OTHER BIOLOGICAL FACTORS

The impact of biological factors is expected to be prominent in major depression, since typical symptoms and signs such as changes in appetite and weight, libido reduction, dysmenorrhea and sleep disturbances seem to reflect a disorder of biochemical and neurophysiological functions. Investigations of monoamine metabolism (e.g., norepinephrine, serotonin, dopamine) as well as studies of other neurotransmitter systems (e.g., GABA, glutamic acid) and neuropeptides (e.g., somatostatin, corticotropin-releasing factor or CRF) have taken a major role in research into depression. Moreover, recent progress in understanding receptor structure and function and the regulation of endocrine systems (notably, thyroid hormones and the hypothalamic-pituitary-adrenal axis) has provided new insights into the biological deviations in depression (Syvälathi, 1994).

Halbreich & Lumley (1993) have reported gender differences in the function of two neurotransmitter systems that have been traditionally implicated in the pathophysiology of depression, namely norepinephrine and serotonin. The major difference between males and females with depression was in the rate of change in plasma levels of 3-methoxy-4-hydroxyphenilglycol (MHPG) with age. Whereas most depressed women were below or above the normal value of MHPG expected by age, most depressed men were within normal limits. By inference, an age-related gender difference in vulnerability to dysregulation of the norepinephrine system was suggested. As to serotonin, the relationships between gender, age and diurnal variations in imipramine binding and serotonin uptake in platelets of normal subjects showed that the aging process of some serotonin systems might be more apparent in females compared to males. It is intriguing that there seems to be a relationship between food intake and weight gain and depressed mood in women, with brain serotonin being involved in these disturbances of mood and appetite (Wurtman, 1993).

Depression also involves functional disorders of endocrine regulatory systems. A prominent role has been attributed to the hypothalamic-pituitary-adrenal axis, since cortisol secretion is frequently increased in depressed subjects and not suppressed by the administration of dexamethasone. Abnormalities in cortisol secretion may stem from dysregulation of neurotransmitter systems that regulate the hypothalamic-pituitary-adrenal axis; in turn, cortisol may affect brain and behaviour, since animal studies have shown that increase in cortisol may be related with neuronal atrophy and cell death in the hippocampus (McEwen, 1992). Halbreich & Lumley (1993) have provided evidence suggesting that the pattern of increase in plasma levels of cortisol with age may differ in males and females. No correlation has been found between plasma levels of cortisol and age in males and postmenopausal women; an increase in cortisol levels associated with age has been detected only in younger women. It follows that hormonal changes during the menstrual cycle may contribute to an imbalance in plasma levels of cortisol; once the destabilizing effects of hormonal cyclicity are over at menopause, this may have a positive effect on the the hypothalamic-pituitary-adrenal axis and delay further increase in plasma levels of cortisol. More recently, Young (1995)

has provided different findings. Post-menopausal women with recurrent depression have higher post-dexamethasone free cortisol than pre-menopausal depressed women, suggesting that in pre-menopausal women estrogens may limit adverse sequelae of hypercortisolemia such as hippocampal neuronal loss. Thus, it still remains unclear whether these changes have a causal role in the pathophysiology of depression.

Another vulnerability factor for depression refers to the activity of the hypothalamic-pituitary-thyroid axis, since about 25% of depressed patients do not show a normal increase of plasma TSH levels after being given intravenous TRH (Syvälathi, 1994). Research findings and epidemiologic evidence suggest a role for autoimmune thyroiditis and other thyroid abnormalities in depression (Whybrow, 1995). Since such abnormalities are more prevalent in women compared to men, it is expected that they may contribute to gender differences in rates of depression.

ENVIRONMENTAL MODELS

The role of environmental factors in the onset of depressive episodes has been widely acknowledged. On the basis of findings from surveys of random samples of women in the inner London area of Camberwell and in the Outer Hebrides, Brown & Prudo (1981) and Prudo et al. (1981) proposed a causal model for depression including three components: the first component concerned important losses and disappointments, called provoking agents, which were responsible for bringing about most cases of depression; the second component included vulnerability factors (e.g., lack of a confiding relationship with a husband or boyfriend; the presence of three or more children under age 14 at home), which increased a woman's chance of developing depression in the presence of a provoking agent; finally, a third component referred to symptom-formation factors, which influenced the form of a depressive disorder, such as duration or comorbidity with anxiety/phobic disorders, but did not increase the risk of it occurring.

Paykel (1994) reviewed research findings concerning life events and social support in clinical depression. Life events that were investigated spanned a wide range of threatening and undesirable experiences, with limited selectivity to separation events and interpersonal losses which are traditionally considered to be prominent in depression. Comparison of recent life events at the onset of a depressive episode and in general population controls showed consistently raised event rates in depression, with little difference between endogenous and non-endogenous depression. The occurrence of life events was also related to worse outcome and higher relapse rates. Finally, absence of social support was found associated with onset and relapse of depression, both acting independently and modifying the effect of life events. There is evidence that females experience more life events and difficulties compared to males (Kessler & McLeod, 1984; Bebbington et al., 1988) or accord greater impact to a life event after experiencing it (Wilhelm & Parker, 1993) and this may partly account for females' increased susceptibility to depression.

An investigation of a series of 130 patients attending psychiatric services with unipolar depression of recent onset and their first-degree relatives did not support a difference in relation to psychosocial adversity between the categories of endogenous and neurotic depression, with the temporal distribution of events being suggestive of a causal role in both types of depression. The rise before onset of depression was apparent both for the more serious events and for events of mild threat, suggesting that also minor events were associated with increased relative risk and that many individuals becoming depressed had a special susceptibility to stressful experience. Comparison with a community sample showed that first-degree relatives of probands with depression had significantly elevated rates of current depression as well as of threatening life events, suggesting that a common familial factor predisposed to both depression and the propensity to experience life events (Bebbington et al., 1988; McGuffin et al., 1988).

There is evidence that the familial and cultural context, with the specific structure of social roles and the expectations surrounding them, may influence both the number of life events experienced by an individual and the associated risk of depression. Comparison between samples of women in South London and the Outer Hebrides showed that life events and ongoing difficulties occurred much less frequently in the rural setting. Analyses within each population revealed that, in London, working-class women were more likely to develop depression compared to middle-class women because they experienced more provoking and vulnerability factors. Within the Hebridean population, women in the least traditional and integrated types of dwelling were at greater risk of depression because they experienced more provoking agents; similarly, non-churchgoing women were at greater risk because of the higher number of provoking agents and the greater vulnerability to them possibly due to enduring feelings of low self-worth induced by irregular churchgoing. Although women in the Hebrides experienced less life events and ongoing difficulties than their London counterparts, this advantage was partly offset by their tendency to become depressed more frequently following the death of close relatives, this vulnerability being interpreted in terms of differences in family structure, marital position and contact with relatives between the two settings (Brown & Prudo, 1981; Prudo et al., 1981).

A few studies have tried to determine the increased risk of developing depression that is associated to stressful life events. The risk in the six months following the most stressful classes of events is approximately six-fold and falls off rapidly with time after the event (Paykel , 1978). Moreover, Cooke (1987) estimated the proportion of depressive disorders caused by life events (attributable risk) and provided values ranging between 29% and 69%, but mainly around 40%. These findings suggest that life events play an important role in the onset of depression alongside with other factors. In addition to genetic and biological factors, developmental models and theories based on sex-roles have been advocated to account for gender differences in depression.

