Gender differences in the epidemiology of affective disorders and schizophrenia

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Division of Mental Health and Prevention of Substance Abuse

World Health Organization
Geneva
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NATIONS FOR MENTAL HEALTH:
An Initiative for Mental Health in Underserved Populations

Objectives of Nations for Mental Health

- To enhance the attention of the people and governments of the world to the effects of mental health problems and substance abuse on the social well-being and physical health of the world’s underserved populations. A first step is to increase awareness and concern of the importance of mental health through a series of key high profile regional and international events. Secondly, efforts will be devoted to building up the will of the key political authorities to participate. Thirdly, and finally, efforts are to be directed at securing political commitments by decision-makers.

- To establish a number of demonstration projects in each of the six WHO regions of the world. They are meant to illustrate the potential of collaborative efforts at country level, with the view of leading on to projects of a larger scale.

The implementation of the programme depends on voluntary contributions from governments, foundations, individuals and others. It receives financial support from the Eli Lilly and Company Foundation. In addition, financial and technical support is also being provided by the Government of the United Kingdom of Great Britain and Northern Ireland, the Institute of Psychiatry at the Maudsley Hospital of London (United Kingdom), the Free and Hanseatic City of Hamburg (Germany), the Villa Pini Foundation (Chieti, Italy), Columbia University (New York, USA), the Laboratoires Servier (Paris, France) and the International Foundation for Mental Health and Neurosciences (Geneva, Switzerland).

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The World Health Organization’s Division of Mental Health and Prevention of Substance Abuse has established an initiative called «Nations for Mental Health» to deal with the increasing burdens of mental health and substance abuse problems worldwide. The main goal of the programme is to improve the mental health and psychosocial well-being of the world’s underserved populations (e.g. women, children and adolescents, refugees and indigenous populations and those who suffer from acute or chronic mental illness that is inadequately treated).

During the launching of the world mental health report prepared by the Department of Social Medicine, Harvard Medical School, the United Nations Secretary-General said of the UN Mission: «Our objective is to promote the mental health of and well-being of all inhabitants of the planet». The Nations for Mental Health programme embodies this mission.

Solutions to mental health and substance abuse problems entail a joint mobilization of social, economic and political forces as well as substantial changes in governmental policies related to education, health and economic development in each country. This demands an intense and sustained effort from the nations of the world, through joint cooperation between governments, non-governmental organizations and the organizations within the United Nations system. The programme is of utmost importance to the work of WHO and is willing to lead and coordinate this ambitious task. Several international meetings and launchings have been organized, in collaboration with other international organizations and academic institutions. A number of demonstration projects related to the programme have already been initiated in several countries. These projects are meant to illustrate and/or demonstrate the potential of collaborative efforts at country level, with the view of leading on to projects of a larger scale.

I am very pleased to present this document as part of the global process of raising awareness and concern for the effects of mental health problems. It is hoped that this important work will be useful in providing health planners and policy-makers with an integrated framework, linked both to specific needs and to epidemiological evidence, for addressing the broad spectrum of issues related to mental disorders and psychosocial problems.

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FOREWORD

by Michele Tansella

For a long time doctors and general practitioners have learned from clinical experience that women receive more services for mental disorder in primary care settings than men do. On the other hand psychiatrists and clinical psychologists are aware that this difference is less marked for specialist mental health services and particularly for hospital-based services. These impressions are confirmed by service research studies: there seems to be good evidence that men come to the attention of health services less often than women, but that men are more likely to be referred for specialist psychiatric care (Goldberg & Huxley, 1992; Jorm, 1995). These service utilization data may have important implications for health policy and service organization. However, they simply indicate the extent of treatment, not the need for treatment (Goldman & Ravid, 1980). The clinicians should therefore go beyond their clinical practice and acknowledge that they need help from epidemiologists and from epidemiologically-based research to be able to understand which sex, or which demographic group within each sex, has the greater risk of experiencing psychological distress and mental illness.

From epidemiological surveys which have attempted to evaluate “true” prevalence by examining random samples of a population and by determining the mental status of the respondents to a questionnaire or interview, these does not appear to be much difference between males and females in the overall prevalence of mental disorders. But evidence does exist that the pattern of the disorders, as well as of psychological symptoms, differs between men and women.

The difference varies in different phases of life, from childhood to adolescence to adulthood. Males are more vulnerable to developing psychiatric disorders arising from insult to the central nervous system during ontogeny, probably because of a greater antigenicity to the pregnant mother. It has been suggested that this antigenicity may induce a state of maternal immunoreactivity which can lead, directly or indirectly, to fetal damage and thus to greater male susceptibility to environmental insults (Gualtieri & Hicks, 1995). Most studies show a higher prevalence of mental health problems in younger boys than in girls, the former experiencing more conduct disorders, with aggressive and antisocial behaviors. During adolescence the difference become smaller because girls experience more emotional problems, with fearful, anxious or overcontrolled behaviors. In adulthood men experience more alcohol and drug abuse and antisocial behavior, while women experience more anxiety, depression and eating disorders. Moreover, it is well known that males are much more likely to commit crimes (and more serious crimes) than women, as indicated by their higher arrest and imprisonment rates, and are more likely to commit suicide or to become homeless. Although there is no single cause of suicide, more than 90% of those who commit suicide have a
mental disorder and between a quarter and a half of single homeless men are suffering from severe mental disorder (Jorm, 1995).

The World Bank (1993) recently tabulated disability-adjusted life years. Depressive disorders account for almost 30% of the disability from neuropsychiatric disorders among women, but for only 12.6% among men. On the other hand, alcohol and drug dependence accounts for 31% of neuropsychiatric disability among men, but for only 7% of the disability among women. Desjarlais et al. (1995) reviewed 15 studies focusing on psychiatric disorders as well as on psychological distress, carried out over the last decades in many parts of the world, including Africa, Asia, the Middle East and Latin America, and stated that “comparative analysis of empirical studies of mental disorders reveals a consistency across diverse societies and social contexts: symptoms of depression and anxiety as well as unspecified psychiatric disorder and psychological distress are more prevalent among women, whereas substance use disorders are more prevalent among men”. In other words “men tend to externalize their suffering through substance abuse and aggressive behavior, resulting in an under reporting of psychological distress. Women, in turn, more often suffer distress in the form of depression, anxiety, ‘nerves’, and the like” (Desjarlais et al., 1995, p.180).

Four questions need to be addressed at this point. First, what is the present “state of the art” with regard to the difference between men and women in the frequency of well-defined psychiatric disorders, when the literature is critically examined, paying attention to the main methodological factors and biases that may affect the results; and what are the differences when incidence and prevalence studies, as well as overall rates and rates of specific disorders are analyzed separately? Second, is the difference between men and women consistent when we move from the level of psychiatric disorders (including those considered more severe) to that of psychological distress and to the level of individual symptoms or complaints relating to (less severe) disorders? These various expressions of suffering, from the most severe psychiatric disorders to the individual symptoms or complaints, differ in many ways and are likely to be determined by different causes or to be influenced and shaped by different combinations of causal factors. For instance, a gradient of biological factors with a decreasing causal role, from the first to the last level, has been postulated. A difference between males and females in the rate and/or in the phenomenology and/or in the outcome of the condition under study, only at one level or at all levels of the spectrum, would have important theoretical and practical implications. Third, is a gender difference more likely to emerge when we use a longitudinal rather than a cross-sectional approach? Gender, for instance, may influence incidence of depression (females are more likely to make transition from subsyndromal to definite episode of depression) rather than course of illness and transition to recovery, while the contrary may be true for other disorders such as schizophrenia. Fourth, where a true difference has been convincingly proven we need to go a step further and try to answer another question: what factors account for the differences, or, in other words, why do men and women express their suffering in different ways and experience some symptoms and psychiatric disorders with different frequency?
Furthermore, what are the implications of these differences?

The present Monograph by Dr Marco Piccinelli and his co-worker, Dr. Gomez Homen is a well balanced and meticulous piece of work that will be found extremely useful by those attempting to reply to the first and, in part, to the second question (with reference to affective disorders and schizophrenia). It is also a worthwhile and informative starting point for answering questions three and four. It was a very demanding task to sort out and critically analyze the vast literature related to gender differences in affective disorders and schizophrenia. Other authors will hopefully extend this kind of analysis to other conditions and disorders. The third and fourth questions will need more attention in the future, not only from those collating critical reviews of the literature but also from those planning and designing research studies.

I would like to comment briefly on some aspects of each of the four questions listed above.

The first question (the present “state of the art” of the difference between men and women in the true rates of well-defined psychiatric disorders) is extensively addressed by the authors of this Monograph, with reference to the full spectrum of affective disorders and to schizophrenia. We should, however, put the results of their review of the literature in the context of studies concerning other disorders that they have not analyzed.

It has traditionally been believed that mental disorders are more common in females than in males. More recent evidence has shown that the picture is not so simple and that the difference concerns, as already mentioned, the patterns of disorders and not the overall prevalence. There are therefore differences in results between earlier and more recent studies (mainly general population surveys), due to the fact that earlier surveys concentrated on disorders which mostly affect females.

We must be very selective and critical in analyzing the vast amount of descriptive studies on gender differences in rates of psychiatric disorders and we must discard those that do not meet sufficiently high standards. The main methodological problems to be taken into account are sample size (with particular attention to non-response rates and refusal rates), confounding factors, and diagnostic reliability and validity. Moreover, many studies analyze one variable at a time for its relationships to mental disorder, failing to consider the possibility of multiple interactions among demographic variables (e.g. sex, marital status, employment) (Goldman & Ravid, 1980). For instance, Jablensky and Cole (1997) have recently published data from the extensive WHO-10 countries study of schizophrenia (778 males and 653 females). Applying a generalised linear modelling strategy they show that the gender difference in the age at onset of schizophrenia is not a robust biological characteristic of the disorder. A large part of the differences reported previously (males having an earlier onset) may well be explained by the failure to control for marital status and premorbid personality, when comparing the age of onset in the two sexes. The availability of mod-
ern statistical methods now make it possible to carry out more sophisticated, multivariate analyses and therefore to be more demanding in our selection of the literature, as well as in planning future studies.

The second question (are gender differences limited only to some psychiatric disorders, particularly the less severe, or do they consistently concern the full spectrum of sub-clinical and clinical conditions?) has not been tackled, to my knowledge, by any individual study. This is not surprising, considering that this would have to be a large community-based survey that should include a large number of clinical cases. This is too difficult. The information we have is therefore derived from data taken from research carried out in different places at different times, sometimes with different methodologies. The general impression is that there is not a consistent continuum in gender differences from individual symptoms and complaints to the most severe psychiatric disorders. As far as affective disorders are concerned, it is reported in this Monograph that higher rates have been found in women than in men in studies of the prevalence of intermittent and brief recurrent depression, of dysthymia and of major depression, as well as (less convincingly) in studies of the incidence of depression, but not in studies of the prevalence or incidence of bipolar disorder. Further research which applies this “spectrum approach” is needed; these studies should use, across the spectrum, reliable and valid measures belonging to the same family of instruments and should analyze separately acute and chronic clinical conditions, paying attention to all well-defined subtypes of the disorders.

Differences may emerge only when we look specifically at particular subsyndromes. There is, in other words, a need to be more specific and more selective in future studies, in order to be able to detect gender-related differences that may otherwise be obscured, as well as in order to avoid the undue overestimation and generalization of overall differences.

For example, it is well known that, on the basis of gender differences reported in the literature, a two-syndrome model of schizophrenia has been postulated: an early onset, more chronic syndrome (primarily affecting men), and a later-onset, better prognosis syndrome (mainly affecting women). It is useful therefore to distinguish between these two forms instead of persisting in the study of schizophrenia as a unitary illness. In recent years, much attention has been directed toward the severe, early-onset form. It is now time to focus on the milder, later-onset form to which women appear particularly susceptible (Castle et al., 1995).

We need also to be more specific and more comprehensive in choosing the variables to be studied for the detection of sex differences. For example, neuroimaging studies of schizophrenia have accumulated in the literature over the last 20 years. However, as Vazquez-Barquero et al. (1995) have pointed out, the majority of these studies have not investigated the effect of sex on brain abnormalities.
The third question concerns the longitudinal approach in epidemiological psychiatry. This is increasingly being adopted, since we are increasingly moving from descriptive to outcome studies.

For example, in relation to affective disorders, the importance of adopting such an approach for studying gender influence in the transitions from asymptomatic to subsyndromal depression, to incident depression, to recovery or restitution and to relapse is intuitively clear. Does gender affect the transitions at the left side of the continuum or those at the right, or both? Patton et al. (1996) are actually carrying out a community-based multiwave cohort study of this kind in Australia. More longitudinal studies are clearly needed.

The fourth question (the question of causation and of implications of true gender differences) is a key question, or rather a key series of related questions.

Before discussing this point, I should like to stress that, in the literature, terms such as “sex”, “gender”, “sex-related” and “sex-linked” are often used inconsistently and/or interchangeably. This ambiguity is not just a semantic problem and the choice of the term used may reveal different attitudes and beliefs, as well as implicit assumptions about causality. The term “sex” often reflects a putative biological cause; “gender” a putative environmental (social, cultural, or political) cause of some reported difference. Sometimes (this is, I believe, the case for the authors of this Monograph) the term “sex” is used to refer to the biological aspect only, while “gender” relates to the complex interaction between biological, psychological and social variables. The issue has been widely discussed in the field of normal psychology, but has surprisingly been forgotten or understated in psychopathology where the implications of a semantic misuse may be greater.

As Lewine (1994) pointed out in relation to the study of schizophrenia, a simple distinction between the two terms, without any assumptions about etiology, is the more useful approach. The term “sex” should therefore be used in reference to comparisons based on the demographic categories of female and male, while the term “gender” in reference to comparisons of femaleness and maleness, of masculinity and femininity, as suggested by Deaux (1993). The results of a study by Daniel et al. (1988) may illustrate the usefulness of this distinction: using PET scanning they found a higher rate of cerebral blood flow in healthy women than in healthy men. However, when classified according to the femininity/masculinity score, subjects who had high femininity (both women and men) had higher blood flow than subjects with low femininity score. The difference was therefore related more to gender than to sex.

According to the approach mentioned above, most research on mental symptoms and mental disorders could be defined as “sex” research. It is easier and more straightforward, especially in large epidemiological surveys, to simply classify subjects according to the demographic category they
belong to. The interpretation of the results will depend on the relative weight that each of the biological/psychological/social components may have. These relative weights are often unknown and may only be inferred. In future research the formal assessment of femininity and masculinity, as well as of social role, and economic, political and social status, could be useful for attempting to dissect and take into account separately the weight of each of the three different components. The results of the study on sex differences in the prevalence of minor psychiatric morbidity completed by Jenkins (1985) is exemplary in this respect: if samples of male and female subjects are chosen who are closely comparable from the standpoint of social adjustment, the sex difference completely disappears.

We are in the difficult situation of trying to use gender, "an immutable sociodemographic variable", as a tool to understand etiologic or risk factors of mental disorders, without knowing the relative weight of the various biological and psychosocial factors that make a woman different from a man (and vice versa). On one side there are clear-cut biological factors (for example, the endocrine factors), while on the other side, there are factors related to roles, stereotypes and social circumstances. What really matters?

The answer cannot be straightforward, for many reasons, including the relevance of the interactions between biological, psychological and social factors. For instance, Freud (1905/1953) hypothesized that hormonal changes cause sexual instinctual transformations at puberty as well as the formation of defense mechanisms used to combat these overwhelming libidinal drives. Moreover, we should consider that the sex stereotype belief system has evolved to rationalize the biological difference between the genders and to provide as socialization models (Lieh Mak, 1994).

On the other hand it is helpful to think of two main groups of causes of mental disorders: physical and biological on one hand (genetic component, birth trauma, maternal infections at a particular point in a pregnancy), and on the other hand social, situational and interactional (stressful factors as well as buffers to diminish the impact of unfavorable external events). Again it is not possible to be precise about the relative importance of the biological/physical and social/cultural sets of factors in contributing to mental disorder. The sex/gender variable, as underlined above, contains both types of factors, so a multidimensional and interactive approach needs to be taken.

A large WHO study, carried out in general health care settings, adopted a cross-cultural approach for attempting to evaluate the relative influence on sex differences of biological and social factors (Gater et al., 1996). Prevalence rates of common mental disorders in men and women were assessed using a two-stage design from 26,969 primary care attenders in 15 centres in four continents, including Verona, Italy. The same standardized methods were used across different centres and cultures. Logistic regression analysis was used to test whether sex differences were consistent across centres. We found that the absence of a sex by centre effect for current depression and
agoraphobia or panic disorder was consistent with biological or psycho-social factors, either interacting or working alone, that have a similar final time effect across cultures. It did not support the idea that sex differences in prevalence are caused by local psycho-social factors that vary from country to country. On the other hand, the variation in odds ratio for generalized anxiety disorder suggested that there are differences between the centres that contribute to the sex difference in rates for this disorder. These were most likely to be related to sociocultural differences between the social roles and experiences of women and men.

Little investigation has been carried out until now on the different ways men and women may respond to the same stressful events. This approach could be useful to remove some of the obstacles to progress in clarifying the complex issue of causation of gender differences.

