involuntary treatment in the study sample increases, the likelihood that females will show greater impairment than males also increases; the reverse is the case when the proportion of patients under voluntary treatment in the study sample increases. Treatment facilities may vary in the proportion of patients under voluntary and involuntary treatment they serve, with inpatient settings being likely to have the highest proportion of involuntary patients and outpatient or private settings the lowest. Thus, studies that draw samples from inpatient facilities tend to include females at the more extreme end of the severity continuum for their sex and their findings may be in disagreement with those from studies based on outpatient or private facilities. Unfortunately, the vast majority of the published studies on schizophrenia do not report the determinants of treatment for the subjects in the sample (proportion of voluntary versus involuntary patients).

Another important issue refers to whether subjects with schizophrenia are on their first admission to or contact with psychiatric services, since previous psychotic episodes and institutionalisation may affect the course and outcome of the disorder. Moreover, if patients with schizophrenia are selected irrespective of whether they are on their first admission to psychiatric hospitals, gender differences in outcome may be attenuated or reversed, since patients with a more favourable course of illness will be excluded and these are more likely to be females. Ram et al. (1992) have reviewed the available literature on the natural course of illness among first-admission schizophrenic patients and found a substantial heterogeneity in course and outcome, although relatively more first-admission patients had a positive course than did patients with multiple admissions. However, there was evidence for marked differences and inconsistencies in definitions and criteria used to define a so-called first episode of the disorder. Thus, the operationalization of proper criteria is a crucial task and should include the characterization of onset, illness severity, symptom profile, treatment history and setting (Keshavan & Schuler, 1992).

A final source of bias is represented by the refusal of some patients to participate in a study. Indeed, Walker & Rossiter (1990) have found that males with diagnosis of schizophrenia are more likely than females to deny their illness, and this gender difference is most pronounced for the more severely disturbed patients. Thus, gender differences in outcome of the disorder are expected to be attenuated if the refusal rate differs in the two sexes and is highest for severely ill male patients.

#### **iv) Length of follow-up**

The length of follow-up is a crucial variable, since there is evidence of significant variability in both the type and the power of relevant predictors of outcome depending on length of follow-up. For example, McGlashan (1986) investigated the predictors of outcome in 163 patients with schizophrenia that were divided into three cohorts by length of follow-up interval (i.e., up to nine years; 10 to 19 years; 20 years or more). The most powerful variables predicting outcome differed between follow-up intervals. Characteristics of premorbid functioning were most influential in the first decade of follow-up, family functioning in the second decade, whereas family genetics influenced the third decade and beyond; signs and symptoms proved predictive in consistent ways for midrange and longer-term outcomes. Similarly, a few studies that assessed the same sample of patients repeatedly over time have shown that gender differences in outcome of schizophrenia tended to be evident in the short-term and to disappear in the long run (Nyman, 1989; Angermeyer et al., 1990; Tsoi & Kua, 1992; Thara & Rajkumar, 1992; Thara et al., 1994).

### **POSSIBLE FACTORS ACCOUNTING FOR GENDER DIFFERENCES IN SCHIZOPHRENIA**

The main finding emerging from epidemiologic research on gender differences in schizophrenia is that males tend to fall ill at an earlier age than females. It follows that age at onset is the single most important characteristic of schizophrenia that could yield clues to gender-specific risk factors, since a gender difference has been confirmed after ruling out the confounding effects due to sampling bias, different time occurring between the first appearance of psychotic symptoms and the first hospitalization, and possible gender differences in symptom development (DeLisi, 1992).

Investigations into gender differences in schizophrenia have raised the issue of whether the forms of schizophrenia that occur in males and females are essentially the same disorder with an early onset in males and a later onset in females (timing model) or represent different morbid states (subtype model) (Lewine, 1981). For example, McGuffin et al. (1987) have reviewed the data from family studies and suggested that there may be some evidence for variation in genetic liability to schizophrenia, but not for distinct subtypes. In addition, Vazquez-Barquero et al. (1995a) have found no gender differences in the family history of mental illness, in type of onset of the disease and in clinical characteristics among first-contact patients with schizophrenia. Limited gender differences in clinical features of schizophrenia were also reported by Perry et al. (1995).