DEVELOPMENTAL MODELS

According to classic psychoanalytic theory, females are more prone to depression than males because of the personality structure resulting from females' psychosexual development and leading to narcissistic love relationships, masochism, low self-esteem, dependency and inhibited hostility. Bowlby (1971; 1973; 1980) incorporated in psychoanalytic theory observations from various disciplines, including ethology and experimental psychology, and suggested that personality depends largely upon the type of attachments to caregivers in early life and this, in turn, influences an individual's ability to cope with loss and bereavement. Although Bowlby emphasized the critical influence that death or separation from a parent in childhood may have on psychic maturation, he also claimed that several types of experiences in child-caregiver interaction may affect the cognitive development of a child, and these are likely to vary by gender and across cultures.

Developmental psychopathology is concerned with processes and mechanisms in one phase of development that may influence or modify an individual's set of responses at a later point. Within this theoretical framework, several explanations have been put forward for the higher prevalence of depression among females in adolescence and adult life. Some studies have suggested that girls experience more stress associated with physical maturation and growing up into a woman's role or in their social environment, while others have underlined that girls have less resilience or their coping strategies are less effective and more dysfunctional compared to boys' (Aro, 1994).

In this regard, Ruble et al. (1993) have suggested that socializing agents and gender stereotypes may affect a child's construction of gender identity. In general, parents tend to encourage girls in dependent behaviour and nurturant attitudes, whereas boys are encouraged to be independent and to engage in active, physical behaviour. This conforms with cultural stereotypes that emphasize confidence and competence in males as opposed to passivity, helplessness and dependence in females. The effect of socializing agents and the impact of gender stereotypes both contribute to girls being more likely to exhibit higher levels of self-evaluative concerns than boys. It may be expected that these concerns function as precursors to or risk factors for later development of depression. Indeed, girls' greater concerns to pleasing others make experiences of failure to meet external standards of performance or behaviour more likely and result in a lower sense of mastery and control. The Authors' review of a large body of research has found partial support for gender differences in self-evaluation among pre-adolescents, with girls having lower expectations, more maladaptive attributions and more negative reactions to failure compared to males.

On the other hand, no clear differences in personality between males and females were found in a study conducted among adults. Hirschfeld et al. (1984) compared unipolar depressed patients with never mentally ill control subjects on personality scales indicative of interpersonal dependency and learned helplessness. For both males and females, recovered patients reported greater

interpersonal dependency compared to controls; instead, greater learned helplessness was reported by female patients compared to their controls, but no significant differences were found among males. On both measures, the differences between patients and controls were similar for males and females, in contrast with the hypothesis that females' personality attributes are more consistent with a depressive image.

Nolen-Hoeksema (1987) suggested that there is only weak support for gender differences in personality characteristics of assertiveness and passivity, but rather it is the way males and females respond to depressed mood that account for females' increased vulnerability to depression. The Author provided evidence that males and females tend to show different response patterns to their own feelings of depression, with males engaging in activities designed to distract themselves from their mood (e.g., physical activities) and females being less active and ruminating about the possible causes of their mood and the implications of their depressive episodes. Relative to an active response set, a ruminative response set for depression may amplify depressive episodes by interfering with instrumental behaviour, by leading to failures and a sense of helplessness, by facilitating the accessibility of negative memories and by increasing the chances that an individual considers depressing explanations for his or her depression.

This gender difference in coping style is consistent with the notion that females tend to invoke verbal strategies and males non-verbal strategies, when an opportunity is presented to use either of the two. It is possible that rumination involves increased activity of the left posterior hemisphere (thus maintaining the left-right discrepancy in brain activation that has been shown to be associated with depression), whereas physical activity stimulates the right posterior hemisphere (thus decreasing the discrepancy). To the extent that the right hemisphere is involved in the hypothalamic-pituitary-adrenal axis, physical activity may be able to provide a normative restructuring. It is also possible that the tendency to activate the left hemisphere as opposed to the right hemisphere under a variety of circumstances may lead to a neuropsychological vulnerability toward depression (Heller, 1993).

SEX-ROLE MODELS

The impact of social roles and expectations may be responsible for gender differences in rates of depression. Specific attention has been devoted to the effect of marriage on rates of depression. Being married seems to have a protective effect for males and a detrimental effect for females, since the higher overall rates of depression among females are largely accounted for by higher rates among married females (Weissman & Klerman, 1977). Indirect evidence has been also provided by the effect of marital disruption on major depression in males and females. Using longitudinal data from the New Haven site of the Epidemiologic Catchment Area Study, Livingston Bruce et al. (1992)

found that marital disruption was associated with higher prevalence rates of major depression in both males and females, but only males had a greater risk of first-onset major depression.

A related issue is spouse similarity for psychiatric morbidity, that is the tendency for mated pairs to be more similar for a given psychiatric illness than would be expected if they were chosen at random. Data from clinical samples suggest that wives are more likely than husbands to be concordant with a spouse who suffers from affective disorders (Gershon et al., 1973; Dunner et al., 1976; Merikangas et al., 1982; Colombo et al., 1990). However, observations made in clinical samples are influenced by selection bias, with couples in which both spouses are sick being overrepresented. More recently, Galbaud du Fort et al. (1994) reported a significant spouse similarity for psychological distress and well-being in a general population sample, with marked symmetry in the relation between spouses' scores. Since a significant spouse similarity was found also for couples who had been togehter for less than two years, pre-marital similarity (i.e., assortative mating) seemed more likely than post-marital similarity (i.e., due to spouse interaction and shared environmental factors). In any case, these findings need to be replicated in longitudinal studies assessing pre- and post-marital similarity to dismiss the possibility that females are at greater risk than males for developing psychiatric disorders when they are married to a sick partner, possibly due to their specific social roles.

A further aspect to be considered is parity and childbearing. Brown et al. (1975) examined the relationship between psychosocial stress and subsequent affective disorders and found that working-class married women with three or more children aged less than 14 had the highest rates of depression. Moreover, Gater et al. (1989) investigated the effects of gender, age, marital status and parity on first admission rates for affective psychosis in Manchester, England. First admission rate in females was almost twice that in males and female parity entirely accounted for the gender difference in relative risk, with non-parous females having a lower relative risk of admission compared to males.

These findings suggest that married women with children are at greater risk of depression than comparable men, since their social circumstances are different. For example, most married men have a work outside home, whereas a significant proportion of married women do not. Moreover, women take more responsibility for the domestic sphere and childbearing compared to men. Investigators studying work as a source of stress and psychiatric disorder have observed that married women who do not work must rely on the sole role of housewife for identity and self-esteem, and this role carries many frustrating elements (e.g., no income, routine, isolation) and has been increasingly devaluated in modern society. On the other hand, women entering the marketplace often face economic discrimination and job inequity, with relatively low levels of control over work, low substantive complexity, poor job security and low wages being among the primary characteristics of the jobs women hold. Moreover, due to primary responsibility for household

chores and childcare, working women experience role overload and role conflict. These gender differences in type and structure of occupations and roles are expected to influence mental health outcomes (Gove, 1979; Lennon, 1995). Indeed, Meddin (1986) has shown that social role and experiential variables do account for a significant amount of the gender difference in depression among married persons. Using data from a national quality of life survey in the United States, comparisons were made between male and female respondents whose marriages reflected a 'traditional' division of labour, in which the male worked and the female did not, and between respondents whose marriages reflected a 'non-traditional' division of labour, in which both spouses worked full-time. Females reported more depression than males in both traditional and non-traditional settings. However, gender differences in mean depression scores were smaller for non-traditional than traditional settings, this reduction in gender differences being due both to rising male scores and to diminishing female ones. Regression analysis including a large number of potentially relevant variables showed that female gender was a significant predictor of depression only in the traditional setting, whereas satisfaction with job or homemaking, health and family had significant effects for both settings.