Najman (1995) reports the results of an interesting 30-month longitudinal study by Boyle (1994) on the impact of one specific stressful event - the death of a child - on the mental health of the parents. Mental health was also measured in control parents. It was shown that men and women respond differently to the same events and that the ways this response is measured determines which group is perceived to have the highest rate of mental disorders. When excessive alcohol consumption is excluded as a criterion of mental disorder, mothers have higher rates, regardless of whether they were bereaved. When a high level of alcohol use is included, these previous differences diminish or are eliminated in all groups of parents except those most recently bereaved.

Desjarlais et al. (1995, p. 183)), after reviewing the proposed explanations of observed gender differences in psychiatric morbidity which “taken together, illuminate the quality of women's lives”, conclude that “poverty, domestic isolation, powerlessness (resulting, for example, from low levels of education and economic dependence) and patriarchal oppression, are all associated with higher prevalence of psychiatric morbidity (exclusive of substance disorder) in women. In short, a considerable body of evidence points to the social origins of psychological distress for women”. In their book they underline that the explanations proposed for gender differences in psychiatric morbidity in Asia, Africa, the Middle East and Latin America “echo established associations among poverty, isolation, and psychiatric morbidity for women in Western Europe and the United States” (see Dennerstein et al., 1993). To support the latter statement they quote many studies: a classic research study which found depression to be more prevalent among working-class than middle-class women living in London (Brown & Harris, 1978); studies which reported poor women experiencing more and more severe life events than the general population (Brown et al., 1965; Makosky, 1982); studies reporting that poor women are more likely to have to deal with chronic sources of social stress in the form of low-quality housing or dangerous neighbourhoods (Makosky, 1982); research showing women at higher risk for becoming victims of violence (Belle, 1990); and studies indicating that women are especially vulnerable in encountering problems in parenting and child care (Belle et al., 1988). So, what really matters?
As the authors of this Monograph say in their introduction, "the incorporation of a gender-related perspective into psychiatric research may have important implications for clinical practice, public health policy and theory". I have discussed already the implications for theory, which cannot be separated from issues related to causation. I should like to give now some thought to the other two implications.

Some of the implications for public health policy of higher rates of emotional distress, anxiety and depressive disorders in women, are summarized by the recommendations of the 1991 National Council for International Health's (NCIH) Conference in Women's Health, which take a world perspective. They read as follows: 1) establishing baselines for women's health and well-being and then measuring progress toward those standards; 2) developing ways of monitoring the impact of structural adjustment programmes on women's welfare and establishing programmes to mitigate their adverse effects; 3) enforcing or enacting legislation to improve women's status; 4) addressing women's need for equitable employment and economic development; and 5) expanding education for women and girls (Jacobson, 1993). We could add that an increase in the investment for research and service provision to improve psychological well-being, and to reduce rates of alcohol abuse, aggression and suicide in men are also necessary and will also indirectly address the needs of their wives and children.

Finally, the clinical implications. There is no doubt that the clinician would benefit from increased knowledge of gender-specific factors that may predict and influence the phenomenology, course and outcome of mental disorders. Even if we need more hard data before this hope can become reality, encouraging results are appearing on the horizon. On the biological side, for instance, the psychotropic potential of oestrogens in schizophrenic women before and after the menopause and the hypothesis to adjust, in young fertile women, the neuroleptic dosage to the menstrual cycle are examples of encouraging implications for future clinical practice.

What can we do in the meantime in our daily clinical practice, while waiting for more hard data from research to be translated into the care and treatment of individual patients? Communication among physicians and other health workers and women patients is paternalistic in many parts of the world. As Dejarlais et al. (1995) report, "Women are often neither encouraged not permitted to voice their feelings and complaints. When they do, they are likely to be discounted or dismissed." The results of studies on gender differences in mental disorders may have immediate training implications: "health care professionals must be trained to empower women in the clinical encounter".

In the next decade, we should see to what extent sound research will provide answers to the four questions listed above and will be able to increase our knowledge and improve prevention, care and treatment of psychological suffering and psychiatric disorders both in women and in men.
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Age at onset of major depression ................................................................. 27
Age at onset of bipolar disorder ................................................................. 29
Methodological considerations on age at onset of psychiatric disorders ................................. 30
Temporal trends in depression .................................................................... 31
Old-generation studies ............................................................................... 31
New-generation studies ............................................................................ 33
Temporal trends in bipolar disorder ........................................................... 37
Factors that may influence temporal trends of affective disorders ................. 37
Selective mortality and/or institutionalization .............................................. 38
Selective migration ..................................................................................... 39
Changes in societal attitudes, diagnostic criteria, and professional practices ............ 39
Recall and memory effects ........................................................................ 41
Possible factors accounting for gender differences in affective disorders .................... 43
Genetic factors .......................................................................................... 43
Reproductive hormones ............................................................................. 45
Other biological factors ............................................................................ 48
Environmental models .............................................................................. 49
Developmental models ............................................................................. 51
Sex-role models ........................................................................................ 52
Neuropsychology ....................................................................................... 54
Conclusions and recommendations for further research ..................................... 55

SCHIZOPHRENIA ......................................................................................... 61

Introduction ............................................................................................... 61

Age at onset of schizophrenia .................................................................... 62
Age at first onset of psychiatric symptoms ............................................... 63
Age at first treatment .................................................................................. 66

Factors that may influence gender differences in age at onset of schizophrenia ........... 69
Sampling biases ......................................................................................... 69
Biases introduced by diagnostic criteria ..................................................... 71
Biases related to the method used to compute the mean age of the sample ............................................... 71

Incidence of schizophrenia ......................................................................................................................... 72
Studies reporting similar incidence rates in males and females .............................................................. 72
Studies reporting higher incidence rates among the males ........................................................................ 77

Factors that may influence gender differences in incidence rates of schizophrenia ............................... 80
Sampling methods ........................................................................................................................................ 80
Diagnostic criteria ...................................................................................................................................... 82
Methods used to compute incidence rates ................................................................................................. 83
Time trends ................................................................................................................................................. 83
Morbidity risk for schizophrenia .................................................................................................................. 84
Prevalence of schizophrenia ....................................................................................................................... 85

Factors that may influence prevalence rates of schizophrenia ............................................................... 87

Naturalistic outcome of schizophrenia ....................................................................................................... 87
Clinical status at follow-up .......................................................................................................................... 88
Social adjustment at follow-up ..................................................................................................................... 90
Inpatient treatment during follow-up .......................................................................................................... 92
Mortality ...................................................................................................................................................... 93

Factors that may influence gender differences in naturalistic outcome of schizophrenia .................. 94
 Diagnostic criteria ...................................................................................................................................... 94
 Outcome criteria ......................................................................................................................................... 96
 Sample selection .......................................................................................................................................... 97
 Length of follow-up ................................................................................................................................... 99

Possible factors accounting for gender differences in schizophrenia ............................................... 99
Genetic factors .............................................................................................................................................. 101
Brain abnormalities .................................................................................................................................... 104
Endocrine factors ....................................................................................................................................... 106
Environmental factors ............................................................................................................................... 108

Conclusions and recommendations for further research ........................................................................ 110

References .................................................................................................................................................. 113
INTRODUCTION

Epidemiologic research in the field of psychiatry has shown that gender is a crucial variable influencing the distribution and features of mental disorders. Thus, the incorporation of a gender-related perspective into psychiatric research may have important implications for clinical practice, public health policy and theory. On a clinical ground, since gender can be considered an ‘immutable sociodemographic variable’ that cannot be influenced by the disease, it would be useful to identify gender-specific factors that may influence and predict symptom patterns, co-morbidity, course, outcome and response to treatment. From the public health perspective, gender differences in rates of a disorder and its characteristics may help to understand the health needs and treatment expectations of a population, to set the techniques for the monitoring of the health of a population, to plan treatment decisions and health services, to allocate the existing resources or to search for new resources. Theoretically, since gender is a proxy for a complex of psychosocial and biological variables, much can be known about specific etiologic or risk factors that underlie the association, interactions or processes by which vulnerability progresses into clinical disorders (Goodwin & Blehar, 1993).

The aim of this work is to report the main epidemiologic findings on gender differences in affective disorders and schizophrenia. In addition, methodologic difficulties that might bias research findings and be artefactual determinants of gender differences are discussed. Finally, the main factors that can best explain the gender differences in affective disorders and schizophrenia will be outlined as suggested by different theoretical approaches.
METHOD

Papers were collected using four strategies. First, the Medline data base was searched for the years 1985 to January 1995, using the keyword ‘mental disorders’ matched with any of the following in the title or abstract: ‘sex’, ‘gender’, ‘male’, ‘female’, ‘men’, ‘women’, ‘boys’, and ‘girls’. This search was originally aimed at locating papers on gender differences in any type of mental disorders, not only in affective disorders and schizophrenia. Thus, we integrated this search by consulting the Medline CD ROM database for the period 1985 to May 1996, using the keywords ‘schizophrenia’, ‘affective disorder’, ‘bipolar disorder’, ‘mania’, ‘depressive disorder’, ‘mania’, ‘depression’ and ‘dysthymia’ matched with the keywords ‘sex’ and ‘gender’ in the title or abstract. Second, literature was supplemented by hand-searching psychiatric journals and by consulting recent published reviews and bibliographies. Third, secondary references were identified by examining the reference sections of the papers located with the methods listed above. Finally, seven renowned experts in the field (see Acknowledgements) were contacted by mail and asked to select the most relevant papers recently published on gender differences in affective disorders and schizophrenia.
AFFECTIVE DISORDERS

INTRODUCTION

A wide variety of principles and criteria are being used in the assessment and classification of affective disorders. For example, Angold (1988) has suggested that at least eight distinctions can be made in the use of the term ‘depression’, some of which consider ‘depression’ as referring to a single item or state or trait and others refer to a mood state plus its biological, cognitive and/or behavioural concomitants. Similarly, Farmer & McGuffin (1989) have reviewed the ‘contemporary confusion’ surrounding the classification of depression and noted how the approaches advocated by nosologists vary considerably, some subdividing depression into one or two subtypes, while others proposing multiple different categories. Although different diagnostic concepts may serve specific research or clinical purposes, few of them have been sufficiently explored and validated (Jablensky, 1987). Indeed, research in the field of affective disorders faces specific methodological difficulties. Since biological or trait markers are relatively few and of unclear specificity, they are of little help in the identification of homogeneous diagnostic subtypes. Moreover, given the dimensional nature of much psychiatric morbidity and the absence of rarity points or interruptions in the symptom distribution, the definition of psychiatric ‘caseness’ is often arbitrary (Kendell, 1988). In light of these limitations, we have decided to present findings according to well-known systems for classifying mental disorders (e.g., the Research Diagnostic Criteria, the International Classification of Diseases, and the Diagnostic and Statistical Manual of Mental Disorders), since they have tried to reduce heterogeneity of diagnostic categories and limit criterion variance to an acceptable degree.

Although several forms of affective disorders have been investigated and described, epidemiologic evidence pertains mainly to bipolar disorder and major depression. Thus, these disorders are the main focus of the present work. In addition, epidemiologic findings on dysthymia (DSM-III - APA, 1980 - and DSM-III-R - APA, 1987), intermittent depression (Research Diagnostic Criteria - Spitzer et al., 1978) and brief recurrent depression (ICD-10 - WHO, 1992) are presented together under the heading ‘persistent and recurrent depression’. A detailed review of similarities and differences between these diagnostic categories has been recently published after a working party of renowned experts summoned by the World Psychiatric Association (Costa e Silva & Freeman, 1994).

In the present work, epidemiologic findings are reported on gender differences in affective disorders among the adults, since published research suggests that gender differences are limited or even absent in either childhood or old age (Jorm, 1987; Burvill, 1995). Possible reasons for this age-related effect will be discussed alongside with the factors accounting for gender differences in affective disorders.
PREVALENCE OF MAJOR DEPRESSION

Current prevalence rates

Table I sets out the results of general population studies investigating current prevalence rates of major depression by sex of respondents. Current major depression was defined as criteria for major depression being fulfilled at the time of the examination or during the previous month.

Three studies were carried out in the United States. Weissman & Myers (1978) reported rates of affective disorders from the first epidemiologic survey applying Research Diagnostic Criteria to a community sample; the findings refer to a 1975 follow-up of a probability sample initially selected and studied in 1967. Prevalence estimates reported by Regier et al. (1993) were derived from the NIMH-Epidemiologic Catchment Area Study, a large-scale survey in which five sites geographically distributed throughout the United States were each randomly sampled to yield an estimate of rates of psychiatric disorders among noninstitutionalized adults aged 18 years and older. Finally, Blazer et al. (1994) presented one-month prevalence rates of major depression from the National Comorbidity Survey, in which a structured psychiatric interview was administered to a representative national sample of community residents in the United States aged 15 to 54 years. Although direct comparison between these studies is limited by a number of methodological factors (including differences in research instruments, diagnostic criteria, age range and size of the samples), a common finding was that rates of major depression were higher among females, with a female-to-male sex ratio ranging between 1.6 and 1.8.

In Florence, Italy, Faravelli et al. (1990) reported the highest female-to-male sex ratio (3.2) in a sample of subjects randomly selected from the lists of seven primary care physicians with postgraduate training in psychiatry; respondents were interviewed by primary care physicians, using a flow-chart that included the hierarchical system of diagnosis for affective disorders drawn from DSM-III.

Females were at increased risk for major depression compared to males also in Hollifield et al.'s (1990) study, in which a random sample of the families living in a small lowland town in Lesotho was examined. Moreover, when rates of current psychiatric disorders were corrected for gender and for alcohol abuse (due to a higher proportion of males being missed at interview and a sizeable proportion of individuals with major depression abusing alcohol), the same female-to-male sex ratio (1.6) was found, estimated rates for major depression being 7.1% in males and 11.7% in females.

Finally, Stefánsson et al. (1994) investigated rates of psychiatric disorders in a cohort of subjects including half of the population born in Iceland in 1931 and living there on December 1986.
Table I - Current prevalence rates of major depression from general population studies

<table>
<thead>
<tr>
<th>Author Country, time</th>
<th>Sample (N)</th>
<th>Age range (years)</th>
<th>Instruments Diagnostic Criteria</th>
<th>Rates (%) Males</th>
<th>Females</th>
<th>Total</th>
<th>Female-to-Male Sex Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weissman &amp; Myers (1978)* USA, 1975-76</td>
<td>511</td>
<td>26 and over</td>
<td>SADS RDC</td>
<td>3.2</td>
<td>5.2</td>
<td>4.3</td>
<td>1.6 : 1</td>
</tr>
<tr>
<td>Regier et al. (1993)** USA, 1980-83</td>
<td>18,571</td>
<td>18 and over</td>
<td>DIS DSM-III</td>
<td>1.6</td>
<td>2.9</td>
<td>2.2</td>
<td>1.8 : 1</td>
</tr>
<tr>
<td>Blazer et al. (1994)** USA, 1990-92</td>
<td>8,098</td>
<td>15 - 54</td>
<td>CIDI DSM-III-R</td>
<td>3.8</td>
<td>5.9</td>
<td>4.9</td>
<td>1.6 : 1</td>
</tr>
<tr>
<td>Faravelli et al. (1990)* Italy, 1984</td>
<td>1,000</td>
<td>15 and over</td>
<td>Flow chart DSM-III</td>
<td>1.3</td>
<td>4.1</td>
<td>2.8</td>
<td>3.2 : 1</td>
</tr>
<tr>
<td>Hollifield et al. (1990)** Leshoto, 1986-1987</td>
<td>356</td>
<td>19 - 93</td>
<td>DIS DSM-III</td>
<td>8.8</td>
<td>14.5</td>
<td>12.4</td>
<td>1.6 : 1</td>
</tr>
<tr>
<td>Stefansson et al. (1994)** Iceland, 1987-88</td>
<td>862</td>
<td>55-57</td>
<td>DIS DSM-III</td>
<td>0.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.2 : 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.0 : 1</td>
</tr>
</tbody>
</table>

* Major depression present at interview
** 1-month prevalence rates for major depression
<sup>a</sup> Major depressive episode (total)
<sup>b</sup> Major depression, single episode
<sup>c</sup> Major depression, recurrent

Rates of major depression were low compared to the other studies. The preponderance of major depression among females was accounted for by recurrent major depression, whereas a female-to-male sex ratio equal to 1.0 was obtained for subjects suffering from a single episode of major depression over the month preceding the examination.