On the other hand, some investigators have proposed that there may exist an early-onset (or congenital) form of schizophrenia that can be distinguished from other types of the disorder, occurring in adult life. Early-onset schizophrenia shows a male preponderance, poor outcome (chronicity),

low familial predisposition for psychosis and the presence of structural cerebral pathology and of cognitive impairment as a consequence of aberrant brain development during fetal or neonatal life. Late-onset schizophrenia, instead, is possibly heterogeneous and characterized by female preponderance, more positive symptoms, more affective features, more favourable outcome, high familial predisposition for psychosis and no or less pronounced structural cerebral involvement. It has been argued that these distinct forms may derive from the differential hemispheric organization of the brain in males and females and this, in turn, may determine the male susceptibility to other psychopathological syndromes, such as psychopathy and sexual deviations, as well as the excess of females in schizoaffective states and affective disorders (Flor-Henry, 1990; Murray et al., 1992).

The existence of different subtypes of schizophrenia has been also suggested by two recent studies. Castle et al. (1994) performed a latent class analysis in a sample of first contact patients with a broad diagnosis of schizophrenia and found evidence for three subtypes: a 'neurodevelopmental' type, which was characterized by early onset, poor premorbid social adjustment, restricted affect and a male-to-female ratio of 7:3; a 'paranoid' type with later onset, persecutory delusions and an almost equal sex ratio; a 'schizoaffective' type (though less clear cut), almost entirely confined to females and characterized by dysphoria, persecutory delusions and negligible familial risk for schizophrenia. Moreover, Sham et al. (1994) investigated a typological model for schizophrenia based on gender, age at onset and familial morbidity. On the logarithmic scale, the age-at-onset distribution of schizophrenia in both male and female relatives of probands was bimodal, suggesting that broadly defined schizophrenia may be a mixture of two, possibly related, disorders; a third disorder, related to affective psychosis, showed an intermediate age at onset and a female preponderance.

These findings have stimulated the search for putative etiological or risk factors that may exert a sex-specific effect in schizophrenia, including genetic factors, brain abnormalities, endocrine factors and environmental factors. Before reviewing them, it should be stated that, at present, a speculative comprehensive model for the etiology of schizophrenia should make provision for some primarily environmental causes (including those secondary to drug intoxication by dopamine agonists or to brain lesions), for rare single locus causes as well as for complex multifactorial and multigenic components (Gottesman, 1994). For example, a general vulnerability model incorporating the idea of distinct subtypes of schizophrenia has been suggested by Eaton et al. (1988). According to this model, vulnerability to schizophrenia arises from two distinct sources with different distributions in the general population. The first source consists of polygenic influences on personality, which are largely inherited and normally distributed. The deviant end of such distribution includes the so-called schizophrenia-spectrum disorders, which are genetically related to schizophrenia. The second source of vulnerability stems from a structural change in the brain, which occurs early in life and is relatively permanent. Vulnerability interacts with stress over the course of an individual's life to produce episodes of schizophrenia. Thus, early onset schizophrenia occurs among highly vulnerable individuals, whose initial and recurrent episodes are triggered by relatively trivial stresses.

These individuals have lower genetic loading for schizophrenia and a high proportion of them have structural brain abnormalities. In contrast, later-onset schizophrenia is found especially among individuals with higher genetic loading for the disorder, moderate vulnerability and no history of highly stressful events. This model may account for gender differences in age at onset of schizophrenia in light of possible gender differences in genetic liability, brain abnormalities and exposure (or sensitivity) to stressful environmental factors. On the other hand, a possible limitation of this model refers to the lack of attention paid to personality traits that are not inherited, but acquired during development and influenced by child-parent interactions as well as by social norms and expectations.

## GENETIC FACTORS

The familial nature of schizophrenia is well documented, the closer the genetic relationship of an individual to an affected proband the more likely he/she is to have the disorder (Kaplan & Sadock, 1991, pp. 327-328). Although the exact nature of the illness transmission remains uncertain, a polygenic threshold model allowing for environmental sources of familial resemblance has been shown to fit the observed familial risks (McGue & Gottesman, 1985).

There is evidence that relatives of female probands have a higher risk for schizophrenia than relatives of male probands and this effect is consistent for both male and female relatives of the proband (Bellodi et al., 1986; Goldstein et al., 1990b; Wolyniec et al., 1992; Maier et al., 1993a). In addition, two studies have investigated the familial risk for other psychotic and schizophrenia-related disorders and conflicting results have been reported. Goldstein et al. (1990b) found that gender differences in familial risk were attenuated, when the definition of illness in relatives was expanded to include the full spectrum of schizophrenia-related disorders (i.e., schizophrenia; schizophreniform, schizoaffective, paranoid and atypical psychoses; schizotypal personality disorder). On the contrary, Maier et al. (1993a) reported that schizophrenia-spectrum disorders (i.e., schizoaffective and other non-affective psychoses; schizotypal personality disorder) were more frequent in families of female compared to male probands with schizophrenia, whereas the proband's gender failed to be of significant impact on the risk for affective disorders in relatives.