NEUROPSYCHOLOGY

Neuropsychology research on the topic of depression has rarely addressed the issue of gender differences. Otto et al. (1987) reviewed several lines of investigation, including the behavioural effects of inactivation of each cerebral hemisphere, the relative activation of the hemispheres during different mood states or in different clinical conditions (e.g., pain disorders), the performance of depressed patients before and/or after specific treatment for depression, and the behavioural indices of hemispheric arousal in negative emotional states. Converging evidence was provided for a critical role of the right hemisphere in depression. The specific nature of the right hemisphere involvement consisted of a tendency to become activated by aversive aspects of the environment and to process stimuli according to a more negative affective tone. These observations were used to explain gender differences in rates of depression, since females appear to have a greater lateralization of emotional processing to the right hemisphere, more chronic activation of the right hemisphere and greater susceptibility to the effects of negative emotional stimuli on right hemisphere activation. Moreover, the Authors suggest that learned coping skills may have a regulatory effect, since a tendency towards negative evaluations of ongoing events (as in learned helplessness, which is traditionally described to be more common among females) may increase right hemisphere activation and processing and this, in turn, may potentiate negative evaluations and the likelihood of negative memories.

More recently, Heller (1993) has argued that depression is associated with a reciprocal relationship between frontal and posterior regions of the brain, with relatively low left frontal activity

accompanied by relatively low right posterior activity. Unfortunately, the studies that were reviewed provided little or no information on gender differences. However, the observation that males and females differ in brain organization and function and in the maturation of cerebral hemispheres may be relevant for research on gender differences in depression. For example, females tend to perform better than males on tasks that involve processing emotional information (a right hemisphere specialization) and to display greater right hemisphere advantages for such tasks. Moreover, specific behavioural coping strategies may influence the neurophysiological mechanisms underlying mood and there is evidence that females are more likely to ruminate when depressed, whereas males are more likely to involve themselves in distracting activities. It is suggested that rumination tends to maintain or increase the left-right imbalance in cerebral activation associated with depression, whereas physical activity decreases it, and this may be responsible for a greater vulnerability to depression in females.

CONCLUSIONS AND RECOMMENDATIONS FOR FURTHER RESEARCH

The main findings gender differences in affective disorders can be summarized as follows.

- Although prevalence rates of major depression and dysthymia vary by country, a consistent finding is that rates are higher in females compared to males, with about a twofold gender difference on average. Similar findings are reported for intermittent depression and brief recurrent depression, although these disorders have been less investigated in general population samples. Gender differences in prevalence rates of bipolar disorder vary across studies and no consistent pattern is reported.

- Relatively few recent studies provide data on incidence of depression, but all show convincingly that rates are higher in females compared to males. No consistent gender differences in incidence rates of bipolar disorder are reported.

- Lifetime morbidity risk for depression is high and females are at greater risk compared to males. Lifetime morbidity risk for bipolar disorder is similar for males and females.

- Age at first onset of depression is similar in males and females and peaks between 20 and 40 years. Age at first onset of bipolar disorder is similar in the two sexes, first onset of bipolar disorder occurring mainly between 10 and 30 years.

- An increase in rates of major depression has possibly occurred over time. A temporal trend is operating for higher cumulative rates of major depression at an earlier age of onset in younger birth cohorts. The cumulative lifetime rates of major depression are still higher in females

compared to males, although some studies suggest that the magnitude of the male-to-female difference is diminishing in recent years. A progressive increase in cumulative risk for successive birth-cohorts is reported also for bipolar disorder. However, several potential biases have been suggested that may be responsible for these findings on temporal trends in affective disorders and, in general, methodological concerns have been expressed by several investigators about the supposed cohort effects in psychiatric disorders.

- Several hypothetical explanations for the preponderance of females in rates of depression have been suggested, including genetic factors, reproductive hormones, monoamine and other neurotransmitter systems, regulation of endocrine systems (notably, thyroid hormones and the hypothalamic-pituitary-adrenal axis), developmental models, environmental factors (e.g., life events and social support), sex-role conflicts and findings from neuropsychology. However, relatively little effort has been made to integrate putative risk factors from different fields of research into comprehensive etiologic models.

Although extensive research has been carried out, a number of issues deserve discussion and represent priorities for closer investigation and future research.

(i) The definition of homogeneous diagnostic subtypes is a key issue in research on gender differences in affective disorders. There is evidence that females' increased risk varies widely by diagnostic subtypes. It may be more pronounced for seasonal winter depression and atypical depression with so-called 'reverse neurovegetative' somatic symptoms of hyperphagia, weight gain and hypersomnia. Even for bipolar illness, females predominate in forms such as rapid cycling and mixed state bipolar disorder as well as bipolar II disorder; moreover, bipolar illness in females is characterized by relatively more depressive and fewer manic episodes compared to males (Blehar & Oren, 1995). This issue poses specific methodological difficulties, since affective disorders are thought to be comprised of multiple subtypes, but biological or trait markers are relatively few and of unclear specificity. One possible approach has been recently suggested by Merikangas et al. (1994), who used the longitudinal course of illness as the criterion to define different subtypes of major depression.

(ii) Most studies of affective disorders have compared males and females that satisfied severity criteria according to well-known systems for classifying mental disorders. Using this approach, it is assumed that a discontinuity occurs between 'normal' depressive mood and clinical depressive disorders. On the other hand, developmental psychology has often assumed that there is a continuum extending from normal sadness to severe depressive feelings, and has made the 'grey area' between the two the focus of interest and empirical study (Aro, 1994). Since there is no clear means by which to distinguish between the mood states that are quantitative variations from normality and those that are qualitatively distinct disorders, research on gender

differences may take advantage of different levels of analysis and assessment. For example, Angold (1988) has suggested at least eight distinctions in the definition of 'depression' and these can be variously combined in a useful analytical approach. Similarly, increased attention should be directed at gender differences in comorbidity, since the identification of mental and physical disorders that are comorbid with affective disorders may provide important clues to common vulnerability factors and shared pathophysiological mechanisms.

(iii) It is important to distinguish between the quantitative (i.e., symptom level) and qualitative (i.e., subjective) aspects of depression, in order to elucidate also gender differences in style of coping with depression. Using a psychoanalytic framework for object relations, Blatt (1974) described two fairly distinct forms of subjective depressive experience, with anaclitic depression involving feelings of helplessness, loss and abandonment, and introjective depression entailing feelings of guilt, self-criticism and inferiority. Males and females may differ in vulnerability to anaclitic and introjective depression and this may be understood in terms of socialization experiences and social roles (Sanfilipo, 1994).

(iv) A clear definition of 'gender' is essential, since 'gender' is neither a unitary nor a causal variable. Indeed, it may refer to biological sex as well as to developmental processes leading to the acquisition of gender identity and related social roles (Blehar & Oren, 1995). There is evidence that some depressive symptoms or behaviours may relate to biological sex, while others are better understood in terms of gender identity and sex roles (Wilhelm & Parker, 1993). This observation underlines the importance of adopting both perspectives in the investigation of gender differences in affective disorders.

(v) Since cultural norms and beliefs strongly influence sex roles and the expectations surronding them, cross-cultural studies are clearly needed in order to better understand the interplay between biological and social factors. Two studies provide evidence to the importance of investigating gender differences in various cultural settings. Among the Old Order Amish, equal numbers of males and females received a diagnosis of unipolar depression in contrast with the findings of most epidemiologic surveys. As possible explanations, it has been argued that, among the Amish, female social roles are more protective against depression than in modern societies, that females are no more likely than males to mask depression with somatic or neurasthenic symptoms (given the dominant work ethic and the need for females to be efficient mothers and housekeepers) and/or that males are not allowed to mask depression by using alcohol or adopting violent behaviour (Egeland et al., 1983). More recently, Loewenthal et al. (1995) investigated gender-differences in prevalence of depression and associated risk factors among Jews affiliated to orthodox synagogues in the London area. Prevalence of depression was similar in males and females. Moreover, social factors that have been found to be associated with depression in other samples (e.g., number of life-events and difficulties, no paid

employment, homemaker role only) did not function as risk factors among the Jews, suggesting the importance of specific cultural and religious values such as the esteem attached to females' central role in family management and the low use of alcohol and suicide to escape depression. Thus, studies conducted in well-defined communities can provide excellent testing grounds for the role of genetic and cultural/environmental factors in the expression and transmission of affective disorders and can suggest specific prevention and intervention strategies.