For comparison, Table II shows the results of studies which investigated rates of depressive disorders in the general population, using the Present State Examination. The Present State Examination is a semistructured psychiatric interview for eliciting and rating psychiatric symptoms present during the month preceding the evaluation; the interview is supplemented by a computer program (CATEGO), which allows the allocation of patients into classes according to their current symptoms (Wing & Sturt, 1978). The decision to consider these studies separately was based on two reasons. First, the Present State Examination by itself does not generate diagnoses, although it provides a symptom profile that allows the approximate allocation of patients into one of the ICD-
Table II - One-month prevalence rates of depressive disorders according to PSE-ID-CATEG0 and ICD-8

<table>
<thead>
<tr>
<th>Author Country, time</th>
<th>Sample (N)</th>
<th>Age range (years)</th>
<th>Rates (%)</th>
<th>Female-to-Male Sex Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>Orley &amp; Wing (1979) Uganda, 1972</td>
<td>206</td>
<td>18 - 65</td>
<td>14.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22.6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Henderson et al. (1979) Australia, 1977</td>
<td>756</td>
<td>18 and over</td>
<td>2.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6.7&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bebbington et al. (1981) UK, n.r.</td>
<td>310</td>
<td>18-64</td>
<td>4.8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9.0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mavreas et al. (1986) Greece, n.r.</td>
<td>489</td>
<td>18-74</td>
<td>4.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10.1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mavreas &amp; Bebbington (1987) UK*, n.r.</td>
<td>219</td>
<td>18-64</td>
<td>4.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7.0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lethinen et al. (1990) Finland, 1985-87</td>
<td>747</td>
<td>30-80</td>
<td>2.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6.5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* Study conducted among Greek Cypriot immigrants in London
<sup>a</sup> Depressive disorders not otherwise specified
<sup>b</sup> Including ICD-8 categories 296.2 (manic-depressive psychosis, depressed type) and 300.4 (depressive neurosis)
n.r. = not reported

8 categories. Second, the investigators using the Present State Examination in surveys of the general population reported overall prevalence rates of depressive disorders without distinction between 'depressive neurosis (300.4)' and 'manic-depressive psychosis, depressed type (296.2)', whereas recent epidemiologic findings on sex and age distribution of bipolar disorder, major depression and dysthymia support the separation of bipolar disorder from other types of affective disorders (Weissman et al., 1988). As a result of differences in geographical location, survey designs and socio-demographic characteristics of populations where surveys were carried out, only gross comparisons can be made among these studies. In spite of these limitations, all the studies pointed to a preponderance of depressive disorders among females, with a female-to-male sex ratio ranging between 1.6 and 2.7.

Six-month prevalence rates

Table III sets out the results of general population studies investigating six-month prevalence rates of major depression by sex of respondents. The six-month prevalence rates reported here
included those subjects who met lifetime criteria for major depression and experienced relevant symptoms or an episode of the disorder during the six months preceding the examination.

Six studies used the Diagnostic Interview Schedule, a structured psychiatric interview designed for administration by lay interviewers in large-scale epidemiologic surveys to detect psychiatric disorders according to the DSM-III criteria. Four of these studies relied on a two-stage probability sample design: at the first stage, households were systematically sampled from lists of residential addresses; at the second stage, a listing of residents was obtained for each sample household and one household member was randomly selected among those eligible. Canino et al. (1987) selected individuals living in households throughout Puerto Rico as well as household members temporarily away and those in institutions. Bland et al. (1988a) examined a sample of community residents in Edmonton, Canada, aged 18 years and older in addition to a systematic sample of residents in a nursing home/auxiliary hospital group; the findings presented here refer to the noninstitutionalized individuals only. In New Zealand, Oakley-Browne et al. (1989) selected household members aged 18 to 64 years resident in the Christchurch Urban Area, including the city itself, suburbs and the semi-rural margins. Since affective disorders and eating disorders were of particular interest, females aged 18 to 44 years were oversampled to increase the yield of these disorders. In France, Lepine et al. (1989) conducted their survey in Savigny, a newly built town located near Paris. The rates of major depression in Christchurch were clearly higher than at the other three sites; there was a predominance of females as compared to males in the rates of major depression at all sites, with a female-to-male sex ratio ranging between 1.3 and 2.4.

Higher rates of major depression among females were also found in the other two studies using the Diagnostic Interview Schedule and DSM-III criteria. In the National Survey of Deviant Behavior conducted in the United States only young adults aged 18 to 24 years were assessed for psychiatric status (Elliott et al., 1985). In the Icelandic sample studied by Stefánsson et al. (1994) recurrent major depression was responsible for the predominance of females in the overall rates of major depression, whereas the two sexes did not differ in reporting a single episode of major depression.

Finally, Levav et al. (1993) selected a probability sample of first generation Jewish Israelis of either European or North-African parents using a two-stage design, in which final diagnoses were made by psychiatrists on the basis of the Schedule for Affective Disorders and Schizophrenia-Research Diagnostic Criteria. The female-to-male sex ratio for major depression was slightly greater than 1.0 when major depression was assessed both at the probable and at the definite level of diagnostic confidence.
### Table III - Six-month prevalence rates of major depression from general population studies

<table>
<thead>
<tr>
<th>Author Country, time</th>
<th>Sample Size (N)</th>
<th>Age range (years)</th>
<th>Instruments</th>
<th>Rates (%)</th>
<th>Female-to-Male Sex Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canino et al. (1987)</td>
<td>1,513</td>
<td>18 - 64</td>
<td>DIS DSM-III</td>
<td>2.4</td>
<td>3.3</td>
</tr>
<tr>
<td>Puerto Rico, 1984</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bland et al. (1988a)</td>
<td>3,258</td>
<td>18 and over</td>
<td>DIS DSM-III</td>
<td>2.5</td>
<td>3.9</td>
</tr>
<tr>
<td>Canada, 1983-86</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oakley-Browne et al.</td>
<td>3,498</td>
<td>18-64</td>
<td>DIS DSM-III</td>
<td>3.4</td>
<td>7.1</td>
</tr>
<tr>
<td>New Zealand, 1986</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lepine et al. (1989)</td>
<td>749</td>
<td>18 and over</td>
<td>DIS DSM-III</td>
<td>1.5</td>
<td>3.6</td>
</tr>
<tr>
<td>France, n.r.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elliott et al. (1985)</td>
<td>1,496</td>
<td>18 - 24</td>
<td>DIS DSM-III</td>
<td>3.1*</td>
<td>8.0*</td>
</tr>
<tr>
<td>USA, 1983</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stefansson et al. (1994)</td>
<td>862</td>
<td>55 - 57</td>
<td>DIS DSM-III</td>
<td>1.1b</td>
<td>3.6b</td>
</tr>
<tr>
<td>Iceland, 1987-88</td>
<td></td>
<td></td>
<td></td>
<td>0.9b</td>
<td>0.7b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.7c</td>
<td>1.7c</td>
</tr>
<tr>
<td>Levav et al. (1993)</td>
<td>2,741</td>
<td>24 - 33</td>
<td>SADS RDC</td>
<td>3.8d</td>
<td>4.5d</td>
</tr>
<tr>
<td>Israel, 1982-88</td>
<td></td>
<td></td>
<td></td>
<td>2.6e</td>
<td>3.4e</td>
</tr>
</tbody>
</table>

* Data derived from Weissman et al. (1988)
  
  * Major depressive episode (total)
  
  a Major depression, single episode
  
  b Major depression, recurrent
  
  c Either probable or definite level of diagnostic accuracy
  
  d Only definite level of diagnostic accuracy

n.r. = not reported

### Twelve-month prevalence rates

Table IV sets out the results of general population studies investigating 12-month prevalence rates of major depression by sex of respondents. The 12-month prevalence rates reported here included those subjects who met lifetime criteria for major depression and had experienced relevant symptoms or an episode of the disorder during the 12 months preceding the examination.

In five studies, rates of major depression were expressed according to the DSM-III criteria. In the United States, the nationwide survey carried out by Uhlenhuth et al. (1983) primarily to determine the prevalence and patterns of psychotropic drug prescriptions and the NIMH-Epidemiologic Catchment Area Study (Robins & Regier, 1991) were based on a stratified multistage probability
sample of subjects in the noninstitutionalized civilian population. In Florence, Italy, Faravelli et al. (1990) selected a random sample of the general population from the lists of primary care physicians. Ernst & Angst (1992) selected a cohort of young males and females from the Kanton Zürich in Switzerland, who were born in 1957 and 1958. Finally, Stefánsson et al. (1994) selected half of the population born in Iceland in 1931.

On the other hand, prevalence rates of major depression were expressed according to the DSM-III-R criteria in the survey conducted in Savigny, France (Lepine et al., 1993) and in the National Comorbidity Survey in the United States (Kessler et al., 1994).

Despite wide variation in rates of major depression across the studies (between 2.7% and 10.3%), rates were higher in females compared to males and this trend was consistent across all the studies, with a female-to-male sex ratio ranging between 1.7 and 2.9.

**Table IV - Twelve-month prevalence rates of major depression from general population studies**

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample (N)</th>
<th>Age range (years)</th>
<th>Instruments Diagnostic Criteria</th>
<th>Rates (%)</th>
<th>Female-to-Male Sex Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uhlenhuth et al. (1983)</td>
<td>3,161</td>
<td>18 - 79</td>
<td>Symptom checklist DSM - III</td>
<td>2.8</td>
<td>6.9</td>
</tr>
<tr>
<td>USA, 1979</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robins &amp; Regier (1991)</td>
<td>18,571</td>
<td>18 and over</td>
<td>DIS DSM-III</td>
<td>1.4</td>
<td>4.0</td>
</tr>
<tr>
<td>USA, 1980-83</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faravelli et al. (1990)</td>
<td>1,000</td>
<td>15 and over</td>
<td>Flow chart DSM-III</td>
<td>3.5</td>
<td>8.8</td>
</tr>
<tr>
<td>Italy, 1984</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ernst &amp; Angst (1992)</td>
<td>591</td>
<td>20 - 21</td>
<td>Semistructured interview DSM-III</td>
<td>4.8</td>
<td>10.8</td>
</tr>
<tr>
<td>Switzerland, 1979</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Stefansson et al. (1994)</td>
<td>862</td>
<td>55 - 57</td>
<td>DIS DSM-III</td>
<td>1.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Iceland, 1987-88</td>
<td></td>
<td></td>
<td></td>
<td>0.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.9&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lepine et al. (1993)</td>
<td>1,746</td>
<td>18 and over</td>
<td>DIS DSM-III-R</td>
<td>3.4</td>
<td>6.0</td>
</tr>
<tr>
<td>France, n.r.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kessler et al. (1994)</td>
<td>8,098</td>
<td>15 - 54</td>
<td>CIDI DSM-III-R</td>
<td>7.7</td>
<td>12.9</td>
</tr>
<tr>
<td>USA, 1990-92</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Major depressive episode (total)
<sup>b</sup> Major depression, single episode
<sup>c</sup> Major depression, recurrent
n.r. = not reported
Lifetime prevalence rates

Table V sets out the results of general population studies investigating lifetime prevalence rates of major depression by sex of respondents. The lifetime prevalence rates of major depression reported here included those subjects who ever met the criteria for the disorder during the entire lifespan prior to the examination.

Nine studies used the Diagnostic Interview Schedule and DSM-III criteria. The surveys carried out in Puerto Rico (Canino et al., 1987), Edmonton (Bland et al., 1988a) and Christchurch (Wells et al., 1989) and the NIMH-Epidemiologic Catchment Area Study (Robins & Regier, 1991) were based on household probability samples, with estimated rates for major depression being obtained by weighting the collected data to correct for the selection procedure. The studies carried out in Savigny (Lepine et al., 1989) and in Iceland (Stefánsson et al., 1991) were drawn as random samples and, thus, the weighting procedure was not required. The Taiwan Psychiatric Epidemiology Project sampled three populations in metropolitan, township and rural areas, using a multistage random sampling method that did not create skewed sampling weights in a specific sampling area (Hwu et al., 1989). The Korean Epidemiologic Study of Mental Disorders was a nationwide survey including households in Seoul and in rural locations scattered over the country; in each household all family members aged 18 to 65 years were interviewed, provided that they had lived there for more than three months (Lee et al., 1990a, b). The Münich Follow-up Study (Wittchen et al., 1992) was a seven-year prospective and retrospective follow-up investigation of a stratified random sample of the general population of former West Germany; the stratification method used at follow-up included all the individuals reporting high scores on the clinical rating scales at the baseline evaluation plus a 39.8% random sample of those with low scores. Finally, the Shatin Community Mental Health Survey randomly selected households in Hong Kong, with one member between 18 and 64 years of age being randomly interviewed from each selected household (Chen et al., 1993). The lifetime rates of major depression varied widely by site, ranging between 3.3% and 16.8%. However, there was a predominance of females as compared to males in the rates of major depression at all sites, with a female-to-male sex ratio ranging between 1.4 and 3.4.

Two studies were based on different research instruments and diagnostic criteria. Weissman & Myers (1978) relied on the Schedule for Affective Disorders and Schizophrenia-Research Diagnostic Criteria. Kessler et al. (1994) used the Composite International Diagnostic Interview, a structured interview that was derived from the Diagnostic Interview Schedule and generates diagnoses according to the DSM-III-R criteria. Both studies showed a predominance of females as compared to males in the rates of major depression.

In Table V are also reported (when available) the female-to-male sex ratios resulting from rates of major depression at each site being standardized to the Epidemiologic Catchment Area five site household sample. This work was undertaken by the Cross National Collaborative Group, formed in 1990 by investigators having epidemiologic community data based on the Diagnostic Interview
Table V - Lifetime prevalence rates of major depression from general population studies

<table>
<thead>
<tr>
<th>Author Country, time</th>
<th>Sample Size (N)</th>
<th>Age range (years)</th>
<th>Instruments Diagnostic Criteria</th>
<th>Rates (%)</th>
<th>Female-to-Male Sex Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canino et al. (1987) Puerto Rico, 1984</td>
<td>1,513</td>
<td>18 - 64</td>
<td>DIS DSM-III</td>
<td>3.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Bland et al. (1988b) Canada, 1983-86</td>
<td>3,258</td>
<td>18 and over</td>
<td>DIS DSM-III</td>
<td>5.9</td>
<td>11.4</td>
</tr>
<tr>
<td>Wells et al. (1989) New Zealand, 1986</td>
<td>1,498</td>
<td>18 - 64</td>
<td>DIS DSM-III</td>
<td>8.8</td>
<td>16.3</td>
</tr>
<tr>
<td>Robins &amp; Regier (1991) USA, 1980-83</td>
<td>18,571</td>
<td>18 and over</td>
<td>DIS DSM-III</td>
<td>2.6</td>
<td>7.0</td>
</tr>
<tr>
<td>Lepine et al. (1993) France, n.r.</td>
<td>749</td>
<td>18 and over</td>
<td>DIS DSM-III</td>
<td>8.5</td>
<td>21.9</td>
</tr>
<tr>
<td>Stefansson et al. (1991) Iceland, 1987-88</td>
<td>862</td>
<td>55 - 57</td>
<td>DIS DSM-III</td>
<td>2.9a</td>
<td>7.8a</td>
</tr>
<tr>
<td>Hwu et al. (1989) Taiwan, 1982-85</td>
<td>11,004</td>
<td>18 and over</td>
<td>DIS DSM-III</td>
<td>7.3d</td>
<td>10.2d</td>
</tr>
<tr>
<td>Lee et al. (1990a,b) Korea, n.r.</td>
<td>3,134</td>
<td>18 - 65</td>
<td>DIS DSM-III</td>
<td>2.4g</td>
<td>4.1g</td>
</tr>
<tr>
<td>Wittchen et al. (1992) Germany, 1981</td>
<td>483</td>
<td>25 - 64</td>
<td>DIS DSM-III</td>
<td>4.0</td>
<td>13.6</td>
</tr>
<tr>
<td>Chen et al. (1993) Hong Kong, 1984-86</td>
<td>7,229</td>
<td>18 - 64</td>
<td>DIS DSM-III</td>
<td>1.3d</td>
<td>2.4a</td>
</tr>
<tr>
<td>Weissman &amp; Myers (1978) USA, 1975-76</td>
<td>511</td>
<td>26 and over</td>
<td>SADS RDC</td>
<td>12.3</td>
<td>25.8</td>
</tr>
<tr>
<td>Kessler et al. (1994) USA, 1990-92</td>
<td>8,098</td>
<td>15 - 54</td>
<td>CIDI DSM-III-R</td>
<td>12.7</td>
<td>21.3</td>
</tr>
</tbody>
</table>

* Rates of major depression at each site were standardized to the Epidemiologic Catchment Area five site household sample for the age group 18-64 years.

a Major depressive episode (total)
b Major depression, single episode
c Major depression, recurrent
d Metropolitan Taipei
e Small towns
f Rural villages
g Urban area
h Rural area
n.r. = not reported
Schedule and DSM-III criteria, in order to analyze the data and compare the findings using a common data plan and the same definitions (Weissman et al., 1993). The Epidemiologic Catchment Area Study was designated as the reference sample since it had the largest sample size and a sampling scheme robust enough to ensure stability of findings. Prevalence rates standardized in this way produced estimates as if the population at each site had the same sex and age distribution of the Epidemiologic Catchment Area Study sample. Since the age ranges sampled at each site differed, analyses were limited to individuals aged 18 to 64 years. Females retained their predominance over males in rates of major depression at all sites, the female-to-male sex ratio ranging between 1.6 and 2.6.

**PREVALENCE OF PERSISTENT AND RECURRENT DEPRESSION**

Table VI sets out the results of general population studies investigating lifetime prevalence rates of dysthymia by sex of respondents.