The interactive effect of proband's gender and age at onset of schizophrenia on the familial risk has been investigated by several studies. In agreement with previous work on this issue (Kendler et al., 1987), Maier et al. (1993a) have shown that neither age at onset nor the interaction between gender and age at onset in probands have a significant impact on the risk for schizophrenia in relatives. Pulver et al. (1990) and Pulver & Liang (1991), instead, have found that the relatives of male probands suffering from schizophrenia when they were younger than 17 years of age have an increased risk compared to the relatives of male probands who had a later onset of the disorder,

whereas no association was found between age at onset and familial risk among female probands. Moreover, for both female and male probands, those born during the period February to May had relatives at highest risk for schizophrenia, although the association between month of birth and familial risk among the male probands pertained only to those relatives who had onset of schizophrenia before the age of 30 years (Pulver et al., 1992).

Maier et al. (1993a) have proposed six alternative models which might account for the increased familial risk of schizophrenia in families of female compared to male probands. They are briefly presented and discussed hereafter in light of the findings reported in the literature.

- i) **Genomic imprinting** describes the modification in the expression of genes or alleles determined by the transmitting parent's gender. According to the evidence about familial transmission of schizophrenia, the expression of the disorder might be expected to be suppressed when it is transmitted from a male proband (father) to the offspring. However, this explanation has not been supported by the finding that children of affected mothers are not at higher risk for the disorder compared to children of affected fathers (Goldstein et al., 1990b; Maier et al., 1993a).
- ii) **A dimension of liability** reflecting the combined effects of genetic and environmental factors may be transmitted in families so that affected subjects with higher liability are more likely to be related to relatives with higher mean liability. If gender-specific thresholds do exist on this dimension, the recurrence rate of the disorder is expected to be higher among the relatives of probands with higher liability. The available data suggest a higher liability for female compared to male subjects with schizophrenia. According to this model, male relatives of a particular proband should be more likely to present with schizophrenia than female relatives. This does not seem the case, since several studies (Bellodi et al., 1986; Goldstein et al., 1990b; Wolyniec et al., 1992; Maier et al., 1993a) have argued for the independence of the recurrence risk of schizophrenia from the relative's gender.
- iii) Under the assumption of **etiological heterogeneity** in schizophrenia, various factors might be expected to contribute differently in males and females. Whereas familial factors may operate irrespective of gender, factors unique to particular subjects and not shared by family members might operate especially in male probands. As a consequence, male probands may be less frequently familial than female probands. No definite answer can be provided on this issue for at least two reasons. First, a review of the theoretical and empirical evidence supporting the distinction between familial schizophrenia (as a mostly genetic entity) and sporadic schizophrenia (as primarily determined by environmental causes) has shown that the scarcity of studies with adequate methodology and stringent definitions of familiarity and sporadicity precludes any definite judgment about the validity of this distinction (Roy & Crowe, 1994). Sec-

ond, exogenous factors disrupting cerebral growth and differentiation have been advocated in the etio-pathogenesis of schizophrenia. Indeed, substantial evidence exists that obstetric complications are related to the development of schizophrenia, possibly due to a deleterious effect produced during pregnancy when critical brain development occurs and resulting in neurodevelopmental abnormalities (McNeil, 1988; 1995; Torrey et al., 1994). In addition, an excess of schizophrenia has been reported among the offspring of women who were pregnant during influenza epidemics (Jablensky, 1995) or suffered from food deprivation during the first trimester of fetal development (Susser & Lin, 1992). Nonetheless, data on gender differences in the relationship between exogeneous factors and schizophrenia are controversial. For example, Jones et al. (1994) have reported differences between children suffering from schizophrenia as adults and the general population across a wide range of developmental domains (including milestones of motor development, educational achievement and social/behavioural characteristics), but no evidence of effect modification by gender was found. Goldstein et al. (1994), instead, have shown that schizophrenics with early developmental problems tended to exhibit significantly more neuropsychological dysfunction as adults than did other schizophrenics and were more likely to be males. On the other hand, prenatal exposure to influenza has been reported to have an effect confined to females (Takei et al., 1994; Kunugi et al. 1995). Similarly, food deprivation may produce an increase in hospitalized schizophrenia in females but not in males (Susser & Lin, 1992).