(vi) Findings generated by epidemiologic, genetic, biological and psychosocial investigations have contributed to identify several risk factors linked to females' increased vulnerability to depression. There is now a strong need for combining putative risk factors from more than one field of research into integrated etiologic models, using a multidisciplinary approach. Recently, Kendler et al. (1993) have developed an exploratory model for the prediction of episodes of major depression, including a comprehensive set of predictor variables such as genetic factors, parental warmth, childhood parental loss, lifetime traumas, personality measures, social support, past depressive episodes, recent difficulties and stressful life events. The model suggested that at least four risk factor domains are needed to understand the etiology of major depression, namely traumatic experiences, genetic factors, personality and interpersonal relations. However, the sample was entirely female and, thus, the effect of gender on risk for depression could not be studied. Moreover, the model did not test the effect of biological and social changes that occur at puberty and during adolescence, when gender differences in depression become apparent. If further progress is to be made, longitudinal studies are needed, based on large samples of prepubescent children who are to be reassessed regularly as they go through puberty, adolescence and adulthood. This type of studies is a complicated and expensive challenge, but would provide valuable information on the onset, course and outcome of affective disorders. Moreover, several of the proposed explanations for gender differences in depression could be tested simultaneously for their ability to predict the appearance of depressive episodes and the emergence of gender differences in depression, provided that genetic factors, biological parameters, personality traits, uncontrollable life events, sex-role indicators and coping style are measured over time.

(vii) A final objective is the investigation of the course, outcome and response to treatment of affective disorders in males and females separately. There is some evidence that females have longer index-episodes of major depression and lower rates of spontaneous remission than males (Sargeant et al., 1990). Moreover, females may be less responsive to tryciclic antidepressants, take longer to respond and require longer course of treatment (Weissman, 1995; Kornstein, 1996). Gender differences in drug absorption, distribution and metabolism may affect drug bioavailability and be responsible for differential response to antidepressants. On the other hand, males and females suffering from major depression have been reported to have similar outcomes over a 16-week course of cognitive-behaviour therapy. However, among individuals

who are severely depressed, males may be more likely to experience remission than females (Thase et al., 1994). Additional confirmation of gender differences in course, outcome and response to treatment are necessary to develop effective intervention strategies and treatment guidelines for males and females with affective disorders.

SCHIZOPHRENIA

INTRODUCTION

A detailed discussion of the concept of schizophrenia and of its evolution over time is beyond the scope of this work. For a comprehensive overview, interested readers are referred to Warner & de Girolamo (1995). Here, we briefly outline some diagnostic issues that may be useful to interpret the findings reported in this chapter.

Before the introduction of explicit operational criteria, there existed marked differences between national diagnostic systems in the diagnosis of schizophrenia. This was clearly demonstrated by an international research project examining the diagnoses given to patients at their admission to hospitals in New York and London. European psychiatrists applied the diagnosis of schizophrenia to a small subgroup of patients with delusions and hallucinations not explicable in terms of affective disturbances and often with long-term deficits, whereas American psychiatrists included anyone with any type of hallucination, delusion or odd behaviour not explicable otherwise. It followed that American psychiatrists were about twice as likely as European psychiatrists to diagnose schizophrenia, but four times less likely to diagnose psychotic depression and ten times less likely to diagnose mania (Cooper et al., 1972).

The introduction of standardized systems for classifying mental disorders provided diagnostic categories that were reliable and widely accepted. However, large differences between the various diagnostic systems still exist as a result of the choice of symptom criteria, the structure of diagnostic algorithms, the duration criteria as well as the evaluation of affective symptoms and can significantly affect the rates of schizophrenia detected in general population studies and treated samples (Warner & de Girolamo, 1995). For example, Endicott et al. (1982) compared the joint frequencies and reliabilities of six sets of criteria for the diagnosis of schizophrenia. The systems differed moderately in the degree to which clinicians using the same criteria agreed on the diagnosis of schizophrenia; nonetheless, a dramatic difference was found in the rates at which schizophrenia was diagnosed in the total sample, the range being between 4% and 26%.

Since the application of a categorical model of schizophrenia as a distinct syndrome may create difficulties in interpreting research findings, a dimensional model based on the distribution of vulnerability along a continuum has been proposed. Three types of evidence have been suggested to support a dimensional model of schizophrenia. First, the onset of the disorder is often preceded by prodromal symptoms, social impairment and cognitive deficits. Second, increased rates of schizoid, paranoid, and eccentric personalities as well as of other psychiatric disturbances are frequently

reported in the families of individuals with schizophrenia. Finally, studies attempting to identify biological trait variables and vulnerability markers produced unimodal continuous patterns of distribution between subjects with schizophrenia and their relatives (Häfner, 1988). The use of a dimensional approach to the pathogenesis of schizophrenia and related disorders may be expected to provide important clues as to the genetic and pathophysiology of schizophrenia and, at the same time, illuminate a set of disorders that may be part of a continuum of schizophrenia-related disorders (Siever et al., 1993).

Since the criteria used to identify subjects with schizophrenia may be an important source of variation across studies, in this chapter diagnostic criteria were specified for each study alongside with the type of diagnostic categories that were considered, that is whether a restrictive definition of schizophrenia (including only schizophrenic psychoses) or a broad definition of schizophrenia (including schizophrenia and schizophrenia-related disorders) was adopted.

AGE AT ONSET OF SCHIZOPHRENIA

A consistent finding in the epidemiology of schizophrenia is the higher mean age at onset of the disorder among females. Angermeyer & Kühn (1988) reviewed 36 studies, published between the beginning of the twentieth century and 1982, on gender differences in onset of schizophrenia. The large majority of the studies showed that the disorder tended to appear later in females, although the frequent lack of an operational definition of the onset of the disorder limited the validity of this finding. In addition, the Authors found 53 studies, published during the period 1926-1983, that reported data on gender differences in age at first hospitalization for schizophrenia. With few exceptions, female patients had their first admission to hospital later than their male counterparts, the difference most commonly reported being between four and five years. When age-specific rates of first admission for schizophrenia were broken down according to gender, higher male-to-female sex ratios were found in the age groups below 25 years. Since no significant gender differences were found in the length of time between the onset of the disorder and first hospitalization, these findings provided further support to a later onset of schizophrenia in females. Finally, in order to control for time trends or regional variations occurring in age at onset or first hospitalization for schizophrenia, a meta-analysis was performed on the studies grouped according to the country of origin and whether they were carried out before or later than 1945. Larger gender differences were observed in Central European and Scandinavian countries both for age at onset and age at first hospitalization. In the same countries, the studies carried out after 1945 reported greater gender differences compared to those conducted before that year.

In order to integrate and update the work of Angermeyer and Kühn (1988), the studies on age at onset of schizophrenia that appeared in the international literature between 1984 and 1995 have

been reviewed. The studies have been grouped according to the operational criteria used to define the onset of the disorder.

AGE AT FIRST ONSET OF PSYCHIATRIC SYMPTOMS

Table X shows the findings from studies in which age at onset of schizophrenia was computed on the basis of the first appearance of psychiatric symptoms. Seven out of nine studies reported that the mean age at onset of psychiatric symptoms was higher in females compared to males, the difference ranging between three and five years.