Nine studies used the Diagnostic Interview Schedule and DSM-III criteria; since dysthymia is a chronic disorder, the Diagnostic Interview Schedule does not attempt to define onset or remission and only lifetime rates of the disorder are assessed. 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), the United States (Robins & Regier, 1991) and Hong Kong (Chen et al., 1993) were based on household probability samples of the general population. The Taiwan Psychiatric Epidemiology Project sampled three populations in metropolitan, township and rural areas (Hwu et al., 1989). The study carried out in Iceland (Stefánsson et al., 1991) included half of the population born in Iceland in 1931 and living there in December 1986. Finally, the München Follow-up Study (Wittchen et al., 1992) was a seven-year prospective and retrospective follow-up investigation of a stratified random sample of the general population of former West Germany. The lifetime rates of dysthymia varied widely by site, ranging between 1.9% and 15.1%. There was a predominance of females as compared to males in the rates for dysthymia at all sites, with a female-to-male sex ratio ranging between 1.2 and 4.8.

On the other hand, in the National Comorbidity Survey the Composite International Diagnostic Interview was used to generate diagnoses according to the DSM-III-R criteria. A predominance of females was observed in lifetime prevalence rates of dysthymia (Table VI). The same study provided also twelve-month prevalence rates of dysthymia, these being 2.1% in males and 3.0% in females, with a female-to-male sex ratio of 1.4 (Kessler et al., 1994).

Intermittent depression, defined by the Schedule for Affective Disorders and Schizophrenia-Research Diagnostic Criteria, was investigated in a sample of first generation Jewish Israelis. At the
definite level of diagnostic confidence, six-month prevalence rates were 2.2% in males and 3.7% in females, with a female-to-male sex ratio of 1.7. The female-to-male sex ratio was 1.8, when intermittent depression was assessed according to both the definite and probable level of diagnostic confidence (Levav et al., 1993).

Finally, brief recurrent depression was investigated in a sample of young adults aged 23-24 years. Twelve-month prevalence rates were 3.9% in males and 4.9% in females, with a female-to-male sex ratio of 1.3. However, these rates were based on different thresholds for case-definition in males and females (3 criterion symptoms for males and 5 for females); using the same threshold in the two sexes, the female-to-male sex ratio was equal to 2.0 (Angst & Dobler-Mikola, 1985).

**Table VI - Lifetime prevalence rates of dysthymia from general population studies**

<table>
<thead>
<tr>
<th>Author Country, time</th>
<th>Sample (N)</th>
<th>Age range (years)</th>
<th>Instruments Diagnostic Criteria</th>
<th>Rates (%)</th>
<th>Female-to-Male Sex Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canino et al. (1987) Puerto Rico, 1984</td>
<td>1,513</td>
<td>18 - 64</td>
<td>DIS</td>
<td>1.6</td>
<td>7.6</td>
</tr>
<tr>
<td>Bland et al. (1988b) Canada, 1983-86</td>
<td>3,258</td>
<td>18 and over</td>
<td>DIS DSM-III</td>
<td>2.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Wells et al. (1989) New Zealand, 1986</td>
<td>1,498</td>
<td>18 - 64</td>
<td>DIS DSM-III</td>
<td>3.8</td>
<td>9.0</td>
</tr>
<tr>
<td>Lee et al. (1990a,b) Korea, n.r.</td>
<td>3,134</td>
<td>18 - 65</td>
<td>DIS DSM-III</td>
<td>1.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>1,966</td>
<td></td>
<td></td>
<td></td>
<td>1.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Robins &amp; Regier (1991) USA, 1980-83</td>
<td>18,571</td>
<td>18 and over</td>
<td>DIS DSM-III</td>
<td>2.2</td>
<td>4.1</td>
</tr>
<tr>
<td>Chen et al. (1993) Hong Kong, 1984-86</td>
<td>7,229</td>
<td>18 - 64</td>
<td>DIS DSM-III</td>
<td>1.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Hwu et al. (1989) Taiwan, 1982-85</td>
<td>11,004</td>
<td>18 and over</td>
<td>DIS DSM-III</td>
<td>6.9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>11.4&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stefansson et al. (1991) Iceland, 1987-88</td>
<td>862</td>
<td>55 - 57</td>
<td>DIS DSM-III</td>
<td>2.3</td>
<td>10.7</td>
</tr>
<tr>
<td>Wittchen et al. (1992) Germany, 1981</td>
<td>483</td>
<td>25 - 64</td>
<td>DIS DSM-III</td>
<td>2.5</td>
<td>5.4</td>
</tr>
<tr>
<td>Kessler et al. (1994) USA, 1990-92</td>
<td>8,098</td>
<td>15 - 54</td>
<td>CIDI DSM-III-R</td>
<td>4.8</td>
<td>8.0</td>
</tr>
</tbody>
</table>

<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  
<sup>n.r. = not reported</sup>
PREVALENCE OF BIPOLAR DISORDER

Since prevalence of bipolar disorder is expected to be low in the general population, only lifetime prevalence rates by sex of respondents are reported in Table VII. Even in this case, gender differences should be interpreted with caution, due to the small number of individuals that satisfied lifetime criteria for bipolar disorder in most of the studies. The lifetime prevalence rates reported here included those subjects who ever met the criteria for bipolar I disorder during the entire lifespan prior to the examination.

Nine studies were based on the Diagnostic Interview Schedule and DSM-III criteria. 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), the United States (Robins & Regier, 1991) 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). The study carried out in Iceland (Stefánsson et al., 1991) included half of the population born in Iceland in 1931 and living there in December 1986. Finally, the München Follow-up Study (Wittchen et al., 1992) was a seven-year prospective and retrospective follow-up investigation of a stratified random sample of the general population of former West Germany. The lifetime rates of bipolar disorder were generally lower than 1% (range between 0.2% and 1.6%); the female-to-male sex ratio ranged between 0.1 and 3.5.

Two studies were based on different research instruments and diagnostic criteria. 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 bipolar I disorder tended to be higher in females at both the definite and probable level of diagnostic confidence (Table VII). For bipolar II disorder, lifetime prevalence rates were 0.8% in males and 0.3% in females at the definite level of diagnostic confidence, with a female-to-male sex ratio of 0.4; the female-to-male sex ratio was 0.5, when bipolar II disorder was assessed according to both the definite and probable level of diagnostic confidence. On the other hand, in the National Comorbidity Survey the Composite International Diagnostic Interview was used to generate diagnoses according to the DSM-III-R criteria, with lifetime rates for bipolar disorder being similar in males and females (Kessler et al., 1994).
<table>
<thead>
<tr>
<th>Author</th>
<th>Sample (N)</th>
<th>Age range (years)</th>
<th>Instruments Diagnostic Criteria</th>
<th>Rates (%)</th>
<th>Female-to-Male Sex Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canino et al. (1987) Puerto Rico, 1984</td>
<td>1,513</td>
<td>18 - 64</td>
<td>DIS DSM-III</td>
<td>0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Bland et al. (1988b) Canada, 1983-86</td>
<td>3,258</td>
<td>18 and over</td>
<td>DIS DSM-III</td>
<td>0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Wells et al. (1989) New Zealand, 1986</td>
<td>1,498</td>
<td>18 - 64</td>
<td>DIS DSM-III</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Lee et al. (1990a,b) Korea, n.r.</td>
<td>3,134</td>
<td>18 - 65</td>
<td>DIS DSM-III</td>
<td>0.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Robins &amp; Regier (1991) USA, 1980-83</td>
<td>1,966</td>
<td>18 and over</td>
<td>DIS DSM-III</td>
<td>0.8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chen et al. (1993) Hong Kong, 1984-86</td>
<td>7,229</td>
<td>18 - 64</td>
<td>DIS DSM-III</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Hwu et al. (1989) Taiwan, 1982-85</td>
<td>11,004</td>
<td>18 and over</td>
<td>DIS DSM-III</td>
<td>1.6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.6&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stefansson et al. (1991) Iceland, 1987-88</td>
<td>862</td>
<td>55 - 57</td>
<td>DIS DSM-III</td>
<td>1.2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.0&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Wittchen et al. (1992) Germany, 1981</td>
<td>483</td>
<td>25 - 64</td>
<td>DIS DSM-III</td>
<td>1.2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.7&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Levav et al. (1993) Israel, 1982-88</td>
<td>2,741</td>
<td>24 - 33</td>
<td>SADS</td>
<td>0.5&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.8&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Kessler et al. (1994) USA, 1990-92</td>
<td>8,098</td>
<td>15 - 54</td>
<td>CIDI DSM-III-R</td>
<td>1.6</td>
<td>1.7</td>
</tr>
</tbody>
</table>

* Either probable or definite level of diagnostic confidence
** Only definite level of diagnostic confidence

a Urban area
b Rural area
c Metropolitan Taipei
d Small towns
e Rural villages
n.r. = not reported
FACTORS THAT MAY INFLUENCE GENDER DIFFERENCES IN PREVALENCE RATES OF AFFECTIVE DISORDERS

A consistent finding from general population surveys of affective disorders concerns the higher rates of depressive disorders in females compared to males, whereas no or inconsistent gender differences were detected for bipolar disorder. However, it is still controversial whether gender differences in depressive disorders are real or an artifact. Four main issues should be considered that might affect gender differences in rates of depressive disorders: i) the definition of caseness and measurement procedures; ii) the recall bias; iii) the course of disorder and mortality rates; iv) the geographical mobility.

i) Definition of caseness and measurement procedures

A few studies examined the hypothesis that gender differences in rates of major depression depends on the criteria used to make the diagnosis. The diagnostic criteria for major depression set out by Spitzer et al. (1978) (Research Diagnostic Criteria), the American Psychiatric Association (DSM-III, DSM-III-R, DSM-IV) and the World Health Organization (ICD-10) are based on a number of criterion symptoms that are associated with depressed mood. Any general tendency for females to report more criterion symptoms than males may contribute to females being more likely to meet diagnostic criteria for major depression, if the same number of symptoms is required to make a diagnosis in both sexes.

In Zürich, Angst & Dobler-Mikola (1984) examined the 12-month prevalence rates of depressive episodes in a cohort of young adults aged 22-23 years. Among probands that reported episodes of depressed mood lasting two weeks or longer, females reported more symptoms compared to males, the median being five symptoms for females and three for males. Had the same number of depressive symptoms been required for both sexes to be assigned a diagnosis, then different rates of depressive disorder would be expected in males and females. Indeed, for the three months preceding examination, the female-to-male sex ratio of 0.6 for episodes of depressed mood turned to 1.9 and 1.8 when the Research Diagnostic Criteria and DSM-III criteria for major depression were applied, respectively. Moreover, males and females suffering from an episode of depressed mood of at least two-week duration gave similar ratings of subjective impairment and were equally impaired socially and occupationally. Thus, when the social impairment criteria were included in the diagnostic decision tree, an equal prevalence of depression was found in males and females. The Authors concluded that episodes of depression occurred at similar rates in males and females and any actual female preponderance resulted from excess reporting of depressive symptoms.
Different results were obtained by Fennig et al. (1994), who investigated the 12-month prevalence rates of DSM-III-R major depression in a relatively homogeneous population of managers and professionals from a large corporation. When the female-to-male sex ratio in rates of depression was examined by progressively increasing the number of symptoms required for a diagnosis of depressive episode, the female preponderance existed at each level, even though it became more pronounced as the number of symptoms increased. For each possible cut-off at five or more criterion symptoms (as required in DSM-III-R) the female-to-male sex ratio was near or above 2.0. The female preponderance persisted even if different cut-offs were used for assigning a diagnosis to males and females, that is five criterion symptoms for males and six for females. Finally, the pattern of association between depressive symptomatology and occupational impairment was very similar for males and females and the female-to-male sex ratio exceeded unity at all levels of impairment beyond the mildest. Thus, the pattern of higher female-to-male sex ratios was similar for the two systems of case identification (i.e., that based on symptoms and that based on impairment).

Similar findings were reported also by Kessler et al. (1993), using the data from the National Comorbidity Survey. About 46% of the males and 58% of the females reported the lifetime occurrence of at least one period of depressed mood or diminished interest in most of the normal activities lasting two weeks or longer. If endorsement of these stem questions was the only requirement for a diagnosis of depression, the female-to-male sex ratio was 1.3. The female-to-male sex ratio became progressively higher as the required number of criterion symptoms was increased: it was 1.7 when four or more criterion symptoms were required, as in the DSM-III-R criteria, and 2.5 when all the eight depressive symptoms included in DSM-III-R had to be present.

A true gender difference in lifetime rates of major depression rather than a general trend for females to report more criterion symptoms was suggested also by Young et al. (1990a) in a sample of first-degree relatives of probands who participated in the NIMH-Collaborative Study of the Psychobiology of Depression. Among those individuals who experienced depressed mood or loss of interest or pleasure of at least one week duration (criterion I of the Research Diagnostic Criteria) and impaired functioning or treatment-seeking (criterion II of the Research Diagnostic Criteria), similar proportions of males and females reported no, one and two criterion symptoms associated to depression. A gender difference in symptom count was found once three or more criterion symptoms were present (i.e., the cut-off used by the Research Diagnostic Criteria to make a lifetime diagnosis of past probable major depressive episode). The great bulk of the gender difference was based on only the depressed mood and impairment criteria, while using the criterion of three or more symptoms resulted in an increase in the female-to-male sex ratio of only 9%. Since for both males and females the discontinuity in the curve of symptom frequency occurred at the threshold level for a diagnosis of major depression.
according to the Research Diagnostic Criteria, there was no support to the use of gender-specific threshold criteria.

In summary, although there is a tendency for females to report more criterion symptoms associated to depression compared to males, the findings available so far suggest that this does not seem to account entirely for gender differences in rates of major depression.

A related issue is whether males and females differ in the clinical manifestations of depression during a diagnosed depressive episode. Frank et al. (1988) reported on gender differences in a sample of 230 patients with recurrent depression. Females were more likely to report increased appetite and weight gain and less likely to report weight loss than their male counterparts; females also experienced more somatic anxiety, expressed anger and hypochondriasis. Similar results were found by Young et al. (1990b), who examined a sample of 498 probands seeking treatment for current non-psychotic unipolar major depression according to the Research Diagnostic Criteria. Statistically significant differences were detected for two of the 41 clinical features considered, with increased appetite and weight gain occurring more frequently in females compared to males. Analysis of severity for those features that applied to all individuals showed no significant differences between males and females. Finally, Angst & Dobler-Mikola (1984) showed that females were more likely to report disturbance of appetite and sleep compared to males; in addition, reporting of symptoms by males tended to decrease and to be less reliable over a one-year period.

One approach to interpreting the results of these studies is to accept gender differences in clinical manifestations of depression as real; as an alternative interpretation, these findings might simply reflect sociocultural differences in the way males and females perceive their symptoms and respond to them (e.g., males might be engaged in more denial of symptoms than females, according to their socially desirable self-image). Whatever interpretation is endorsed, it might be expected that differences between males and females in experiencing or reporting depressive symptoms might lead to gender-specific response patterns depending on the individual items included in the rating scales for depression. Building on recent advances in structural equation models, Stommel et al. (1993) tested the degree to which the 20-item Center for Epidemiologic Studies Depression Scale (Radloff, 1977) was 'factorially invariant' across groups of male and female cancer patients. Two items were identified as producing biased responses according to sex of respondents: males, who otherwise had the same level of depressive symptoms as females, were less likely to have 'crying spells', but more likely to reduce their verbal communication ('talked less') compared to equally depressed females. When three additional items were excluded on the basis of other psychometric deficiencies, a subset of 15 items was left that captured almost all of the information of the original 20-item scale, but were free of any gender bias. Nevertheless, gender differences in mean levels of depressive symp-
tomatology, although significantly reduced, were not eliminated when the shortened version of the scale was used.

The psychometric properties of another well-known rating scale for depression (i.e., the Beck Depression Inventory - Beck et al., 1979) were compared in male and female psychiatric outpatients with affective disorders according to the DSM-III criteria. Only one of the 21 items differentiated males and females, with males reporting more severe self-dissatisfaction compared to females. Overall, the findings supported the comparability of the psychometric properties of the scale for both males and females and separate sex norms were not necessary for interpreting the scores reported on the scale (Steer et al., 1989).

**ii) Recall bias**

It has been suggested that the preponderance of females in rates of major depression might be the result of a gender difference in recalling past depressive episodes. The introduction of structured psychiatric interviews to generate standardized diagnostic decisions has raised the issues of test-retest reliability and inter-rater agreement as measures of the instrument error. A related paradigm is that of temporal stability, with agreement between assessments given at widely separated points in time (e.g., successive hospital admissions) reflecting 'true' lifetime clinical state and the validity of the underlying constructs (Rice et al., 1992).