- iv) A ***different family structure*** in female and male probands with schizophrenia (i.e., females being more likely to be married and having more children) might explain gender differences in familial recurrence rates of the disorder. However, several independent studies have indicated that differences in the number of children cannot fully explain the excess of familial loading in female probands (Goldstein et al., 1990b; Wolyniec et al., 1992; Maier et al., 1993a). Moreover, Lane et al. (1995) have reported that, although males with schizophrenia are less likely to get married, those marrying have more children than their female counterparts.
- v) ***Sporadic cases among female probands with schizophrenia might be less likely to be hospitalized***, since females tend to have a less severe course of illness compared to males. Protective factors or more efficient coping strategies might be expected to prevent hospitalization especially among females with less familial loading of schizophrenia. Most of the family studies conducted so far have selected samples of hospitalized index cases and this might influence research findings. In this regard, Ritsner et al. (1991) have shown that probands from psychiatric hospitals are characterized by biased clinical parameters. Indeed, when the ascertainment of probands according to place of residence in hospital or in the community allowed for sampling to be representative of all the subpopulations of patients, results appeared to be contradictory to those produced by conventional sampling methods.

- vi) ***Vulnerability to schizophrenia might be expressed as schizoaffective disorder more frequently in females compared to males.*** The higher lifetime risk for depressive disorders in females as well as the higher prevalence of affective symptoms in female compared to male probands with schizophrenia may account for females receiving a diagnosis of schizoaffective disorder more often than males. This alternative expression of the liability to schizophrenia might predominantly occur among females with less familial loading and this might explain the higher familial loading among female probands with a diagnosis of schizophrenia. There is some evidence that this might be the case. Hambrecht et al. (1992c) have examined the sample composition of multicenter studies that were coordinated by the World Health Organization in the field of schizophrenia and found that females were underrepresented in several studies, especially those on first admissions and from developing countries. Moreover, Folnegovic et al. (1990b) have assessed a cohort of schizophrenics over 12 years, using a psychiatric case register in Croatia. It was shown that males more commonly received a diagnosis of schizophrenia at first admission, whereas females more frequently received a diagnosis of affective psychosis or other organic psychosis. A similar bias has been reported also by Lutzhoft et al. (1995), who compared the diagnosis of schizophrenia expressed by Danish psychiatrists with that provided by the PSE-CATEGO program. Danish psychiatrists tended to assign a diagnosis of schizophrenia after negative symptoms had persisted for some time and this delayed assignment occurred more often in females compared to males.

Finally, in addition to the models presented above, ***a pseudoautosomal location for a schizophrenia susceptibility locus*** has been recently proposed (Crow, 1988; Crow et al., 1989), on the basis of both an excess of sex concordance among siblings with schizophrenia and sex chromosomal abnormalities in schizophrenic patients (Crow et al., 1989; Maier et al., 1993b). A gene located in this region would be transmitted in an autosomal manner, but would be passed above chance expectation to children of the same sex when inherited through a male. However, at least two reports have found no evidence for an excess of sex concordance in affected siblings (Sturt & Shur, 1985; Goldstein et al., 1990b). Moreover, when eight markers spanning the most telomeric region to the boundary of the pseudoautosomal region were tested for genetic linkage to schizophrenia, no evidence was found for the presence of a susceptibility locus in this region (Barr et al., 1994).

## **BRAIN ABNORMALITIES**

Non-invasive investigations of the brain structure have been increasingly undertaken in subjects with schizophrenia and conflicting results have been reported, possibly due to the little attention paid to relevant clinical factors such as the stage of illness or the length and type of treatment. Castle & Murray (1991) have reviewed several studies using computerized tomography and mag-

netic resonance imaging in schizophrenic patients and concluded that structural brain abnormalities are more common in males compared to females. The reported abnormalities include increased cortical atrophy, increased ventricle-to-brain ratio, greater temporal horn area, smaller left hippocampus and disproportionate measures of cerebral area to height of the individual. Pre- and perinatal hazards (i.e., obstetric complications) have been suggested to be responsible for such abnormalities of brain structure in subjects with schizophrenia (and especially so in males) compared to normal controls. Thus, Castle & Murray (1991) have proposed a neurodevelopmental perspective to explain gender differences in schizophrenia, with males having a form of disease due to abnormalities in brain development and females having more in common, etiologically, with affective psychoses. At the same time, the Authors have suggested that much of the contemporary confusion about schizophrenia may result from the conflation of two separate subtypes of the disorder, one more common among young males and the other among older females.