Goldstein et al. (1990a) assessed retrospectively a cohort of 332 patients, using all available information from probands, relatives and medical charts. Survival analysis was then used to detect a gender difference in age at onset of psychotic symptoms or bizarre behaviour.

Gureje (1991) evaluated a sample of patients attending a psychiatric hospital for the first time over a six-month period. Males had a significantly earlier age at onset than females, when age at onset was defined as the time of first psychotic symptoms or social dysfunction being apparent to relatives.

Ohaeri (1992) included patients that met the DSM-III-R criteria for schizophrenia at first episode, had at least one relapse of illness in which no affective or organic features were noted and attended follow-up for at least one year.

In the ABC Schizophrenia Study, Häfner et al. (1993a,b) selected all first admissions with a clinical diagnosis of schizophrenia from both the Danish and the Mannheim psychiatric case-registers. In addition, a large representative German sample of first-admitted patients with non-affective functional psychosis was directly assessed, using the Present State Examination and a standardized interview that covered several domains, such as sociodemographic changes, changes in symptoms, negative symptoms, premorbid adjustment, social disability and functional impairment. Females reported a higher mean age at onset of schizophrenia irrespective of the operational definition used (i.e., first signs of mental disorder; first psychotic symptoms; climax of first acute episode).

Faraone et al. (1994) applied a non-parametric method to correct male and female distributions of observed ages at onset of psychotic symptoms for three potential confounders: the age composition of the population of origin, the excess mortality among schizophrenic patients, and the gender difference in mortality among these patients. Before correction, the distribution of the observed ages at onset of psychotic symptoms was biased toward younger ages, with only 5.6% of the males and 18.5% of the females having observed ages at onset greater than 35 years. After

correction, these percentages increased to 11.8% and 30.1%, respectively. Age at onset of psychotic symptoms was higher in females compared to males in both types of analyses.

Gorwood et al. (1995) assessed the impact of family history of schizophrenia on the association between gender and age at onset of the disorder. In the total sample, mean age at first diagnosis of schizophrenia was older in females than in males. When the sample was divided according to the presence of another schizophrenic patient among first- and second-degree relatives of the proband, females with no family history of schizophrenia showed a significantly later age at first diagnosis compared to females with family history, males with a family history and males without a family history of schizophrenia. Instead, no significant differences in age at first diagnosis of schizophrenia were found between the three latter subgroups. Among the males with or without family history and the females with family history of schizophrenia the distribution of ages at first diagnosis showed a single peak between 16 and 30 years, whereas females with no family history of schizophrenia showed two peaks between 16 and 25 years and between 35 and 40 years, respectively.

Finally, Szymanski et al. (1995) investigated gender effects on onset, course of illness and treatment response in a group of patients aged 16 to 40 years that were admitted to hospital for the first time for a psychotic episode and received standard neuroleptic treatment. Females were significantly older than males at the first onset of psychotic symptoms, even though the criteria used to define the first appearance of psychotic symptoms were not provided.

On the other hand, conflicting results have been reported by two studies. Hambrecht et al. (1992a) processed the data from the WHO Disability Study, a transcultural study conducted in three countries of Western Europe, two of the Balkans and two of the Islamic region. Patients were sampled provided that they were aged between 15 and 44 years and had shown first psychotic symptoms during the 24 months prior to the screening. Age at onset was computed on the basis of the age at inclusion into the sample. An earlier onset of psychotic symptoms was found among the males in the European centres only. In the Islamic region an earlier onset was reported for females, although this finding could be attributed to patient selection, since male-to-female differences in age at onset and male-to-female ratios in the samples covaried.

More recently, Beiser et al. (1993) recruited residents of Vancouver aged between 15 and 54 years, who were experiencing a first episode of functional psychosis. Probands were selected from all psychiatric hospitals, general hospitals, private psychiatrists, college and high school counsellors, employment and immigration counselling agencies, community mental health centres and one-in-six general practitioners. Clinicians administered the Present State Examination and conducted an anamnestic interview to elicit premorbid history and details about the progression of the disorder. In addition, at least one first-degree relative or a friend provided information on the onset of illness. No gender difference in age at onset of first noticeable symptoms emerged, when subjects

were diagnosed according to ICD-9 criteria. Instead, females showed earlier onset of symptoms, when the DSM-III criteria were used. Moreover, females experienced longer prodromal phases of the disorder, defined as the time between first noticeable symptoms and first prominent psychotic symptoms.

Table X - Age at first onset of psychiatric symptoms in subjects with schizophrenia

Author Country, time	Sample (N) Males	 Females	Age range (years)	Definition of onset of the disorder	Diagnostic criteria	Mean age at onset Males	 Females
Goldstein et al. (1990a) USA, 1934-44	332 (total)		no age limits	Onset of psychotic symptoms or bizarre behaviour	DSM-III	24.3	27.9
Hambrect et al. (1992a) Bulgaria, Croatia, Germany, Netherlands, Switzerland, Sudan, Turkey 1976-80	277	233	15 - 44	Onset of symptomatology not more than 24 months prior to screening	ICD-9 Bulgaria Croatia Germany Netherlands Switzerland Sudan Turkey	26.6 27.1 24.5 24.9 24.5 23.7 22.9	28.8 29.4 28.0 25.2 25.1 19.4 21.7
Gureje (1991) Nigeria	125	89	10-54	First noticeable symptoms or maladaptive behaviour	RDC	23.5	26.4
Ohaeri (1992) Nigeria, 1988-91	199	141	14-65	First noticeable symptoms	DSM-III-R	24.0	27.0
Beiser et al. (1993) Canada, 1982-84	56	16	< 54	a) First noticeable symptoms b) Prominent psychotic symptoms	DSM-III see text (only statistics provided)		
Häfner et al. (1993a,b) Germany, 1987-89	127	140	12 - 59	a) First sign of mental disorder b) First psychotic symptoms c) First acute episode	ICD-9	a) 24.3* b) 26.5 c) 27.8	27.5* 30.6 31.7
Faraone et al. (1994) USA, 1934-44	162	157	no age limits	First evidence of psychotic symptoms	DSM-III	24.3 26.2*	28.0 31.1*
Gorwood et al. (1995) Reunion Island, 1988	356	307	no age limits	First diagnosis of schizophrenia	DSM-III-R	27.8	31.5
Szymansky et al. (1995) USA, 1986-89	29	25		First evidence of psychotic symptoms	RDC	21.0	24.0

* Rates corrected by the age distribution of the population

AGE AT FIRST TREATMENT

Table XI shows the findings from studies in which age at onset of schizophrenia was computed on the basis of first admission to (or contact with) psychiatric institutions for patients with a diagnosis of schizophrenia. All of the studies confirmed a higher mean age at onset for females compared to males, the differences most commonly reported ranging between three and six years.

Using data collected through the Danish Psychiatric Register, Munk-Jørgensen (1986) sampled all in- and day-patients that were admitted to Danish psychiatric institutions for the first time in 1972 and were assigned a diagnosis of schizophrenia at least once until September 1983.

Psychiatric case register data were used also by Häfner et al. (1989) to draw a comparison between two samples of Danish and German patients. Analyses were first carried out on patients satisfying ICD-8 criteria for schizophrenic psychosis ('restrictive definition' of schizophrenia) and then repeated including also patients with paranoid states, acute paranoid reaction and borderline state ('broad definition' of schizophrenia). According to both the restrictive and the broad definition of schizophrenia, a higher mean age at first hospitalization was found for females, the difference ranging between four and six years. For the restrictve definition of schizophrenia, the exclusion of patients whose first admission occurred beyond the age of 44 years (the age limit required by DSM-III for a diagnosis of schizophrenia) reduced the mean age difference between males and females to 1.6 years in Denmark and 2.3 years in Mannheim.