Comparison of short-term and lifetime prevalence rates of major depression may provide indirect evidence of instability of results. In the NIMH-Epidemiologic Catchment Area Study the ratio of lifetime to six-month prevalence rates of major depression was 2.0, indicating that half of the subjects reporting a lifetime episode of major depression had it in the six months preceding the examination (Weissman et al., 1988). Similar findings were reported by other general population studies using the Diagnostic Interview Schedule and DSM-III criteria: the ratios of lifetime to six-month prevalence rates of major depression were 1.5 in Puerto Rico (Canino et al., 1987), 2.3 in Iceland (Stefánsson et al., 1991; 1994), 2.4 in Christchurch (Wells et al., 1989; Oakley-Browne et al., 1989), 2.7 in Edmonton (Bland et al., 1988 a, b) and 3.0 in München (Wittchen et al., 1992). Although it cannot be excluded that subjects reporting major depression have depressive episodes that are long and/or highly recurrent, these findings suggest that remote episodes might be forgotten, resulting in an under-estimate of lifetime rates of depression. Indeed, Parker (1987) raised doubts about the validity of the lifetime prevalence estimates generated in the reports of the Epidemiologic Catchment Area Study and identified three reasons to suspect their accuracy: the ratio of lifetime and six-month prevalence data, the discordance with previous estimates of lifetime morbidity, and the curvilinear association of lifetime prevalence estimates with increasing age.
The issue of temporal stability in the assignment of psychiatric diagnoses has received direct attention by a number of studies. Mazure & Gershon (1979) interviewed a sample of adult patients hospitalized for a major affective disorder, their first-degree relatives and controls on two occasions separated by a mean interim time of 6.7 months. Overall, 18 of the 21 subjects with major affective disorders on any interview were consistently diagnosed and 10 of the 11 subjects receiving a diagnosis of unipolar depression at the first interview were diagnosed so also at the second. Although high reliability was found for the number of depressive symptom groups, there was only modest reliability between the number of affective episodes reported each time.

Similar results were found by Andreasen et al. (1981), who examined the six-month reliability of lifetime diagnoses in a sample of 50 relatives of affectively ill probands and control subjects. High reliability was shown for the diagnosis of major depressive episode and for the items concerning depressive symptoms (with the exception of agitation-retardation and tiredness), whereas interviewers reported low levels of agreement in the number of depressive episodes that occurred in the past.

Finally, Rice et al. (1992) collected data on 1,629 relatives of probands with affective disorders that were interviewed twice, six years apart. Of those with a lifetime diagnosis of major depression at initial assessment (24% of the sample), 74% were positive also on second interview. The misclassification decreased as disorder severity increased, since individuals reporting more depressive symptoms, more episodes of depression or some type of treatment at initial assessment as well as those who attempted suicide or were incapacitated had higher stability in reporting; instead, sex of respondents was not significantly related to stability.

Although these studies provide important clues on the issue of stability of diagnosis over time, they were not conducted in general population samples. This may be a possible limitation in the generalisation of their results, since diagnostic stability tended to be strongly influenced by such covariates at initial evaluation as the number of symptoms reported and treatment-seeking behaviour. Therefore, different levels of diagnostic stability may be expected in samples including milder cases, like those drawn from the general population. Thus, Bromet et al. (1986) assessed the stability of lifetime episodes of major depression in a community sample of women interviewed on two occasions, 18 months apart. Overall, stability was poor with 'k' for definite major depression being 0.41. Of the 144 women that were diagnosed at either interview as depressed for the period preceding first interview, only 38% consistently reported episodes of major depression on both occasions, 42% of those initially reporting an episode subsequently 'forgot' that episode, whereas 20% of those who initially denied a lifetime episode subsequently 'remembered' an episode. Individuals receiving a diagnosis of major depression at both interviews reported more depressive symptom groups than those diagnosed as depressed.
at either first or second interview. Finally, women who reliably reported lifetime episodes of depression were consistent about details such as medication use, but were inconsistent about number of depressive episodes, length of longest episode and age at first episode. A similar analysis of the data collected during the NIMH-Epidemiologic Catchment Area study revealed that 61% of the 529 respondents with a lifetime diagnosis of major depression at baseline failed to receive that diagnosis when interviewed again one year later (Dohrenwend, 1989).

The findings reported above strongly suggest that passage of time may affect recall of previous episodes of depression. Other studies have specifically investigated possible gender differences in temporal stability which might be artifactual determinants of a female preponderance in rates of major depression. In their cohort of young adults, Angst & Dobler-Mikola (1984) found that 7.4% of males and 4.8% of females reported depressive episodes during the three months preceding examination, whereas only 1.8% of males as opposed to 10.8% of females reported depressive episodes between four and 12 months prior to examination. The Authors argued that the preponderance of females in 12-month rates of major depression could be ascribed to males reporting previous depressive episodes in a less reliable way.

These findings were not replicated by other studies. When two-year stability of recall of DSM-III diagnoses was assessed in a sample of individuals aged six to 23 years, a trend toward better recall of diagnoses was found in boys compared to girls, for all disorders except anxiety. Boys’ recall of DSM-III major depression was excellent (‘k’ = 0.76) and significantly better than girls’ recall (‘k’ = 0.53); moreover, boys showed better recall for major depression even when stricter criteria were used (duration of at least four weeks and impairment in a major social role) (Fendrich et al., 1990).

A slight trend for females to report more distant episodes of major depression was found in a highly-educated white collar sample, even though there- was no significant gender difference in the distribution of episodes over a 12-month period. In addition, a regression analysis found no significant gender-by-time interaction in the prediction of number of symptom criteria, indicating that males did not report relatively fewer symptoms in the remote episodes as compared to females (Fennig et al., 1994). Similarly, when spouses, relatives and controls of affectively ill probands were examined on two occasions, six years apart, females developed major depression during the six-year period at a rate twice that for males; however, male and female subjects did not differ by the year in which they reported their first episode (Coryell et al., 1992).

A more sophisticated approach based on longitudinal design and corroborative witness reports was implemented by Wilhelm & Parker (1994) in a sample of teacher trainees who were assessed for socio-demographic and historical issues at intake and again five and 10 years later.
Although males and females showed similar overall stability in reporting episodes of depression five years apart (mean ‘k’ of 0.49 and 0.55 for males and females, respectively), a closer inspection revealed a differential ‘passage of time’ effect: less immediate or threshold episodes were ‘forgotten’ especially by males, whereas sub-clinical or threshold episodes were subsequently ‘remembered’ or reported as more severe especially by females, thus contributing to a female preponderance in rates of depression. In other words, contrasting phenomena (i.e., males more likely to ‘forget’ over time and females more likely to ‘remember’ previously unreported episodes) suggested similar overall consistency of recall for the two sexes, allowing for a possible artifact in gender differences of depression to be overlooked. After correction for ‘passage of time’ effects on stability of prevalence estimates of depression, a clear evidence of any lifetime gender difference was no longer found.

On the other hand, the higher rate of ‘forgetting’ episodes by males compared to females was not found in other studies. In the sample of young offsprings that were assessed for stability of recall by Fendrich et al. (1990), 10 males met caseness criteria on each occasion (and eight on both), whereas 32 females met caseness criteria on first occasion, 17 on the second, and only 16 on both. As a consequence of differential recall between the two sexes, the gender difference in rates of major depression, which was statistically significant at first occasion, was no longer so at the second. Moreover, when consistency in reporting episodes of major depression by relatives of affectively ill probands was examined separately in the two sexes over a 6-year interval, episodes of ‘forgetting’ and ‘remembering’ compensated for each other in males, whereas females ‘forgot’ previously nominated episodes at a higher rate than ‘remembering’ past episodes previously not nominated (Warshaw et al., 1991).

In summary, the evidence collected so far strongly suggests instability of recall of depressive episodes over time, but does not support the notion that differential recall in the two sexes is entirely responsible for the gender difference in rates of depression.

iii) Course of disorder and mortality rates

Since prevalence is a product of incidence and length of illness, gender differences in the course of the disorder may be responsible for gender differences in rates of depression. For example, Stefánsson et al. (1994) showed that the preponderance of major depression among females was accounted for by recurrent major depression, whereas a female-to-male sex ratio close to 1.0 was obtained for subjects suffering from a single episode of major depression over the 12 months preceding examination. However, the course of disorder loses its relevance in computing lifetime prevalence rates and these were reported to be higher in females compared to males.
In addition, a gender difference in prevalence rates of major depression might be due to mortality rates being different in the two sexes. Since prevalence rates are based on the proportion of survivors experiencing the disorder, gender differences in mortality rates among those with the disorder may have an effect on the observed prevalence rates, with affected individuals of one sex being ‘removed’ from the older population at a higher rate.

Mortality has been reported to be higher in patients with psychiatric disorders compared to the general population, although less excessive since the introduction of modern psychiatric treatments, improved medical care and shorter duration of admissions (Sims, 1987; Amaddeo et al., 1995). However, the vast majority of data on this issue have been provided by studies carried out among patients contacting psychiatric services or in highly selective nonclinical samples (i.e., students or industrial workers). This is likely to be a bias, since individuals selected in terms of their help-seeking behaviour, prior mental morbidity or other characteristics (e.g., age, sex, occupation) do not constitute a representative sample of the individuals with mental disorders from the communities in which they live. For example, individuals receiving psychiatric care, especially on an inpatient basis, are usually more chronically and severely impaired than other members of the general population suffering from mental disorders but not seeking help and this is expected to have a negative effect on their mortality.

Only a few mortality studies were based on epidemiologic surveys of the general population. Most of these studies found no effect of mental health on mortality risk or, when an effect was found, it was entirely explained by the covariation between measures of mental health and other variables, primarily related to physical health problems (Roberts et al., 1990). On the other hand, three community studies found a relationship between mental health and mortality, even after controlling for possible covariates. In a 12-year follow-up of 610 individuals, psychological distress was predictive of mortality (hazard ratio = 1.7), when preexisting disease, smoking habits and a variety of other risk factors (including a social class and a social network index) were controlled for (Somervell et al., 1989). Moreover, in the Stirling County Study the presence of any type of depressive and anxiety disorder had a significant association with excess mortality over a 16-year interval, but did not significantly interact with sex. However, the increased risk (1.6) was mainly due to depression with or without anxiety and the relationship between depression and death was significantly more pronounced in males (increased risk = 2.1) than in females (increased risk = 1.2) (Murphy et al., 1987). Finally, Livingston Bruce et al. (1994) showed that respondents with recent episodes of major depression at initial interview were about two times more likely to die during a nine-year follow-up period compared to those without recent major depression. The increased risk was confirmed when the effect of other comorbid psychiatric disorders was controlled for. A significant interaction between recent major depression and sex indicated that, in spite of major depression being associated with increased mortality in both sexes, the effect was stronger in males (relative risk = 4.2) compared to females (relative risk = 1.7).
Overall, there appears to be controversial evidence from general population studies about the negative effect of mental disorders on mortality. The disparate findings reported so far may be attributed to study differences in period, place and design, including sample size, length of follow-up, efforts made to reduce attrition and case ascertainment procedures. The two studies showing a relationship between premature mortality and depression suggest that some portion of the preponderance of females in rates of depression is possibly due to differential mortality rates between the two sexes. It is not clear whether higher rates of mortality in males can account entirely for the gender difference in prevalence rates of depression.

iv) Geographical mobility

Gender differences in rates of depression may be influenced by selective migration, with females moving into the catchment areas of university-based research centres. This explanation seems unlikely, since gender differences have been detected in general population studies that sampled individuals living in different countries and areas, including urban, suburban and rural areas.

INCIDENCE OF MAJOR DEPRESSION

Despite the advantage of using incidence rates to study risk factors and to compute age-specific lifetime prevalence estimates on the basis of mortality rates (Kramer et al., 1980), incidence studies of psychiatric disorders are rare since they would require the repeated assessment of a well-defined population over a sufficient number of years. The Lundby Study started in 1947 with a psychiatric examination of all the individuals (N = 2,550) living in a geographically defined area near the town of Lund, in the south of Sweden. The Swedish national registration system allowed for these individuals to be followed-up for 25 years until 1972, in spite of about half moving to mainly urban areas. Diagnostic criteria for depressive illness remained similar throughout the whole study and were based on information elicited by psychiatrists during clinical interviews without reference to well-known diagnostic classifications of mental disorders. Incidence rates increased during the 25-year period in both sexes and were higher in females compared to males: in males, incidence rates were 0.14% during the period 1947-1957 and 0.37% during the period 1957-1972; the corresponding figures for females were 0.41% and 0.77% (Hagnell et al., 1982).

Annual first incidence rates of specific psychiatric disorders were also computed from the data collected at four sites (Baltimore, Durham, St. Louis and Los Angeles) of the NIMH-Epidemiologic Catchment Area Study (Eaton et al., 1989). Rates were based on about 80% of the respondents at baseline interview, that were successfully contacted and interviewed one year later. Although inci-
Incidence rates are to be considered with caution, due to small numbers of new cases being diagnosed during the follow-up period, females had higher incidence rates of DSM-III major depression in all age groups compared to males and the overall difference was statistically significant (annual incidence rates of 1.10% and 1.98% for males and females, respectively). Gender-specific predicted probabilities showed that for females there was a rise to the peak years of onset in the middle forties with a decline thereafter; for males, the probability of onset was a monotonically decreasing function of age. The relationship of age to incidence of major depression was statistically significant for females, but not for males.

A study based on medical records of a single general practice in London, England, showed that incidence rates of recognized depression increased for males, but hardly changed for females during the 20 years between 1957 and 1976. Despite the different trends in the two sexes, estimates of annual incidence rates revealed that both in 1962 and in 1972 incidence rates were higher in females compared to males (Dunn & Skuse, 1981).

Finally, using 18 years of data from the Camberwell Psychiatric Case Register, Der & Bebbington (1987) provided incidence of all affective disorders in Camberwell, England. Incidence rates of depression were higher in females compared to males, irrespective of the severity of the disorder. For severe depression, incidence rates were 0.29% and 0.52% in males and females, respectively; for moderate depression, the corresponding figures in males and females were, respectively, 0.85% and 1.69% and for depression not otherwise specified 0.30% and 0.49%.

**INCIDENCE OF BIPOLAR DISORDER**

Incidence of bipolar disorder was estimated using first admission statistics and ranged between 0.9 per 100,000 per year and 6.0 per 100,000 per year (Müller et al., 1968; Eagles & Whalley, 1985; Goodwin & Redfield Jemison, 1990; Sibisi, 1990; Hunt et al., 1993), with admission rates being similar for males and females (Eagles & Whalley, 1985; Goodwin & Redfield Jemison, 1990; Sibisi, 1990). In addition, Goodwin & Redfield Jemison (1990) reported annual incidence rates for people aged 15 years or older seeking treatment and diagnosed as having bipolar disorder. Incidence rates ranged between 11 per 100,000 and 21 per 100,000 per year, with the female-to-male ratio ranging between 0.5 and 3.7.
FACTORS THAT MAY INFLUENCE GENDER DIFFERENCES IN INCIDENCE RATES OF AFFECTIVE DISORDERS

Data provided by general population studies showed that incidence rates for depression are higher in females compared to males. Four main issues should be considered as potential artifactual determinants of gender differences in incidence rates of depression, namely: i) the criteria for case definition, the measurement procedures and the sources of information; ii) the recall bias; iii) the mortality rates; iv) the geographical mobility. These issues have been discussed in the previous paragraph and do not seem to account entirely for gender differences in rates of depression.

For bipolar disorder, incidence rates were based on hospital admission statistics or on people seeking treatment. These methods allow for large numbers of patients to be selected with comparatively small effort; however, merely 'administrative' incidence rates can be derived, depending on the presence of illness and its severity as well as on the availability of in-patient services and community care. This might be responsible for a significant number of patients with bipolar disorder being missed. Indeed, the data collected in the general population during the NIMH-Epidemiologic Catchment Area Study showed that only 9.6% of those with bipolar disorder received inpatient hospitalization within the previous year and 38.5% obtained some form of outpatient mental health care in the six months prior to interview (Robins & Regier, 1991). In addition, statistics based on use of health services can be biased by a general tendency for females with affective disorders to contact psychiatric and medical services more often than their male counterparts.

MORBIDITY RISK FOR DEPRESSION

The morbidity risk (or disease expectancy) refers to the probability of suffering from a disorder within a definite age after controlling for factors (e.g., death, loss of contact) that might result in unaffected individuals being lost from the study before the end of the risk period. Only three studies estimated morbidity risk for depression using data collected in the general population. Helgason (1964) selected all individuals born in Iceland between 1895 and 1897 and surviving to 1910. The cohort of 5,395 subjects was followed until 1957, and for over 99% sufficient information was collected for a psychiatric assessment to be made. In a subsequent study, Helgason (1979) extended the follow-up period of the survivors until the age of 74 years. The morbidity risk for 'affective disorders' were 9.4% in males and 14.4% in females.

On the basis of the longitudinal data collected during the Lundby Study, Hagnell et al. (1982) computed the lifetime expectancy of depression, defined as the probability of suffering from depression before the age of 80 years. For males, the cumulative probability of depression by age 80 years was 11% during the period 1947-1957 and became 26% during the period 1957-1972; for females,
the probability rose from 30% in 1947-1957 to 49% in 1957-1972. The risk of depression increased especially in males aged 20 to 39 years, the risk being 10 times higher during the period 1957-1972 compared to the period 1947-1957.