Although attractive, this hypothesis has not been confirmed by several recent studies. For example, Jones et al. (1994) have investigated volumetric brain measures in subjects with functional psychosis and healthy community controls, using computerized tomography. Although subjects with schizophrenia and those with schizoaffective disorder were both consistently associated with larger lateral and third ventricle volumes, no evidence was found for a gender difference in this association. Moreover, neither obstetric complications nor a family history of schizophrenia or other psychiatric illness was associated with large ventricles in psychotic patients. Similar findings have been reported by Flaum et al. (1995), who compared subjects with schizophrenia and normal controls in terms of the volume of a variety of brain structures and subregions. Although cranial and cerebral sizes as well as superior temporal gyral and third ventricle volumes were larger in males than in females, male probands were not more likely than female probands to differ in any of the brain regions of interest from their normal controls. Moreover, gender differences were often reduced or disappeared, when other confounding factors such as height, ethnicity or social class were controlled for. Finally, Patton et al. (1994) found a significant age-related change in computer tomography findings among patients with schizophrenia, but no gender differences, suggesting that coarse changes in brain structure were unlikely to underlie the gender difference in age at onset of the disorder.

In addition, several investigators have reported a greater occurrence of brain abnormalities in female compared to male subjects with schizophrenia. Shelton et al. (1988) have examined the computerized tomographic scans of subjects with chronic schizophrenia and normal controls for ventricle-to-brain ratio, third ventricle width and prominence of cortical markings in a generalized parieto-occipital distribution compared with the prefrontal area. Patients showed significantly larger ventricle-to-brain ratios, third ventricle widths and prefrontal atrophy than controls. However, when analyses were repeated in the two sexes separately, only female schizophrenics had larger third ventricle widths and prefrontal atrophy than their controls. Similarly, Vazquez-Barquero et

al. (1995b) examined structural brain abnormalities (ventricle-to-brain ratio and third ventricle width) in first episode patients with schizophrenia and found that the ventricle-to-brain ratio was greater in schizophrenic patients than in controls, although this effect seemed to be more marked in females. The changes in the third ventricle width were consistent with the findings for the ventricle-to-brain ratio, although not statistically significant.

Although brain abnormalities have been often reported in schizophrenia, it is still controversial whether these abnormalities are specific to the disorder. For example, Jones et al. (1994) found that both subjects with schizophrenia and those with schizoaffective disorder were more likely than controls to have larger ventricles, but effect sizes of the two groups overlapped. Moreover, Raine et al. (1990) showed that the gender difference in callosal thickness in normal controls was reversed in patients with schizophrenia, but similar findings were observed also in patients with affective or anxiety disorders. On the other hand, Swayze et al. (1992) evaluated the size of the temporal lobe and the basal ganglia in subjects with schizophrenia and bipolar disorder and reported differences in the left-right asymmetry between the two sexes across the diagnostic groups. In conclusion, the question of interest may not be whether subjects with schizophrenia differ in the number of brain abnormalities compared to controls, but rather whether some brain abnormalities are specific to schizophrenia and whether different areas of the brain are differently affected in the two sexes (Goldstein & Tsuang, 1990). For example, Kopala & Clark (1990) have reported that olfactory dysfunctions primarily present among males with diagnosis of schizophrenia compared to females. Similarly, neuroanatomical studies suggest that the neurobiologically determined instability of the dominant hemispheric system in the males due to their more lateralized brain organization may be responsible for the characteristics of schizophrenia in that sex by rendering males less able to compensate for disorganization than females, whose brain is described as more bilaterally functional (Flor-Henry, 1985; Bardenstein & McGlashan, 1990).

## **ENDOCRINE FACTORS**

The role of estrogens as major determinants of gender differences in schizophrenia has been extensively investigated. Seeman & Lang (1990) have suggested that sex hormones may play both organizational and activational effects on the human brain. Organizational effects take place during a critical period of fetal life and put a permanent stamp on the developing brain. This may explain cognitive differences between the two sexes and sexually dimorphic responses to cortical lesions. Cortical functions in males and females differ in the place of early development, with the female brain showing, in general, earlier neuronal myelination, earlier establishment of neuronal connections and earlier lateralization of cerebral functions. It follows that the female brain presents greater maturity at birth and, as a consequence, less vulnerability to the potential trauma of the birth process. On the other hand, the greater vulnerability of the male brain at birth may deter-

mine the earlier age at onset of schizophrenia in males. In turn, earlier age at onset and abnormalities in the brain structure following the birth trauma may result in a more severe course of illness over time in males compared to females.