In Italy, Gozio et al. (1992) selected patients that were admitted for the first time to a psychiatric ward with a diagnosis of schizophrenia. However, the interpretation of these findings is difficult, since no information was provided on the age range and the sex distribution of the sample as well as on the method used to compute the mean age at first admission.

Menazes & Mann (1993) selected hospital-treated patients with diagnosis of schizophrenia in a large urban centre in Brazil, the upper age limit being 44 years.

Albus et al. (1994) investigated the impact of both familial loading and gender on age at onset of schizophrenia. For the total sample, the age at first psychiatric hospitalization was significantly higher in females compared to males. However, when analyses were repeated on the basis of the presence or absence of familial loading, gender differences in age at onset virtually disappeared.

Castle et al. (1994) examined a sample of patients with a broad diagnosis of schizophrenia according to ICD-9, who contacted psychiatric services for the first time. Males exceeded females among those with an onset before age 35; thereafter a female preponderance was found.

The World Health Organization Determinants of Outcome Study (Susser et al., 1994) selected 13 sites in two contrasting sociocultural settings, including three developing countries and eight industrialized countries. The study cohort consisted of patients with a diagnosis of schizophrenia or nonaffective acute remitting psychosis that made a first contact with an helping agency. Nonaffective acute remitting psychosis was defined as a psychotic state characterized by an onset within one week and subsequent complete remission of psychotic symptoms. In each country, rates were corrected by the age distribution of the general population. Both in developing and in industrialized countries the mean age at first contact for schizophrenia was significantly higher in females compared to males, whereas no gender differences were found for nonaffective acute remitting psychosis.

Gorwood et al. (1995) assessed the impact of family history of schizophrenia on the association between gender and age at onset of the disorder. Onset was defined either as the age at first contact for psychiatric care or as the age at which the patients first met the DSM-III R criteria for schizophrenia. Age at first treatment and age at first diagnosis were highly correlated in the total sample as well as in the four subgroups that were derived, i.e. males (and females) without a family history and males (and females) with a family history of schizophrenia. In the total sample, mean age at onset according to both definitions was older in females than in males.

Szymanski et al. (1995) investigated gender effects on onset, course of illness and treatment response in a group of patients aged 16 to 40 years that were admitted to hospital for the first time for a psychotic episode and received standard neuroleptic treatment. Females reported a higher age at first hospitalization compared to males, although the difference was not statistically significant.

Finally, Vazquez-Barquero et al. (1995a) selected all patients aged 15 to 54 years, suffering from a first episode of schizophrenia and making a first contact with any of the public mental health services in Cantabria over a 2-year period.

Table XI - Age at first psychiatric treatment for subjects with schizophrenia

Author Country, time	Sample (N) Males	 Females	Age range (years)	Definition of onset of the disorder	Diagnostic criteria	Mean age of onset Males	 Females
Munk-Jørgensen (1986) Denmark, 1972-83	370	217	no age limits	First admission	ICD-8	27.4	33.7
Häfner et al. (1989)			12 - 59	First admission	ICD-8 Denmark#	33.0	39.0
Denmark, 1976	527	642				34.8*	40.2*
Germany, 1978-80	160	176					
					Germany#	32.4	37.4
						33.1*	37.9*
					Denmark##	31.2	36.3
						32.8*	37.7*
					Germany##	32.0	36.0
						32.5*	36.4*
Gureje (1991) Nigeria	125	89	10-54	First visit to hospital	RDC	23.5 25.2	26.4 28.5
Gozio et al. (1992) Italy, 1977-89	545 (total)		not available	First admission	DSM-III	22.8	24.9
Menezes & Mann (1993) Brasil, 1991	69	55	15 - 44	First admission	ICD-9 DSM-III-R	22.9	26.1
Albus et al. (1994) Germany, n.r.	106	91	no age limits	First admission	DSM-III-R	25.3	30.0
Castle et al. (1994) UK, 1965-84	245	236	16 and older	First contact with psychiatric services	ICD-9	31.2	41.1
Susser et al. (1994)	438	349	15 - 54	First treatment contact	ICD-9 DC°	22.4*	22.4*
India, Colombia, Nigeria				for a psychotic disorder	IC°	25.5*	24.9*
(developing countries, DC)					DC°°	23.0*	25.7*
Denmark, Ireland, Hawaii, Russia,					IC°°	26.0*	30.7*
Japan, UK, Czech Republic, USA							
(industrialized countries, IC)							
Gorwood et al. (1995) Reunion Island, 1988	356	307	no age limits	First contact for psychiatric care	DSM-III-R	28.7	32.6
Szymanski et al. (1995) USA, 1986-89	29	25	16-40	First hospitalization	RDC	22.0	24.0
Vazquez-Barquero et al. (1995a,b) Spain, 1989-90	43	43	15-54	First contact with psychiatric services	ICD-9 DSM-III-R	24.0	27.0

* Rates corrected by age distribution
\# Restrictive diagnostic criteria [ICD-8 295]
\## Broad diagnostic criteria [ICD-8 297, 298.3 and 301.83 (Denmark) or 295.5 (Germany)]
° Non affective acute remitting psychosis
°° Schizophrenia

FACTORS THAT MAY INFLUENCE GENDER DIFFERENCES IN AGE AT ONSET OF SCHIZOPHRENIA

Since schizophrenia is a disorder characterized by low incidence rates and insidious onset with a prodromal phase often developing slowly over years, prospective follow-up studies of the general population would require large sample sizes and long-term observation and, thus, represent a complicated and expensive effort. As a consequence, epidemiologic studies defined the onset of schizophrenia as either the time of first contact with psychiatric services or the first appearance of psychiatric symptoms, the latter dated through information collected retrospectively from probands, relatives and/or medical charts. In general, there is large concordance between studies, supporting the notion that females tend to present a higher mean age at onset of schizophrenia, when age at onset is defined as either the first contact with psychiatric services or the first appearance of psychiatric symptoms. However, three types of biases may influence the findings on age at onset of schizophrenia and may be artifactual determinants of gender differences: i) sampling biases; ii) biases introduced by diagnostic criteria; iii) biases depending on the method used to compute the mean age of the sample.

i) Sampling biases

Sampling biases refer to the procedure adopted to select the sample under investigation and may influence the size and representativeness of the sample and its sex ratio. Hambrecht et al. (1992c) have examined the sample composition of multicenter studies on schizophrenia carried out by the World Health Organization, in order to ascertain whether females are underrepresented. Severity of symptoms is not responsible for imbalances in the male-to-female sex ratio, but three sources may be artifactual determinants of an underrepresentation of females in research on schizophrenia. First, male patients more often exhibit maladaptive illness behaviours and accessory symptoms that are less tolerated by the society and lead to hospital admission. Second, socio-cultural influences 'protect' females from hospitalization for a disorder which is prone to stigmata and this effect is evident especially in more traditional societies. Third, availability and accessibility of psychiatric services differ between countries and sexes. This latter finding applies mainly to developing countries, where males have higher education and economic status and, as principal earners of family income, receive priority in the scarce treatment, whereas females appear to seek first help more frequently from traditional and religious healers.

In addition, Wahl & Hunter (1992) have reviewed research on schizophrenia, published in four professional journals between 1985 and 1989, examining the gender composition of patient samples and analyses of findings by gender. A clear male bias in selection of schizo-

phrenic subjects was evident, since males outnumbered females two to one, researchers working with single-sex samples were far more likely to choose all-male than all-female samples and possible gender differences within mixed-sex samples were frequently neglected.

Equally important is the definition of onset of schizophrenia. To date, the literature has provided no standardized and replicable methods to establish illness onset. Using reports by family and friends about a sample of 141 subjects with first-episode psychosis, Beiser et al. (1993) derived a checklist of behaviours describing the evolution of various phases of illness. Supplied with the checklist, clinician pairs independently rated the critical phases in the evolution of illness. Good reliability was achieved in assigning age at the first appearance of psychotic symptoms and at initiation of treatment seeking; instead, judging the beginning of the prodromal phase proved to be difficult.