Finally, Newman et al. (1988) used cross-sectional data collected in Edmonton to compute morbidity risks of specific DSM-III psychiatric disorders. The main difference from previous (longitudinal) studies is that age-specific incidence rates (from which morbidity risks were derived) were estimated on the basis of the age at onset of the first symptom of a disorder as recorded retrospectively at the time of the survey. In this regard, a recall period spanning the 15 years prior to the survey was defined. Individuals with a history of a disorder preceding the specified recall period were excluded, leaving a group of individuals at risk for the disorder that were ‘followed-up’ to the time of the survey. Since respondents were aged 18 to 89 years, information on onset of psychiatric morbidity was collected for the age range 3 to 89 years. Morbidity risk for major depression were 16.4% in males and 22.3% in females, the difference being statistically significant.

Although differences in study design, diagnostic criteria ans statistical methods do not allow for direct comparison between these studies, a consistent finding was that morbidity risks for depression were high, with females being at a far greater risk compared to males.

**MORBIDITY RISK FOR BIPOLAR DISORDER**

Two studies reported morbidity risks of bipolar disorder by sex. In Iceland, Helgason (1977) estimated the morbidity risk to be 0.67% in males and 0.91% in females. In Edmonton, Newman et al. (1988) found a morbidity risk for manic episodes of 1.4% in males and 0.6% in females; this gender difference was not statistically significant. Despite differences in morbidity risk estimation, these findings suggest that the morbidity risk for bipolar disorder is close to 1% for both males and females.

**AGE AT ONSET OF MAJOR DEPRESSION**

Table VIII shows the mean age at onset of major depression by sex.

Using the data from the NIMH-Epidemiologic Catchment Area Study, Weissman et al. (1988) found that age at onset of major depression differed significantly by site, although the Authors considered these differences as modest and of little clinical value. After controlling for the age distribution of the population at each site, no significant gender differences were found in mean age at onset of major depression. Similarly, no significant gender differences in mean age at onset of
major depression were detected in the National Comorbidity Survey (Kessler et al., 1993) and in Edmonton (Bland et al., 1988c).

Table VIII - Mean age at onset for major depression from general population studies

<table>
<thead>
<tr>
<th>Author Country, time</th>
<th>Instruments Diagnostic criteria</th>
<th>Age range (years)</th>
<th>Sample (N)</th>
<th>Site</th>
<th>Mean age at onset Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weissman et al. (1988) USA, 1980-83</td>
<td>DIS DSM-III</td>
<td>18 and older</td>
<td>5,034</td>
<td>New Haven</td>
<td>25.2</td>
<td>26.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3,481</td>
<td>Baltimore</td>
<td>32.5</td>
<td>28.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3,004</td>
<td>St. Louis</td>
<td>21.8</td>
<td>27.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3,921</td>
<td>Piedmont</td>
<td>31.9</td>
<td>29.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3,132</td>
<td>Los Angeles</td>
<td>22.8</td>
<td>26.4</td>
</tr>
<tr>
<td>Kessler et al. (1993) USA, 1990-92</td>
<td>CIDI DSM-III-R</td>
<td>15 - 54</td>
<td>8,098</td>
<td>not specified</td>
<td>24.0</td>
<td>23.5</td>
</tr>
<tr>
<td>Bland et al. (1988c) Canada, 1980-83</td>
<td>DIS DSM-III</td>
<td>18 and older</td>
<td>3,258</td>
<td>Edmonton</td>
<td>25.8</td>
<td>23.4</td>
</tr>
</tbody>
</table>

In addition, the median age at onset of major depression in Edmonton was the same in males and females, i.e. 21 years; for both males and females the decades with the highest percentage of first onsets of depressive symptoms were the ages 10 to 19 and 20 to 29 years (Bland et al., 1988c; Spaner et al., 1994).

Moreover, Weissman et al. (1993) compared the findings from epidemiologic surveys in the United States, Canada, Germany and New Zealand by standardizing the mean age at first onset of major depression at each site to the age and sex distribution of the general population in the United States. Among individuals aged 26 to 64 years at interview, mean age at onset of major depression was 27.2 years in males and 28.2 years in females at the five sites of the NIMH-Epidemiologic Catchment Area Study; 28.5 years in males and 25.5 years in females in Edmonton; 26.2 years in males and 31.3 years in females in Münich; 30.7 years in males and 28.3 years in females in Christchurch. Again, no statistically significant gender differences were found at each site.

Finally, two papers applied survival methods to compute hazard rates for depression for specific time intervals across the lifespan. Using the data from both household and institutional residents of the NIMH-Epidemiologic Catchment Area Study, Burke et al. (1990) found that adolescence and young adulthood were important periods for the development of major depression. For both males and females, the highest hazard rates occurred at ages 15 to 19 years and 25 to 29 years; however, females displayed higher hazard rates than males and the difference was statistically significant.
Similarly, in the National Comorbidity Survey females had higher hazard rates than males, beginning at age 10 and continuing through the mid-fifties. For females higher hazard rates occurred at ages 25 to 29 years and 15 to 19 years; for males, hazard rates at ages 35 to 39 years and 40 to 44 years were slightly higher than those at ages 15 to 19 years and 25 to 29 years (Kessler et al., 1993).

AGE AT ONSET OF BIPOLAR DISORDER

Table IX shows the mean age at onset of bipolar disorder by sex.

Using the data from the NIMH-Epidemiologic Catchment Area Study, Weissman et al. (1988) found that age at onset of bipolar disorder differed significantly by site, although the Authors considered these differences as modest and of little clinical value. After controlling for the age distribution of the population at each site, no significant gender differences were found in mean age at onset of bipolar disorder.

Similarly, no significant gender difference in mean age at onset of bipolar disorder was detected in Edmonton. In addition, the median age at onset for bipolar disorder in Edmonton was 18 years in males and 19 years in females; for both males and females the decades with the highest percentage of first onsets of bipolar disorder were the ages 10 to 19 and 20 to 29 years (Bland et al., 1988c; Fogarty et al., 1994).

Finally, Burke et al. (1990) applied survival methods to the data from both household and institutional residents of the NIMH-Epidemiologic Catchment Area Study and found that the highest hazard rates for the development of bipolar disorder occurred at age 15 to 19 years in both sexes. No significant difference in hazard rates was found between males and females.

Table IX - Mean age at onset for bipolar disorder from general population studies

<table>
<thead>
<tr>
<th>Author Country, time</th>
<th>Instruments Diagnostic criteria</th>
<th>Age range (years)</th>
<th>Sample (N)</th>
<th>Site</th>
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</tbody>
</table>
METHODOLOGICAL CONSIDERATIONS ON AGE AT ONSET OF PSYCHIATRIC DISORDERS

Setting age at onset of psychiatric disorders is important for both research and public health purposes (Burke et al., 1990). First, the identification of ages of vulnerability may help in planning preventive interventions and treatment facilities. Second, knowing the risk period for developing a disorder may aid in designing prospective follow-up studies to investigate the incidence of specific disorders and the sequence of onset of multiple disorders, when they occur in the same individual. For example, recent findings on the onset of affective disorders suggest that the period of life with higher first incidence of affective symptoms and syndromes lies outside the age limits of most of the epidemiologic studies carried out so far in the adult population (Ernst & Angst, 1992). Third, defining the differential onset of a disorder may provide information about subtyping or etiology. Indeed, there is converging evidence that some cases of major depression have their onset in childhood and adolescence and that these early-onset forms may be associated with high familial loading of major depression and specificity of transmission, suggesting that early-onset depression is a single homogeneous disorder (Weissman et al., 1984). Finally, knowing the pattern of risk would be useful to family studies and genetic investigations to estimate the probability for relatives of a proband to develop a disorder in the future.

Despite the well-known importance, investigators still face several problems in fixing age at onset of psychiatric disorders. Age-specific incidence rates based on a defined population and follow-up interval would be useful to examine the pattern of onset of a disorder. However, longitudinal studies conducted in the past were based on less reliable and precise methods to determine psychiatric diagnosis (Hagnell et al., 1982) or were limited to females (Sashidaran et al., 1988). On the other hand, the incidence data from the NIMH-Epidemiologic Catchment Area Study (Eaton et al., 1989) were based on a single year interval between the first and second evaluation and this might affect the stability of the incidence estimates that were drawn. Moreover, the exclusion of subjects below the age of 18 years at baseline evaluation prevented from examining the incidence of psychiatric disorders in childhood and adolescence.

The setting from which samples are drawn is also important and studies based on clinical samples are likely to provide biased estimates. Indeed, age at onset of a disorder cannot be defined as age at first treatment or at first hospitalization, since there is often a delay between first appearance of symptoms and treatment or hospitalization. Moreover, only a proportion of individuals with any psychiatric disorder seek or receive treatment, this proportion depending on the availability and accessibility of services as well as on the severity of the disorder.

Studies based on adult respondents in the general population reporting occurrence of a disorder anytime in their lives provide estimates for the onset of that disorder over the entire lifespan.
However, three potential limitations are to be considered (Bland et al., 1988c). First, the mean and median ages at onset of a disorder (although useful) do not provide information about the pattern of onset across the lifespan or about the peak age of onset and both depend on the population from which cases are drawn. As an example, if equal incidence of a disorder is found for those aged 15 to 19 years and those aged 20 to 24 years, but the population includes more individuals aged 20 to 24 years than those aged 15 to 19 years, then more cases with an onset between 20 and 24 years are expected, with mean and median ages at onset of the disorder being higher than is actually the case. Second, most individuals in the younger age groups are still in the period at risk for developing psychiatric disorders and are expected to experience a first episode sometime in the future, thus raising the mean age at onset. Finally, distortion can be introduced by differential mortality among individuals with and without psychiatric disorders. On the basis of these considerations, life-table methods have been increasingly used to compute more accurate estimates of the onset of a disorder, by accounting for these 'censored' data and permitting calculation of the probability of onset at a particular age interval given that the individual has lived to that interval.

**TEMPORAL TRENDS IN DEPRESSION**

**OLD-GENERATION STUDIES**

Several reports suggest that the epidemiology of affective disorders in the general population may have changed over the last century. Murphy (1986) summarized the findings of four longitudinal studies that were carried out during the third quarter of the 20th century and reported temporal trends pertinent to depression and anxiety.

The Lundby Study (1947-1972) in Sweden (Hagnell et al., 1982) and the Midtown Manhattan Study (1954-1974) in the United States (Srole & Fisher, 1980) made use of a cohort follow-up strategy, with individuals being followed over time to locations both inside and outside the original place of study. The members of the Lundby cohort were residents of two rural parishes when the study started; 25 years later, information was collected for approximately 98% of the cohort, in spite of 40% having moved to densely populated areas in Sweden or elsewhere. The Midtown cohort consisted of subjects aged 20 to 59 years who were originally residents of a district in New York City; by the time data collection was concluded, about 54% of the survivors were located in widely scattered but mainly urban areas.

On the other hand, the Stirling County Study (1952-1970) in Canada (Murphy et al., 1984) and the Survey Research Centre's National Sample Study (1957-1976) in the United States (Kessler & McRae, 1981) were based on a repeated cross-sectional survey design, each having drawn one early sample and another recent sample to represent their respective populations. The Stirling
Study concerned a rural county in Canada which experienced small-scale urbanization over the period of the survey, whereas the National Sample Study selected both rural and urban areas in the United States, having the whole nation as its population of reference.

In the Stirling County Study the point prevalence of both depression and anxiety remained essentially the same in the early compared to the recent period (12.5% and 12.7%, respectively). Combined rates of the two types of disorder were higher among females compared to males in both years of study, in spite of a slightly falling aggregated rate for females and a slightly rising rate for males.

Opposite results were reported by the Lundby Study and the Midtown Manhattan Study. In the Swedish study, the incidence of depression with severe or medium impairment increased significantly over time: for the population as a whole, the incidence was 0.18% per year in the early period and became 0.45% per year in the recent one. The increase applied to both males and females, with females showing higher incidence than males in both periods. However, incidence rates for males aged 20 to 39 years increased sharply over the period of study and were very similar to those of young females in the recent period, in contrast to their being far apart earlier.

On the other hand, the Midtown findings indicated an improvement in mental health for the followed cohort as a whole, the rates of mental morbidity being 14.2% at the beginning of the study and 11.9% in the recent year. When the rates based on the 1954 and 1974 assessments were compared to each other among males and females aged 40-49 and 50-59 years, the rate of mental morbidity remained at 9% for males aged 40-49 years irrespective of time of birth, whereas among the other age and sex groups the rates were lower for those recently born than those born earlier. As a consequence, by the end of the period of study middle-aged males and females displayed rates that were close together, while at the beginning they were far apart.

Finally, the findings of the Survey Research Centre’s National Sample Study were presented as mean levels of psychological distress and compared across time. The level of symptomatology increased significantly over time, with both males and females displaying this increase. While females reported higher levels of symptomatology than males in both years of the study, the difference between the two sexes fell by approximately 38% over time due to a rising level of symptomatology among the males.

In summary, each of these studies showed that females had higher rates of depression and/or anxiety or reported more psychological symptoms than males at the beginning of the investigation (mid-century); in three of the studies (Lundby, Stirling and Survey Research Centre’s National Sample) the rates and symptom reports persisted in being higher among females compared to males over the third quarter of the century. Evidence was provided that the difference between males and
females diminished over time, with two studies (Survey Research Centre’s National Sample and Lundby) emphasizing a rising rate among the males, one (Midtown Manhattan) a falling rate among the females, and the other (Stirling County) giving evidence of both. Each of these studies suggested that these changes might relate to historical influences on social roles.

Although these studies fulfilled the criteria of within-study consistency and approximated the criteria of between-study comparability, the reported trends are difficult to interpret due to differences in data collection (cohort follow-up versus repeated cross-sectional investigation), diagnostic concepts and methods of analysis. As to diagnosis, the two investigations carried out in the United States used diagnostically unspecified concepts derived from self-reported inventories (i.e., ‘general mental health’ in the Midtown Manhattan Study and ‘psychological distress’ in the Survey Research Centre’s National Sample Study). The Lundby Study reported only on episodes of ‘depression’ as identified by psychiatric interviewers making use of diagnostic principles that reflected the clinical procedures in a university department where they each had received training. Finally, in the Stirling County Study diagnoses of ‘depression and anxiety’ were made by a computer program that involved steps for essential features of low mood and/or apprehension, for number and frequency of symptoms associated with the two syndromes, for reduced functioning in the work role and for the duration of impairment.

The studies also varied in terms of analyses performed to present findings. Thus, the Lundby Study used sex- and age-standardized incidence rates per year, while the Stirling County Study compared sex- and age-standardized point prevalence rates using information from the early and the recent samples of the population. The Midtown Manhattan Study referred to the number of cohort members found to be in the mental morbidity category at the time of each interview; however, since the cohort was dispersed at the time of the last evaluation and was no longer representative of a geographically defined population, the recent rates lack the proper meaning of prevalence. Finally, the Survey Research Centre’s National Sample Study did not use epidemiologic rates, but reported frequency-weighted levels of symptomatology.

NEW-GENERATION STUDIES

In recent years, the situation has greatly changed. Large data sets now exist that derive from the application of standardized diagnostic interviews and specified diagnostic algorithms for mental disorders to clinical, family and general population samples. Furthermore, although temporal changes in psychiatric disorders should be ideally assessed through the longitudinal monitoring of the psychiatric state of successive birth cohorts, multivariate statistical techniques for analysing time-dependent data (e.g., life-table methods and survival analysis) allow for the investigation of temporal trends using data collected during cross-sectional investigations.
Temporal trends are variations in rates over time and can be analysed as age, period or cohort effects and their interactions. Age effects refer to the changes in age-specific rates of illness (usually the age of first onset of the disorder) either because individuals are more vulnerable at a given age or because age is a proxy for cumulative exposure. Period effects refer to the changes in rates of illness associated with a demarcated calendar period or starting at a set time for all individuals. Cohort effects refer to the changes in rates of illness among individuals sharing some continued temporal experience, as defined by the year or decade of their birth. Finally, there can also be interactions among these effects, since many time-limited causes of illness affect individuals differently depending on age, resulting in a age-period interaction.

In 1989, Klerman & Weissman reviewed 10 general population studies in the United States, Canada, New Zealand, Germany, Puerto Rico, Korea and Sweden as well as three studies of relatives of affectively ill probands, that were conducted within the previous decade using systematic diagnostic assessments. Ten of the studies found an increase in lifetime rates of major depression in the younger birth cohorts (usually those born after 1940), a decrease in lifetime prevalence in the older cohorts and higher rates among females compared to males. On the other hand, no increase in lifetime prevalence of major depression with age was found in three studies carried out in Puerto Rico, Korea and among Mexican-Americans living in Los Angeles.

A further advance in understanding these phenomena occurred with the application of the life-table methodology. The data provided by nine general population studies that used the Diagnostic Interview Schedule and the DSM-III criteria to determine cumulative rates of major depression by defined birth cohort and age of onset showed an overall trend for increasing rates of major depression over time at all sites, with this trend being entirely due to the effect of birth cohort rather than to the period. Similar patterns of higher rates of major depression in younger birth cohorts were also found in three family studies that derived data from first-degree relatives of probands with major depression or other affective disorders (Cross-National Collaborative Group, 1992).