The activational effects, instead, are exerted by circulating hormones. Thus, they appear when hormonal levels rise and wane when hormonal levels drop. Since estradiol seems to affect many neurotransmitter systems, a sudden surge of gonadal steroids in either sex may set off a chain of chemical events leading to illness in individuals that are genetically predisposed. This reflects current thinking about the trigger mechanism of post-partum psychosis. In addition, it is expected that puberty, a time of sudden and dramatic hormonal and neurochemical changes, is a risk period for the development of schizophrenia. Indeed, several lines of evidence support the notion that a substantial reorganization of cortical connections, involving a programmed synaptic pruning, takes place during adolescence in humans. A review of neurobiological abnormalities in schizophrenia has indicated that the neurobiological parameters that undergo peripubertal changes may be abnormal in this disorder (Keshavan et al., 1994).

According to the neurodevelopmental hypothesis of schizophrenia, maturational events in the brain at puberty interact with congenital defects to produce psychotic symptoms. Indeed, epidemiologic data on admissions to psychiatric units in England and France as well as the examination of 97 psychotic adolescents referred to an adolescent psychiatric unit revealed that girls showed earlier onset of psychotic symptoms arising around puberty compared to boys (this was expected, since girls reach puberty at an earlier age than boys) and onset of psychosis in girls was related to menarche (Galdos et al., 1993).

Several experimental studies have investigated the effects of gonadal hormones on dopaminergic neurotransmission in neonatal and adult rats treated with haloperidol and apomorphine. Estradiol significantly reduced the behavioural changes induced by both haloperidol (catalepsy) and apomorphine (oral stereotypes, grooming and sitting behaviour), this effect being more pronounced in neonatal rats. It was suggested that estradiol might act as a protective modulator in schizophrenia by enhancing the vulnerability threshold for psychosis through the downward regulation of dopaminergic neurotransmission. Indeed, sulpiride binding determinations in brain homogenates from the same animals showed that estradiol caused an almost threefold reduction of dopaminergic receptor affinity to sulpiride. Instead, no consistent effects of testosterone have been observed (Häfner et al., 1991a, b).

In addition, the antipsychotic properties of estradiol in humans were examined by testing whether the acute symptomatology of 32 female schizophrenic patients fluctuated with estradiol serum levels throughout the menstrual cycle. In all patients, the estradiol serum levels were markedly reduced as compared with the normal population and fluctuations throughout the cycle were

dampened. Nevertheless, a significant association emerged between estradiol levels on one hand and psychiatric symptomatology, behaviour on ward, paranoid tendencies and general well-being on the other, with psychopathology tending to improve when estradiol levels rised and viceversa (Häfner et al., 1993b; Riecher-Rossler et al., 1994). This finding is further supported by the evidence of premenstrual and post-partum exacerbations of schizophrenic symptoms. The protective effects of estradiol on the female brain in between puberty and menopause may help to explain the higher relative risk and the more severe form of late-onset-schizophrenia in females, whereas in males late-onset schizophrenia is less frequent and milder on average than early-onset schizophrenia. These effects may explain even the tendency for females to have a better short- and middle-term outcome, but a similar long-term outcome compared to males (Häfner et al., submitted for publication).

Finally, Seeman & Lang (1990) have proposed that the cyclic fluctuation of hormone levels in females may result in sensitized hormone receptors that underrespond at different time periods. This may lead to affective lability and ego disturbances, whose superimposition on schizophrenic symptomatology may explain the higher prevalence of affective and paranoid symptoms in female compared to male probands with schizophrenia.

## **ENVIRONMENTAL FACTORS**

Environmental theories suggest that familial, social and cultural forces external to the individual patient may trigger or channel the expression of schizophrenia. It is contended that males are subjected to higher expectations than females that they work, support a family, assert themselves and suppress signs of weakness or helplessness. The higher expectations and the need to deny dependency aspirations may place more pressure and stress upon young males and hasten the appearance of schizophrenia in those that are vulnerable. Once the disorder has appeared, the same factors may influence the type of treatment that is received, the compliance to treatment and the course of illness. Thus, differences in social roles and cultural norms are thought to influence, at least partially, gender differences in risk, onset, course and outcome of schizophrenia (Seeman, 1985; Bardenstein & McGlashan, 1990).