More recently, Hambrecht et al. (1994a) compared retrospective reports given by patients and their significant others about emerging symptomatology during the early course of schizophrenia in a representative sample of first-admitted patients. A comprehensive interview assessing early signs and symptoms revealed that, in most cases, patients as well as informants perceived negative, depressive and unspecific symptoms as early signs of the disorder. Pairwise agreement was good for those items concerning abnormal behaviours that could be observed easily, such as paranoid delusions, suicidal behaviour, substance abuse, parental and marital role deficits. In contrast, there was little agreement between reports about perceptual and formal thought disorder (i.e., subjective internal phenomena). It follows that, although dating the onset of illness phases may be feasible, further efforts to improve reliability are needed.

Finally, the finding that mean age at first contact with psychiatric services is higher in females compared to males does not necessarily imply that the 'actual' onset of the disorder differs between the two sexes. It might as well be that early manifestations of the disorder occur at approximately the same age in the two sexes, but the time between the onset of illness and first contact with psychiatric services is shorter in males than in females. Possible determinants of this gender difference might be the type of onset (for example, acute versus insidious) or symptomatology (for example, positive versus negative symptoms or the occurrence of deviant behaviours), the patterns of illness behaviour and the degree of tolerance that family and friends may eventually have to symptoms and impairment in occupational, social and personal activities according to the sex of the proband. A related issue refers to the type of services from which patients are sampled, since barriers to access may lead to an under-representation of specific groups of subjects suffering from the disorder.

ii) Biases introduced by diagnostic criteria

Setting age limits beyond which a diagnosis of schizophrenia cannot be assigned may result in a sex-specific distortion of the mean age at onset of the disorder, since females with later onset of illness are excluded. According to the DSM-III criteria, schizophrenia can only be diagnosed provided that symptoms are present before age 45 years. Using data from the World Health Organization Determinants of Outcome Study, which selected patients up to the age of 54 years, Hambrecht et al. (1992b) have shown that 5% of the males as opposed to 12% of the females in the sample would have been excluded according to the DSM-III criteria. Additional evidence has been provided by the ABC Schizophrenia Study. Although the lifetime risk of schizophrenia was essentially the same for males and females, the distribution of onsets across the life cycle pointed to a later increase and a second lower peak between the ages 45 to 54 years among females compared to males (Hambrecht et al., 1992b; Häfner et al., 1993a,b). This type of bias might explain the lower age at onset in females compared to males that was found in studies using DSM-III criteria (e.g., Beiser et al., 1993).

A second issue refers to the stringency of diagnostic criteria. There is evidence that more males than females receive a diagnosis of schizophrenia, when restrictive diagnostic criteria are applied, since females are frequently assigned a less severe diagnosis (Lewine et al. 1984). In addition, gender differences in the age at onset may vary according to schizophrenic subtypes. In a sample of 200 patients with paranoid schizophrenia, the onset of the disorder occurred earlier in males than in females: 72% of the males developed the disorder before age 30 years, whereas females had an even distribution of the onset before and after age 30 years. On the other hand, Beratis et al. (1994) have shown that the disorganized subtype tended to occur earlier in females, whereas no significant gender differences were found in age at onset for the undifferentiated and the residual subtypes.

iii) Biases related to the method used to compute the mean age of the sample

The high proportion of younger males and/or older females among patients with first episodes of schizophrenia might simply reflect the age and sex distribution of the general population from which the sample is drawn. In order to exclude this possibility, absolute values of the mean age at onset of schizophrenia in the sample should be corrected on the basis of the age and sex distribution of the general population. This correction is often neglected, as demonstrated by the fact that only six of the studies that have been reviewed corrected the reported mean age at onset for this potential bias (Häfner et al. 1989; Häfner et al. 1993a, b; Albus et al. 1994; Castle et al. 1994; Faraone et al. 1994; Susser et al. 1994).

INCIDENCE OF SCHIZOPHRENIA

Most studies computed incidence rates on the basis of first admissions to or first contacts with psychiatric services made by patients with a diagnosis of schizophrenia. Only few studies selected general medical services and social agencies alongside with psychiatric services, in order to identify also people with schizophrenia that did not receive psychiatric care. Eleven out of 18 studies reported incidence rates that were similar in males and females, whereas the remainders found higher incidence rates among the males. In the Tables XII and XIII studies have been grouped according to gender differences in rates of the disorder.

STUDIES REPORTING SIMILAR INCIDENCE RATES IN MALES AND FEMALES

Eleven studies reported incidence rates that were similar in males and females. Their main characteristics are summarized in Table XII.

Bland (1977) reviewed the Canadian national statistics on functional psychoses for 1972 and reported annual incidence rates of first admissions for patients with a restrictive diagnosis of schizophrenia according to the ICD-8 criteria (295). Rates were slightly higher in males than in females, although statistical tests were not performed.

Goldstein et al. (1984) estimated incidence rates of schizophrenia in New South Wales, using both psychiatric case register data and hospital morbidity statistics. Incidence rates were based on patients admitted for the first time in their lives with a diagnosis of 'schizophrenia' or 'paranoid states' according to the DSM-III criteria. Rates were slightly higher in males compared to females, although statistical tests were not performed.

NiNullain et al. (1987) investigated the incidence rates of schizophrenia in three counties of Ireland, each having a psychiatric case register that recorded all first contacts with public and private psychiatric services made by patients who had lived in the area for the year preceeding contact. For each patient, two diagnoses were available: the diagnosis recorded at the time of contact with psychiatric services and the diagnosis made by investigators using the Present State Examination. Four diagnostic categories of increasing restrictiveness were used: a) a service diagnosis of schizophrenic psychosis or paranoid state; b) a service or CATEGO equivalent diagnosis of schizophrenic psychosis; c) a CATEGO equivalent diagnosis of schizophrenic psychosis; d) a CATEGO class S+. Incidence rates were higher in males than in females according to each of the four diagnostic categories, but in no case gender differences reached statistical significance.

Using the data provided by the Danish and the Mannheim psychiatric case registers, Häfner et al. (1989) examined all the hospital admissions for schizophrenia and related diagnoses made in

Denmark in 1976 and in Mannheim over the period 1978 to 1980. Incidence rates were computed separately for a 'restrictive' diagnostic definition of schizophrenia (including only the ICD-8 category 295) and for a 'broad' diagnostic definition of schizophrenia (including the ICD-8 categories 295, 297, 298.3 and 301.83). In Denmark, first admission rates were slightly higher in males compared to females for the 'restrictive' definition of schizophrenia and the reverse was true for the 'broad' definition of schizophrenia. In Mannheim first admission rates were essentially the same in males and females according to both definitions of schizophrenia. These contrasting findings might be partially due to local diagnostic preferences resulting in an underrepresentation of females with a diagnosis of schizophrenia (ICD-8 295) in the Danish case register (Löffler et al., 1994).

Folnegovic et al. (1990a) calculated hospital-based annual incidence rates of schizophrenia over the period 1965 to 1984, using national data from the Croatia's Psychiatric Case Register. First admission rates were slightly higher in males compared to females across all the time intervals considered, but gender differences did not reach statistical significance.