Similarly, life-table survival methods were applied to the data collected in the United States during the NIMH-Epidemiologic Catchment Area Study to examine whether a shift in major depression to younger ages of onset or an increased prevalence in younger age periods were occurring for recent birth cohorts. The findings were consistent with a gradual shift to increased rates of major depression between the ages of 15 and 19 years for respondents born more recently (i.e., between 1953 and 1966) (Burke et al., 1991). Similarly, age at onset of first episode of major depression declined across successive birth cohorts in a clinical sample of children aged eight to 13 years (Kovacs & Gatsonis, 1994).

Growing evidence has been collected that temporal trends of major depression may vary according to sex of respondents and geographical location (Weissman et al., 1993). In the United
States, the cumulative lifetime rates of major depression were higher in females compared to males beginning with the 1935-1944 birth cohort and appeared to be so with each successive younger cohort. Age-, period- and cohort-models of these findings have been provided by Wickramaratne et al. (1989). For females, there was a sharp increase in the risk of major depression among individuals born during the years 1935-1944; subsequently, the rates increased very gradually with each successive birth cohort, resulting in a levelling off of the cohort effects. For males, there was an increase in the risk of major depression among individuals born during the years 1935-1944 and the risk continued to rise sharply in cohorts born during the years 1945-1954, after which there was a slight decrease in risk in the most recent birth cohort. Although the cumulative risk for major depression (from birth to any given age at interview) was consistently higher among females compared to males for each of the birth cohorts considered, the female-to-male differences seemed to be decreasing among the more recent birth cohorts. Finally, for both males and females, there was a steadily increasing period effect in the rates of major depression between the years 1960 and 1980.

The data from Edmonton differed from those collected in the United States. For females, the rates of major depression increased substantially between 1915 and 1925 and stabilized for individuals born after 1945; for males, the rates seemed to be increasing among individuals born in 1955 and later.

At Christchurch the overall cumulative rate of major depression was higher for females compared to males in the cohorts born before 1955, whereas the males born during the years 1955-1964 displayed a higher cumulative rate by age 25. For the same site, Joyce et al. (1990) reported that lifetime prevalence rates of major depression were higher among females compared to males, although the difference between the two sexes decreased in the younger birth cohorts. Furthermore, the males born in the years 1961-1968 had higher six-month prevalence rates of major depression compared to females, although the difference was not statistically significant.

Finally, in München, cumulative rates of major depression were substantially higher in females than in males and a greater increase in rates by age 25 in the 1925 and 1935 birth cohorts was observed in females compared to males.

The extent of the female preponderance in rates of major depression and its change over time have been investigated also in first-degree relatives of probands with affective disorders from the NIMH- Collaborative Study of the Psychobiology of Depression. In a sample of 2,289 first-degree relatives of 523 probands, Klerman et al. (1985) showed a progressive increase in rates of major depression in successive birth cohorts through the 20th century and a progressively earlier age at onset of depression in each birth cohort since the early decades of the century. For females the cumulative rates varied between less than 20% in individuals born before 1910 and more than 60% in those born after 1950; a similar trend was found for males, with rates ranging between less than
10% and around 40%. The magnitude of the male-to-female difference varied across the cohorts, with minimal male-to-female difference for more recent birth cohorts due to increasing rates among the males.

More recently, Warshaw et al. (1991) used graphs of conditional probabilities of first onset of major depression to describe and compare onset rates in six birth cohorts of first-degree relatives born after 1905 and assessed twice, six years apart. For both males and females there was a large increase in rates of first onset of major depression starting in the sixties and peaking in the mid seventies. This period effect had a differential impact on various age groups (with those who were youngest being the most strongly affected) and was true of all but the oldest cohort. These findings confirmed the conclusions of a previous work that was limited to siblings aged less than 50 years at time of interview in order to minimize the effect of memory loss and differential mortality rates associated with advanced age (Lavori et al., 1987). Moreover, Lavori et al. (1993) used the same data to assess whether secular trends in lifetime onset of major depression changed in size or timing in strata defined by several demographic characteristics of respondents (i.e., sex, religion, education, occupation, income, relationship to proband, parents’ occupation, being raised by both parents, parental separation/divorce, separation from parents before age 15, rural versus urban, location of research medical centre). With few exceptions (less educated and lower income groups; individuals whose parents’ marriage ended in separation/divorce), the cohort trend was consistent and clinically important in the strata that were inspected and showed an approximately linear increasing in time towards increasing rates and younger ages of onset of depression, suggesting either a uniform methodologic artifact or a causal agent with a general impact on all strata. As to gender, there was a slight tendency for females in each generation to have a steeper secular trend compared to males.

Finally, Leon et al. (1993) used the data from a family study to determine the effect of gender, age, period and cohort on major depression by age 35. For females, the prevalence of depression nearly doubled in each successive birth cohort, with rates peaking between adolescence and early adulthood: it was 12% in the 1915-1924 cohort and 61% in the 1945-1954 cohort. The pattern was similar but less exaggerated for males, with rates ranging between 6% in the 1915-1924 cohort and 31% in the 1945-1954 cohort. The gender gap did not diminish as the overall rates increased over time and females were almost twice as likely to become depressed by age 35 compared to males.

In summary, these findings suggest that an increase in rates of major depression over time has occurred both in community and clinical samples as well as in highly loaded families of affectively ill probands. 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 for females compared to males, although some studies suggest that the magnitude of the male-to-female difference is diminishing in recent years.
TEMPORAL TRENDS IN BIPOLAR DISORDER

Using the data collected during the NIMH-Epidemiologic Catchment Area Study, Lasch et al. (1990) reported that white males and females born after 1935 tended to exhibit a greater cumulative risk for mania compared to older birth cohorts. For black individuals, only suggestive trends were found due to small sample size: a sharp increase in the cumulative risk for mania was detected in the cohort born after 1955 for males and in the two cohorts born after 1945 for females. The birth-cohort effect was not explained by temporal trends of major depressive disorder, since it persisted when individuals with a lifetime history of major depression were excluded from analyses. Although the hazard rates for bipolar disorder were higher in the younger birth cohorts, there was no apparent shift to an earlier age at onset for those born most recently (Burke et al., 1991).

A birth-cohort effect was also found in a sample of 823 relatives of patients suffering from bipolar or schizoaffective disorder, with higher lifetime prevalence of bipolar plus schizoaffective disorder in the cohorts born since 1940. Life-table analysis showed a progressive increase in cumulative hazard for successive birth-cohorts, the cumulative hazard being greater for the cohorts born since 1940. No significant interaction of sex with the birth-cohort effect was detected (Gershon et al., 1987).

FACTORS THAT MAY INFLUENCE TEMPORAL TRENDS OF AFFECTIVE DISORDERS

It has been suggested that the temporal trends in rates of affective disorders are unlikely to be entirely due to artifacts for at least five reasons. First, when temporal trends in rates of major depression were investigated across several international sites using similar statistical models, long- and short-term cohort and period effects varied by site, suggesting that these variations were not entirely a consequence of methodological biases or a function of statistical power (Cross-National Collaborative Group, 1992).

Second, increasing birth cohort trends have been reported not only for affective disorders, but also for suicide, which is sometimes a consequence of severe depression, and for other disorders that may be related to affective illness, such as alcohol and drug abuse (Murphy & Wetzel, 1980; Burke et al., 1991).

Third, when temporal trends in cohort effects were investigated across different psychiatric disorders, the patterns were not similar for all psychiatric diagnoses, leading further support to the claim that artifacts alone cannot entirely explain these findings (Joyce et al., 1990; Burke et al., 1991).
Fourth, the differences in temporal trends that were consistently reported for males and females in both general population and family studies claim against a purely artifactual explanation, since differential survival and recall or diagnostic changes alone are unlikely to explain the different patterns observed in the younger cohorts (Wickramaratne et al., 1989).

Finally, age, period and cohort trends should be considered as accounting variables, that is markers or proxies for explanatory factors with which they covary. Once a temporal trend has been identified, it is necessary to search for the underlying processes and to speculate on the biological, social and/or historical factors that may account for it. Research is currently under way to elucidate the role of different factors in temporal trends of major depression. An explanation involving some gene-environment interaction is currently favoured, with an inherited vulnerability being more likely to be expressed in younger birth cohorts possibly due to the dramatic social changes affecting family structure, social roles, occupational patterns and urbanization after the Second World War (Gershon et al., 1987; Wickramaratne et al., 1989). Moreover, Silverstein & Perlick (1991) explored the hypothesis that gender differences in rates of major depression were greater among generations that reached adolescence when women had greater opportunities than their mothers for academic or professional achievement. Using an index of generational change in female college graduation rates as possible marker for discrepancy between female aspirations and fulfilment and for conflict regarding non-traditional gender roles, the Authors found that gender differences in rates of major depression varied over time and the preponderance of females was highest among individuals aged 40 years or older in the cohorts reaching adolescence during periods of increasing opportunities for female achievement. Among cohorts that reached adolescence during periods of stable or decreasing opportunities for women, gender differences in depression were not significant at any age.

Although these observations suggest that temporal trends in rates of major depression are not merely due to artifacts, efforts have been undertaken to assess also this possibility. Klerman & Weissman (1989) identified a number of methodological limitations that might be artifactual determinants of temporal trends, including: i) selective mortality and/or institutionalization; ii) selective migration; iii) changes in societal attitudes, diagnostic criteria, and professional practices; iv) recall and memory effects.

**i) Selective mortality and/or institutionalization**

If depression is associated with increased mortality, cohorts of older individuals would have lower rates of depression, since an increasing number of depressed members would be lost by death. This explanation does not seem to account entirely for temporal trends in depression. When Lavori et al. (1987) examined a homogeneous sample of relatives of affectively ill probands
under 50 years of age in order to minimize the confounding effect of differential mortality rates, a strong secular trend was found with a dramatic change in risk starting around the mid-sixties. The Authors pointed out that the effect of mortality would act by reducing the rates of major depression in the older cohorts, whereas the locus of the observed trend was in the surprisingly high rates among the younger cohorts, which were more than twice the rates of the older cohorts. In addition, strong birth cohort effects were found in school-age depressed children (Kovacs & Gatsonis, 1994) and in a large community sample of students aged 14 to 18 years (Lewinshon et al., 1993).

Similar considerations apply to institutionalization, which might remove individuals from older cohorts in the general population. However, long-term institutionalization for depression is probably low, especially in the countries placing greater emphasis on community care of patients with psychiatric disorders. Indeed, Simon & Von Korff (1992) showed that higher rates of mortality and/or institutionalization among older respondents with histories of major depression are unlikely to account for the differences in prevalence among birth cohorts. Using the data from the NIMH-Epidemiologic Catchment Area Study, the aggregate mortality from age 40 to age 70 among female community residents with major depression would have to be approximately 92% (i.e., an average mortality rate about eight times that in the general population) in order to account for the reported birth cohort differences in rates of major depression. Similar calculations demonstrated that, under the conservative assumptions of a doubling of mortality rate among community residents with history of major depression and no first depressive episodes after age 40 years, over 80% of the remaining residents with histories of depression would have to be institutionalized by age 70 to account for the reported birth cohort differences in rates of major depression.

**ii) Selective migration**

The increase in rates of depression among the younger cohorts might be due to geographic mobility, with younger individuals with depression moving into metropolitan areas, which are usually the catchment areas of the university-based research centres. This explanation seems unlikely, since temporal trends have been detected in several countries and in general population studies that sampled individuals living in urban, suburban and rural areas.

**iii) Changes in societal attitudes, diagnostic criteria, and professional practices**

Changes in the cultural meaning of depression might increase the likelihood for younger individuals to view periods of being upset as episodes of psychological problems compared to mem-
bers of older cohorts. It follows that differing orientations may influence the way individuals respond to questions covering criteria for major depression, with younger individuals being more likely than older subjects to respond positively to questions that relate to experiences which they previously characterized as 'depression'. Hasin & Link (1988) tested the effect of age on the recognition of major depression as a psychological or emotional problem, using the responses of community residents to a vignette describing a case of major depression according to the DSM-III. Only 11.5% of those aged 35 or younger failed to identify the case-vignette as a psychological or emotional problem as opposed to 33.9% of those aged 50 years or older, with the middle-aged respondents falling in between the percentages for the older and younger groups. Even when the relationship of age to recognition of major depression as a psychological or emotional problem was controlled for other variables (gender, education, marital status, religion, severity and type of impairment reported in the vignette) using logistic regression analysis, older respondents were less likely to characterize major depression in this way.

It follows that changing diagnostic thresholds or diagnostic concepts may affect temporal trends, since it can be expected that mainly what was conceptualized as depression in a given context in the past may be identified as depression in retrospect too. In this regard, an example is provided by the diagnosis of neurasthenia, which became increasingly popular at the end of the nineteenth century in developed countries. During the course of the twentieth century, 'out of the heterogeneous matrix of neurasthenia it was possible to identify a number of discrete psychiatric and medical disorders. What remained was a mixture of nonspecific, functional somatic symptoms and psychological distress, which became increasingly unfashionable and disappeared from the clinical scene' (Abbey & Garfinkel, 1991) to be partly resumed recently in the diagnosis of chronic fatigue syndrome.

An alternative explanation for the lower rates of depression among older cohorts may be that the complex symptom probing required by standardized diagnostic interviews exceeds the cognitive capacity of older individuals, resulting in systematic response bias. Using data based on the Diagnostic Interview Schedule, Knäuper & Wittchen (1994) found that older respondents reported lifetime depressive symptoms with the same frequency as younger respondents. However, older respondents more often attributed these symptoms to physical illness and this resulted in the exclusion of reported symptoms as a basis for the diagnosis of depression. A laboratory study revealed that 'working memory capacity' was a good predictor of this response behaviour, suggesting that attributing depressive symptoms to a physical illness might be a heuristic strategy to simplify complex recall and judgment during interview.

Whereas these findings provide support to the claim that temporal trends may be partly artifactual, different conclusions were reached by other investigators. Since the definition of major depression set out by the Schedule for Affective Disorder and Schizophrenia-Research
Diagnostic Criteria requires help-seeking for dysphoric symptoms, medicine use to relieve symptoms and/or impaired functioning, it might be expected that younger cohorts with greater psychological orientation may be more likely to define their depressive symptoms as being worth of professional attention, to receive more mental health care, to take medicine for these symptoms and/or to report that symptoms led to impaired functioning (Anthony, 1987). As a consequence, the inclusion of individuals suffering from milder depression in the younger cohorts might generate an apparent increase in rates. In order to test this possible artifact, Klerman (1987) examined the effect of varying the severity criteria applied to a sample of relatives of affectively ill probands. By whatever degree of stringency adopted - duration of symptoms, hospitalization, treatment with drugs or electroconvulsive therapy - the same temporal trends occurred with increasing rates in the younger cohorts.

Moreover, indirect evidence that younger individuals do not label milder symptoms as clinical depression is provided by two studies. Lavori et al. (1987) examined the duration of episodes and the rate of hospitalization across cohorts among individuals meeting criteria for major depression and found that younger cohorts did not significantly differ from older ones. In Italy, Bebbington & Tansella (1989) used psychiatric case register data to test predictions about the effect of age on the inception rates for affective disorders treated at in- and out-patient psychiatric services. Inception rates for affective psychosis tended to increase with age, although the effect was not statistically significant; rates for depressive neurosis also increased with age, reaching a plateau beyond age 45.

**iv) Recall and memory effects**

Poor reporting of symptoms or of age at onset by older respondents may be a potential bias in retrospective analyses of cross-sectional data. To circumvent the problem of recall in elderly individuals, Lavori et al. (1987) selected only subjects aged less than 50 years and still found significant cohort and period effects. Moreover, Coryell et al. (1992) examined relatives, spouses and controls of affectively ill probands on two occasions, six years apart, and individuals younger than 40 years were three times more likely than older subjects to develop depression, with females being approximately twice as likely as males to develop depression irrespective of age. Finally, birth cohort trends were detected among school-age children, in whom the time between the onset of depression and study participation was short (six months or less for 72% of the sample), thus minimizing memory bias and faulty dating of episodes (Kovacs & Gatsonis, 1994). Although these findings do not allow to conclude that depression is rare in older individuals, they suggest that cohort and/or age effects are 'real' and relevant.

Reliability of recall for self-reported age at onset of major depression in older respondents has been investigated by several studies and conflicting results were reported. Simon & Von Korff
(1992) found that episodes of major depression detected in the NIMH-Epidemiologic Catchment Area Study appeared to cluster in the 10 years prior to interview irrespective of respondent's age. It followed that, for older respondents, the period of greatest risk was after age 50 years. This clustering of onset in recent years was possibly due to underreporting of past depressive episodes or to 'telescoping' (i.e., the tendency to recall remote events as having occurred more recently). Similar conclusions were reached from the analysis of data from an international study of psychological problems in primary care: respondents of all ages typically reported first onset of depression during the last five years, with lifetime prevalence being only 2.02 times current prevalence (Simon et al., 1995). Finally, Prusoff et al. (1988) reported a satisfactory three-to-five year stability of the diagnosis of lifetime depression, although older individuals tended to increase age of first episode over the interviews.

Opposite results were reported by Farrer et al. (1989). Over one year, test-retest reliability for self-reported age at onset of major depression was significant across all age groups up to 80 years. However, when the interval between the current age and age at onset of the disorder was examined, older individuals tended to decrease their age at onset of depression at second interview.