Poorer premorbid adjustment and quality of life among male subjects with schizophrenia compared to female counterparts has been reported by several studies. Done et al. (1994) have examined the social adjustment in childhood of individuals developing psychiatric disorders as adults. At the age of seven, children who later developed schizophrenia were rated by their teachers as manifesting more social maladjustment than controls. This finding was more common in boys than in girls and related to overreactive (i.e., externalising) behaviour. Thus, gender and the rate of development of different skills for social interaction appeared as important determinants of the risk

for psychosis in adulthood. Poorer premorbid adjustment and more behaviour abnormalities or psychiatric consultations during childhood or adolescence for minor mental disorders have been reported also by Vázquez-Baquero et al. (1995a) in male compared to female subjects with schizophrenia.

The complex interplay between psychological disturbance and social development in patients with schizophrenia has been investigated by Salokangas (1983), in order to identify the prognostic components related to social interaction that may be linked to patient's gender. In general, premorbid psychosocial development was poorer in males compared to females, since asocial traits, poor psychosexual development, reduced bonding ties with the family of origin and poor adjustment to working life occurred more often in males than in females. The Author suggested that schizophrenia and its associated tendency towards social withdrawal adversely affect the male social role (which involves greater activity and the need to demonstrate competence) considerably more than the female role, whose passive aspects are merely accentuated by the illness. Furthermore, the greater amount of hospital treatment provided to male patients to increase their independence and social functioning often fails its aim and may have the contrary effect of weakening social skills in male patients. The hypothesis that the younger age at onset of schizophrenia, with the associated impediment of individual social development at an earlier age, might contribute to the poorer social course of the disorder in males compared to females has been confirmed also by Häfner et al. (submitted for publication), who found that males were hit by the onset of the disorder at a significantly lower average level in terms of steps of social development such as employment, own accommodation and marriage or stable partnership. Moreover, Goldstein (1988) suggests that premorbid functioning may be a strong predictor of gender differences in outcome in the earlier stages of the disorder, with other factors becoming more prominent predictors in the long term. Indeed, a multivariate regression analysis showed that premorbid functioning explained up to 50% of the effect of gender on outcome of schizophrenia over one year, whereas it was responsible for only 1.9% of the effect of gender over 10 years.

Premorbid abnormalities in a child are expected to produce negative feelings in the parents and this may lead to more negativity in the child, with the family being then caught in a system of reciprocal negative feelings. Onstad et al. (1994) have examined 12 monozygotic and 19 dizygotic twin pairs of the same sex, that were discordant for DSM-III-R schizophrenia. Schizophrenic twins described their parents as less caring and more overprotective compared to their non-schizophrenic co-twins, with difference in paternal overprotection being the most important discriminating variable. In addition, social norms and expectations associated with being a male or female may specifically influence the attitudes and responses of family members to schizophrenic relatives and, in turn, the course of treatment and the outcome of the disorder. It has been shown that ill sons are sent to hospital more often and remain in hospital longer than ill daughters, due to gender differences in family responsibility for care and tolerance of symptom deviance (Goldstein & Kreisman,

1988). Similarly, Haas et al. (1990) have examined the critical and rejecting attitudes of the families toward the patients hospitalized for an episode of schizophrenic disorder. The families of female patients were less critical than the families of male counterparts. Moreover, the treatment with an inpatient family intervention was associated with less critical attitudes at follow-up among families of the female patients. These findings should be viewed in the light of research on 'expressed emotion', showing that male schizophrenics are more sensitive to critical over-involvement in families and relapse quicker with injuries to their self-esteem compared to females (Kuipers & Bebbington, 1988).

## **CONCLUSIONS AND RECOMMENDATIONS FOR FURTHER RESEARCH**

The main findings emerging from research on gender differences in schizophrenia can be summarized as follows:

- Age at onset of schizophrenia is higher in females compared to males, irrespective of the operational criteria used to define the onset of the disorder. A gender difference of three to five years is reported when the onset of schizophrenia is based on the first appearance of psychiatric symptoms. First admission to psychiatric institutions occurs three to six years later in females compared to males.
- No consistent pattern of gender differences in incidence rates of schizophrenia is reported. There is some evidence that higher incidence rates among the males occur especially in the younger age groups, whereas a female preponderance is reported among individuals with first-onset of schizophrenia after age 45.
- The lifetime morbidity risk for schizophrenia is around 1%, with little difference between males and females.
- Lifetime prevalence rates of schizophrenia vary by country and across studies, but no consistent gender differences are reported.
- Females are reported to have a better clinical outcome than males in the short term (i.e., within five years after discharge from hospital), whereas gender differences tend to disappear over longer periods. Most of the studies have shown a better social adjustment for females compared to males and this finding is in agreement with the frequent observation that females have a better premorbid functioning than males. No gender differences in number of re-admissions or length of hospital stay during follow-up have been reported by most studies; when gender differences are reported, females tend to receive less inpatient care compared to males.