In the WHO Collaborative Study on Determinants of Outcome of Severe Mental Disorders (Sartorius et al., 1986; Jablensky et al., 1992), eight catchment areas throughout seven countries provided annual incidence rates of schizophrenia. The case-finding strategy consisted of a prospective surveillance (two or more years) of specified psychiatric, other medical and social services (including 'helping agencies' in the community, such as religious institutions and traditional healers) located in a given catchment area in each setting. This strategy allowed for the identification of all the individuals aged 15 to 54 years making a first lifetime contact with such services at any time in the last 3 months and exhibiting signs and symptoms of a possible schizophrenic illness. Two diagnostic definitions were adopted. A 'broad' diagnostic definition was based on either a clinical diagnosis according to the ICD-9 categories 295, 297, 298.3 (.4, .8, .9), 291.3 (.5) and 292.1 or a operationalised CATEGO diagnosis S, P, O. A 'restrictive' diagnostic definition was based on the criteria for the CATEGO class S+. For the 'broad' diagnostic definition, annual incidence rates were slitghly higher in males than in females at five sites (Aarhus, Dublin, Honolulu, Nagasaki and Nottingham) and slightly higher in females at three sites (Chandigarh, rural and urban, and Moscow). For the 'restrictive' diagnostic definition, incidence rates were higher in males than in females at six sites (Aarhus, Chandigarh rural, Dublin, Honolulu, Nagasaki, and Nottingham) and higher in females at two sites (Chandigarh urban and Moscow). However, gender differences in incidence rates never reached statistical significance.

In Italy, Tansella et al. (1991) computed incidence rates of schizophrenia based on first-ever contacts with psychiatric services made by South-Verona residents over the period 1979 to 1988. Incidence rates were slightly higher in males compared to females, but statistical tests were not performed.

De Salvia et al. (1993) provided incidence rates based on first contacts with (or first admissions to) psychiatric services located in the Portogruaro Health District, Italy. In both cases, incidence rates were essentially the same in males and females.

In the ABC Schizophrenia Study, Häfner et al. (1993b) and Hambrecht et al. (1994b) selected all the individuals aged 12 to 59 years in the Mannheim/Heidelberg region of Germany that were admitted for the first time between 1987 and 1989 with a clinical diagnosis of schizophrenia or schizophrenia-like disorder. A history of previous symptoms, episodes and prodromal signs was collected to ensure inclusion of individuals in their first episodes. Cumulative incidence rates until the age of 60 were almost equal in the two sexes among individuals with a diagnosis of schizophrenia. Including also individuals with schizophrenia-like disorders resulted in incidence rates being higher in females compared to males, although the difference was not statistically significant due to the small number of cases. Finally, the Present State Examination was administered to 70,4% of the sample to derive operational diagnoses according to the CATEGO program; incidence rates based on operational diagnoses were almost equal in the two sexes.

Goldacre et al. (1994) used routine statistical records to estimate population-based admission rates for schizophrenia in Oxfordshire. Incidence rates were computed separately for three groups of patients: a) those whose first admission with a diagnosis of schizophrenia was also their first psychiatric admission (this group was termed 'first admission' in the Table); b) those who received a diagnosis of schizophrenia at an admission following their first psychiatric admission (these individuals were joined to the patients in the previous group to account for 'any admission'); c) those receiving a diagnosis of schizophrenia for the first time at any contact with specialist psychiatric care ('any contact'). Whichever measure of schizophrenia was used, rates were slightly higher in males compared to females, although statistical tests were not performed.

Finally, Vazquez-Baquero et al. (1995a) found no significant gender differences in incidence rates of schizophrenia computed both for the general population of Cantabria and for the age group 15 to 54 years. In addition, in the age group 15 to 54 years no gender differences were detected when incidence rates were computed according to the restrictive definition based on the CATEGO class S+.

Table XII - Studies reporting similar incidence rates in male and female subjects with schizophrenia

Author Country, time	Population (N) Age	Diagnostic criteria	Incidence rates (rate/100,000/year) Males	 Females	Male-to-female sex ratio
Bland (1977) Canada, 1972	21.9 million (t) no age limit	ICD-8 (cl,re)	29.0	26.0	1.12
Goldstein et al. (1984) Australia, 1974-77	4.3 million (r) 0 - 54	DSM-III (cl,br)	23.9	20.3	1.18
NiNuallain et al. (1987) Ireland, 1973-75	150,000 (t) 15 - 64	CATEGO/ICD-9 (op,re)	20.6	15.8	1.30
Häfner et al. (1989)					
Denmark, 1976	5.6 million (t) 12 - 59	ICD-8 (cl,re)	10.7	8.1	1.32
Germany, 1978-80	307,000 (t) 12 - 59	ICD-8 (cl,re)	32.1	32.3	0.99
Denmark, 1976	5.6 million (t) 12 - 59	ICD-8 (cl,br)	21.0	25.1	0.84
Germany, 1978-80	307,000 (t) 12 - 59	ICD-8 (cl,br)	35.9	36.9	0.97
Folnegovic et al. (1990a)	4.6 million (t)	ICD-8 (cl,re)			
Croatia, 1980-84	no age limits		23.0	21.0	1.10
	> 15		29.0	26.0	1.12
Sartorius et al. (1986) and Jablensky et al. (1986)					
Denmark, 1978	314,344 (r)	ICD-9 (cl,br)	18.0	13.0	1.39
	15 - 54	CATEGO-S+ (op)	9.0	5.0	1.80
India, rural, 1978	61,642 (r)	ICD-9 (cl,br)	37.0	48.0	0.77
	15 - 54	CATEGO-S+ (op)	13.0	9.0	1.44
India, urban, 1978	205,786 (r)	ICD-9 (cl,br)	34.0	35.0	0.97
	15 - 54	CATEGO-S+ (op)	8.0	11.0	0.73
Ireland, 1978	149,879 (r)	ICD-9 (cl,br)	23.0	21.0	1.10
	15 - 54	CATEGO-S+ (op)	10.0	8.0	1.25
Hawaii, 1978	210,020 (r)	ICD-9 (cl,br)	18.0	14.0	1.29
	15 - 54	CATEGO-S+ (op)	10.0	8.0	1.25
Japan, 1978	267,149 (r)	ICD-9 (cl,br)	23.0	18.0	1.28
	15 - 54	CATEGO-S+ (op)	11.0	9.0	1.22
UK, 1978	202,214 (r)	ICD-9 (cl,br)	28.0	15.0	1.87
	15 - 54	CATEGO-S+ (op)	17.0	12.0	1.42
Russia, 1978	231,866 (r)	ICD-9 (cl,br)	25.0	31.0	0.81
	18 - 54	CATEGO-S+ (op)	10.0	14.0	0.71

Table XII - following

Author Country, time	Population (N) Age	Diagnostic criteria	Incidence rates (rate/100,000/year) Males	 Females	Male-to-female sex ratio
Tansella et al. (1991) Italy, 1979-88	75,000 (r) > 13	ICD-9 (cl,br)	11.3	8.5	1.33
De Salvia et al. (1993) Italy, 1982-89	72,512 (r) > 14	ICD-9 (cl,br)	17.0[a] 16.0[b]	17.0[a] 15.0[b]	1.00 1.07
Häfner et al. (1993b) and Hambrecht et al. (1994b) Germany, 1987-89	1,012,406 (r) 12 - 59	ICD-9 (cl,re) ICD-9 (cl,br) CATEGO S+ (op)	16.4 18.2 12.3	16.6 20.5 15.0	0.99 0.89 0.82
Goldacre et al. (1994) UK, 1975-86	540,000 (t) no age limits	ICD-9 (cl,re)	8.7[a] 10.3[b] 15.1[c]	5.6[a] 8.2[b] 11.4[c]	1.55 1.26 1.32
Vazquez-Barquero et al. (1995a) Spain, 1989-90	560,000 (r) 15-54	ICD-9 (cl, br) CATEGO S+ (op)	18.8 12.7	19.3 14.4	0.97 0.88

[a] first ever contacts
[b] first admissions
[c] any admission
[d] any contact
br =broad cl=clinical op=operational r=risk re=restrictive t=total