Although absolute mortality rates are usually higher in males than in females, age-specific relative risk is generally higher in females, particularly in the younger age groups. However, comparison across studies is difficult due to differences in diagnostic standards, research instruments and outcome criteria. In addition, several methodological limitations have been suggested to influence these findings on outcome of schizophrenia.

- It is still controversial whether the forms of schizophrenia that occur in males and females are essentially the same disorder with an early onset in males and a later onset in females (timing model) or represent different morbid states (subtype model). Several etiological or risk factors that may exert a sex-specific effect in schizophrenia have been suggested, including genetic factors, brain abnormalities, endocrine factors and environmental factors. However, the extent and nature of the contributions provided by these factors are still to be clarified.

In spite of extensive research on gender differences in schizophrenia, there still remain several issues that deserve discussion and represent priorities for closer investigation and future research.

- (i) Although a particular construct of schizophrenia can be defined with reasonable inter-rater agreement by several standardized diagnostic systems, different sets of rules are often recommended. Indeed, the lack of external validating criteria for the diagnosis of schizophrenia still creates problems in research on gender differences. For example, setting age limits beyond which a diagnosis of schizophrenia cannot be assigned may result in a sex-specific distortion in selection, since females with later onset of the disorder are likely to be excluded. Similarly, there is evidence that more males than females receive a diagnosis of schizophrenia when restrictive diagnostic criteria are applied as opposed to a broad definition of schizophrenia including also schizophrenia-spectrum disorders. Thus, refining diagnostic criteria and achieving consensus about definitions is fundamental to further advance investigation into gender differences in schizophrenia.
- (ii) The majority of studies investigating gender differences in outcome of schizophrenia have relied on a naturalistic design and paid little attention to the type of treatment received by patients before and during follow-up. Whereas the effect of treatment on outcome of schizophrenia has long been recognized, possible gender differences in response to treatment have been less investigated. There is some evidence that differences in drug bioavailability may occur between male and female patients with schizophrenia. For example, females have been reported to have higher levels of prolactin and homovanillic acid while taking neuroleptics, suggesting greater sensitivity to neuroleptic blockade compared to males and, possibly, a gender effect on treatment response (Meltzer et al., 1983; Nathan et al., 1983; Szymanski et al., 1995). Alternatively, Hogarty et al. (1974) have suggested that females' better response to medications may be explained merely in terms of their greater compliance to drug treatment.

It follows that research on gender differences in schizophrenia is expected to pay increasing attention to this issue through the careful planning of case-control studies assessing the specific response of male and female patients with schizophrenia to different types of treatment.

- (iii) Most of the instruments used to assess the level of social adjustment, the quality of life and the unmet needs of patients with schizophrenia have not been created to examine the relationship of gender to other significant factors and, thus, to detect gender-specific differences. Indeed, Solomon & Draine (1993) have complained of a paucity of gender-sensitive measures available to identify needs that are specific to male or female patients with schizophrenia, to plan gender-specific interventions and to evaluate mental health services according to the unique needs related to patients' gender. There is a compelling need of knowing more of how the lives of males and females with schizophrenia differ and of how best to meet their specific needs. Future research is expected to fill this gap through the identification of those risk factors that may be uniquely linked with adverse clinical and social outcomes in male and female patients with schizophrenia. This would allow to design and evaluate intervention programs valuing individualized planning according to gender-specific needs.
- (iv) Research in the field of schizophrenia has been devoting increasing attention to genetic and biological factors operating in the disorder. Although the current view of schizophrenia as a 'brain disease' has promoted investigations and mobilised public interest, Herrman (1989) has warned against a new biological determinism in schizophrenia, that could restrict research and clinical advances. Future investigations into gender differences in schizophrenia should cover more than one domain, with genetic and biological factors as well as environmental influences and epidemiologic findings being investigated and integrated into comprehensive etiologic models.
- (v) There is some evidence that the effects of risk factors, such as pregnancy and birth complications as well as institutional rearing in early childhood, in the development of schizophrenia may differ in individuals at high risk for the disorder compared to low-risk controls. Moreover, the role of these factors may differ in schizophrenia as opposed to spectrum disorders (Schulsinger et al., 1987). Thus, there is a strong need for longitudinal studies of individuals at high and low risk for schizophrenia in order to explore the complex interplay between hereditary and environmental factors and to reach a better definition of the diagnostic boundaries of schizophrenia and spectrum disorders. These studies may also allow for the identification of those risk factors that may play a different part in male and female patients with schizophrenia.