More recently, Warshaw et al. (1991) compared the first set of data collected from relatives of affectively ill probands with the results of a second interview carried out six years apart by interviewers blind to the original assessment. A substantial number of lost or changed diagnoses was found; however, older respondents were as likely as younger ones to lose diagnoses, so differential dropping of diagnoses was not responsible for the observed differences in rates of major depression. In addition, for those individuals reporting a lifetime diagnosis of major depression at both interviews, the reported age at onset remained fairly stable (median change in age of zero years) and was not affected by the respondent's age at interview.

Finally, Gershon et al. (1987) investigated the potential artifact of recall by examining the year of onset of major affective illness (bipolar, unipolar and schizoaffective disorders) in different birth cohorts of relatives of bipolar and schizoaffective patients. An artifact would be expected if individuals had more selective recall for initial affective episodes that occurred recently than for those that occurred long ago. Indeed, no evidence was found for this artifact: for the oldest cohorts the sharpest increase in onset rates was observed decades prior to interviews and for recent years the cumulative risk function was somewhat flat, as expected in traditional descriptions of age at onset of affective illness; for younger birth cohorts, the slopes were steepest during recent years, again as would be expected from the known distribution of age at onset of these disorders.

In conclusion, the issue of temporal trends in affective disorders carries important implications for the understanding of factors that may influence onset and for planning clinical care and prevention. Longitudinal studies carried out in the past were based on less reliable and precise
methods to determine psychiatric diagnosis. More recent cross-sectional surveys have used advanced research methods, but are subject to the artifacts discussed above. At this point, the presence and size of recent increases in the risk of affective disorders cannot be defined. Overall, the findings available so far seem to suggest that several artifacts may explain a portion of the reported temporal trends in rates of affective disorders, but do not account for them entirely. Continued monitoring of the current prevalence rates of mental disorder and longitudinal studies with repeated assessment of the psychiatric state of successive birth cohorts are required to reach firm conclusions on this issue.

POSSIBLE FACTORS ACCOUNTING FOR GENDER DIFFERENCES IN AFFECTIVE DISORDERS

The gender difference in depression is limited in either childhood or old age and notable in middle life. The gender difference is due to rates for females rising sharply from childhood to adulthood and then declining somewhat in old age; by contrast, rates for males show a small rise in early adulthood, but are otherwise fairly stable throughout life (Jorm, 1987). Whereas the social and biological changes occurring at puberty have been advocated for the increase in rates of depression and associated gender differences at this time, the low rates of depression in the elderly are still debated and several explanations have been suggested, including inappropriate diagnostic criteria, higher mortality, a shorter duration of depressive episodes, a reduction of causal factors, and an increased resistance to depression and adverse experiences in late life (Henderson, 1994). Although several artifactual determinants have been proposed and investigated, the evidence available so far suggests that gender differences in rates of depression are real and occur in different ethnic groups and cultures (although best established in industrialized countries). Several hypothetical explanations for the preponderance of females in rates of depression have been suggested and are briefly reviewed here.

GENETIC FACTORS

McGuffin & Katz (1989) have reviewed the studies investigating the role of genetic factors in affective disorders. Four sources of data were used: family studies comparing illness rates within and between generations of a particular family, on the assumption that members of the same family share genes to varying degrees; twin studies comparing illness rates in monozygotic twins with those of dizygotic twins; cross-rearing studies; family linkage studies, with genetic markers being used to follow the cosegregation of a disease through several generations or in siblings. Although there is compelling evidence for a genetic influence operating in the transmission of affective disorders, relatively little is known about gender differences in modes of transmission in affective disorders.
A possible explanation for the female preponderance in depression rates is based on the location of dominant genes on the X-chromosome, with females being at greater risk for depression than males since they have two X-chromosomes. However, X-linkage seems to account for the transmission of only a small proportion of cases of familial affective disorder, especially where the probands have bipolar disorder. Indeed, Faraone et al. (1987) found no support for X-linked transmission in unipolar depression, whereas the fit of a nonfamilial model suggested that environmental factors contribute largely to the increased risk of major depression among females.

A second approach used a liability threshold model, with individuals manifesting the disorder when their liability exceeds a certain threshold. Using survival methods, Rice et al. (1984) found that females had a higher mean liability towards depression compared to males and this might be due to systematic biological and/or cultural differences, with parental transmission contributing to variation about the means. The same findings were incompatible with the hypothesis that females simply had a lower threshold for reporting depressive symptoms.

More recently, genetic imprinting with different phenotypes based on transmitting parents and clinical evidence of mitochondrial inheritance in affective disorders have provided further genetic models to explain the higher prevalence of affective disorders in females (Blehar & Oren, 1995).

Findings from general population and family studies suggest that rates of major depression have increased over the last century, with male-to-female differences becoming less pronounced in younger birth cohorts. Crow (1986) has offered an exclusively genetic interpretation of secular trends and suggested that a variable gene was involved, with new mutations between generations. The effect of these changes would be to reduce the age at onset of depression and increase the risk.

Despite these observations, it is widely believed that the etiology of depression cannot be explained by a simple genetic theory and some complex gene-environment interaction is operating (Klerman, 1988; McGuffin & Katz, 1989). It is likely that major depression is genetically heterogeneous, with possible subtypes related to single major loci as well as other polygenic forms. There may be gender differences in the inheritance of predisposing susceptibility traits, with environmental factors and cultural transmission from same-sex identification modulating the clinical manifestation of the disorder differently in the two sexes (Faraone et al., 1987; Blehar & Oren, 1995).
REPRODUCTIVE HORMONES

Puberty — Before adolescence, there is a slight tendency for boys to have more depressive symptoms than girls. Gender-related differences in depression are typically apparent by the age of 12 to 14, when girls' risk increases dramatically compared to boys', and higher female rates of depression are then reported throughout adult life. Since the change in risk for depression occurs at about the same time as puberty, it has been assumed that the physiological changes of puberty may be involved (Nolen-Hoeksema, 1987; Ruble et al., 1993; Nolen-Hoeksema & Gigrus, 1994).

Angold & Worthman (1993) reviewed several lines of research from child and adult psychopathology and endocrinology to understand the relationship between depression and the physiological changes of puberty. Although both chronological age and pubertal stage correlate with endocrine parameters, hormone levels explain on average less than half the variance in morphological pubertal development and growth in girls and about 80% in boys. It follows that morphological pubertal stage is an imprecise index of individual endocrine status, especially in females.

Research exploring both visible markers and endocrine status fairly consistently demonstrated that it is the endocrine, rather than the visible pubertal changes, that best predict the negative/depressive affect at puberty. However, the studies linking the development of depression in adolescence with the biological changes of puberty are few in numbers and inconclusive. For example, Nottelmann et al. (1990) showed no direct relationship between hormone levels and mood in girls. Moreover, in a longitudinal study of depression in adolescence female gender did not increase the risk for depression when psychosocial and life event variables were controlled for (Lewinshon et al., 1994).

Among possible reasons for the lack of conclusive results, Angold & Worthman (1993) pointed to the little attention paid to the complexity of the concept of 'pubertal status', which cannot be adequately described by a single parameter. The Authors suggested at least seven parameters of pubertal change that may be relevant for psychopathological research: the maturational pubertal status; the relative timing of puberty; the rate of change of pubertal status; the synchrony of pubertal change; the salience of the events of puberty; the personal meaning of the events of puberty; the cultural meaning of the events of puberty. A model was then proposed in which girls' increased vulnerability to depression depended on a complex interplay of biological, social and developmental factors. Indeed, Nolen-Hoeksema & Gigrus (1994) reviewed the evidence for specific etiological factors that may account for the emergence of gender differences in depression during adolescence. Included were personality characteristics of respondents (dependence on others for self-esteem; assertiveness; self-confidence), biological challenges of early adolescence (dysregulation of ovarian hormones; body dissatisfaction and its interaction with negative life events) and social challenges of early adolescence (sexual abuse; parental and peer expectations and attitudes). There appeared
to be many pathways leading to depression and it was unlikely that only one factor or even a small set of factors could account for the emergence of gender differences in depression in early adolescence. Gender differences in personality or behavioural style before early adolescence were risk factors for girls and interacted with the increased challenges and changes in the conditions of girls’ lives to make adolescent girls and then adult women more prone to depression than their male counterparts.

Menstrual cycle – The effects of the biological changes associated with the menstrual cycle on mood and behaviour may serve as a model to understand females’ greater vulnerability to depression (Parry, 1995). Endicott (1993) has reviewed and discussed the evidence suggesting that for a subset of women there is a relationship between phases of the menstrual cycle and increased vulnerability for the development of a new episode or exacerbation of an ongoing period of depression. Depressive syndromes of various severity are commonly described in women who are having regular menses and no other concomitant mental or physical disorders. The prevalence of dysphoric mood changes peaking in the late luteal phase of the cycle and of sufficient severity to meet DSM-III-R criteria for late luteal phase dysphoric disorder is approximately 4%, with further 30%-40% of women reporting symptoms of mild to moderate severity. Moreover, the late luteal phase of the cycle seems to be often associated with exacerbation of mood symptoms in women who suffer from ongoing dysthymic or major depressive disorders. Similarly, the risk for relapse after recovering from severe post-partum mood disorders has been found to be increased during the premenstrual phase of the cycle soon after the resumption of regular menses.

The mechanisms by which changes in reproductive hormones during the menstrual cycle may influence severe changes in mood are not yet established. Some investigators support the view that women have a specific vulnerability for mood disorders that is triggered by menstrual cycle biological changes acting as ‘kindling’ factors (Rubinow, 1992), whereas others believe that unstudied metabolites of the gonadal steroids may account for the appearance of dysphoric syndromes that are limited to the late luteal phase of the cycle (Backstrom, 1990). In this regard, Halbreich & Lumley (1993) provide experimental evidence that gonadal hormones may influence neurotransmitter functioning in multiple and diversified ways, including both genomic and non-genomic effects; as a consequence, they may alter sensitivity of synaptic connections and shift the balance between systems. More recently, Parry (1995) has suggested that the biological changes in the late luteal phase of the cycle may lead to alterations in circadian rythms, and indeed there is some evidence that gonadal steroids may influence circadian rythms in humans, with estrogens shortening the circadian period, advancing sleep onset, lengthening and consolidating sleep (Leibenluft, 1993).

In spite of these observations, the contribution of late luteal phase mood changes to greater vulnerability to depression in females is somewhat unclear. Although females have a greater life-
time risk of developing major depression compared to males, among those who have experienced at least one episode of major depressive disorder the risk of recurrence is apparently similar for males and females (Keller et al., 1992; Kessler et al., 1993), and this would not be expected if menstrual cycling was a major vulnerability factor.

Postpartum period – The contribution of postpartum psychosis to higher rates of mood disorders in females seems to be limited, since the disorder occurs in 1 to 2 per 1,000 deliveries (Kaplan & Sadock, 1991, p. 359). Although the sudden fall in estrogen and progesterone levels immediately after pregnancy may contribute to the disorder, treatment with those hormones has not proved successful (Kaplan & Sadock, 1991, p. 359). Similarly, there is little evidence of direct causal relationship between postpartum dysphoria and thyroid and adrenal changes during late pregnancy and the puerperium (Pedersen et al., 1993).

On the other hand, women do not appear to be at higher risk for non-psychotic depression postpartum than at other times (O'Hara et al., 1990). Moreover, Richman et al. (1991) have investigated the extent to which depressive symptomatology after childbirth differs in males and females. The transition to parenthood failed to show a female predominance in depressive symptomatology at two months after childbirth. Actually, females manifested a decrease in depressive symptoms and males a slight increase from the prepregnancy point. Although both sexes experienced a decrease in spouse support after childbirth, females received more social support from external sources and this partially accounted for the lack of a female predominance in postpartum depressive symptoms. Gender roles involving occupational identities in addition to family roles seemed to be protective, since lack of social support was more strongly associated with depression in homemakers compared to employed women or those on maternity leave.

Menopause – Despite earlier beliefs in involutional melancholia, current evidence suggests that menopause is not associated with an increased risk of affective disorders (Weissman, 1979). Actually, rates of depression tend to decrease in older individuals and gender differences narrow with age. Whereas dysphoric mood, sleep disturbance and somatic complaints increase in the perimenopause, the onset of menopause is associated with improvement of these symptoms (Avis et al., 1994).

Although estrogen therapy can alleviate the mood and somatic symptoms of the perimenopause and may be useful as adjunct to antidepressant treatment in some women with depression at the time of the perimenopause, no antidepressant effect has been found in women postmenopausally. Such effect would be expected if direct relationship between decrease in estrogen and mood disorders was indeed a major etiologic factor in this phase of female reproductive cycle (Blehar & Oren, 1995).
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 (Syvälath, 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 (Syvalathi, 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 together 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 devalued 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 surrounding 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 tricyclic 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**

<table>
<thead>
<tr>
<th>Author Country, time</th>
<th>Sample (N)</th>
<th>Age range (years)</th>
<th>Definition of onset of the disorder</th>
<th>Diagnostic criteria</th>
<th>Mean age at onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein et al. (1990a) USA, 1934-44</td>
<td>332 (total)</td>
<td>no age limits</td>
<td>Onset of psychotic symptoms or bizarre behaviour</td>
<td>DSM-III</td>
<td>24.3 27.9</td>
</tr>
<tr>
<td>Hambrect et al. (1992a) Bulgaria, Croatia, Germany, Netherlands, Switzerland, Sudan, Turkey 1976-80</td>
<td>277</td>
<td>233</td>
<td>15 - 44</td>
<td>Onset of symptomatology not more than 24 months prior to screening</td>
<td>ICD-9 Bulgaria Croatia Germany Netherlands Switzerland Sudan Turkey</td>
</tr>
<tr>
<td>Gureje (1991) Nigeria</td>
<td>125</td>
<td>89</td>
<td>10-54</td>
<td>First noticeable symptoms or maladaptive behaviour</td>
<td>RDC</td>
</tr>
<tr>
<td>Beiser et al. (1993) Canada, 1982-84</td>
<td>56</td>
<td>16</td>
<td>&lt; 54</td>
<td>a) First noticeable symptoms</td>
<td>DSM-III</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>b) Prominent psychotic symptoms</td>
<td></td>
</tr>
<tr>
<td>Härnner et al. (1993a,b) Germany, 1987-89</td>
<td>127</td>
<td>140</td>
<td>12 - 59</td>
<td>a) First sign of mental disorder b) First psychotic symptoms c) First acute episode</td>
<td>ICD-9</td>
</tr>
<tr>
<td>Faraone et al. (1994) USA, 1934-44</td>
<td>162</td>
<td>157</td>
<td>no age limits</td>
<td>First evidence of psychotic symptoms</td>
<td>DSM-III</td>
</tr>
</tbody>
</table>

* 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 restrictive 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

<table>
<thead>
<tr>
<th>Author Country, time</th>
<th>Sample (N)</th>
<th>Age range (years)</th>
<th>Definition of onset of the disorder</th>
<th>Diagnostic criteria</th>
<th>Mean age of onset Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Munk-Jørgensen (1986) Denmark, 1972-83</td>
<td>370</td>
<td>217</td>
<td>no age limits</td>
<td>First admission</td>
<td>ICD-8</td>
<td>27.4</td>
</tr>
<tr>
<td>Hafner et al. (1989) Denmark, 1976</td>
<td>527</td>
<td>642</td>
<td>12 - 59</td>
<td>First admission</td>
<td>ICD-8 Denmark#</td>
<td>33.0</td>
</tr>
<tr>
<td></td>
<td>Germany, 1978-80</td>
<td>160</td>
<td>176</td>
<td></td>
<td>Germany#</td>
<td>32.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>33.1*</td>
</tr>
<tr>
<td></td>
<td>Germany#</td>
<td>32.8*</td>
<td>37.7*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gureje (1991) Nigeria</td>
<td>125</td>
<td>89</td>
<td>10-54</td>
<td>First visit to hospital</td>
<td>RDC</td>
<td>23.5</td>
</tr>
<tr>
<td>Gozio et al. (1992) Italy, 1977-89</td>
<td>545 (total)</td>
<td>not available</td>
<td>First admission</td>
<td>DSM-III</td>
<td>22.8</td>
<td>24.9</td>
</tr>
<tr>
<td></td>
<td>Brasil, 1991</td>
<td>69</td>
<td>55</td>
<td></td>
<td>landing</td>
<td>22.9</td>
</tr>
<tr>
<td>Albus et al. (1994) Germany, n.r.</td>
<td>106</td>
<td>91</td>
<td>no age limits</td>
<td>First admission</td>
<td>DSM-III-R</td>
<td>31.2</td>
</tr>
<tr>
<td>Castle et al. (1994) UK, 1965-84</td>
<td>245</td>
<td>236</td>
<td>16 and older</td>
<td>First contact with psychiatric services</td>
<td>ICD-9</td>
<td>28.7</td>
</tr>
<tr>
<td>Susser et al. (1994) India, Colombia, Nigeria (developing countries, DC)</td>
<td>438</td>
<td>349</td>
<td>15-54</td>
<td>First treatment contact for a psychotic disorder</td>
<td>ICD-9 DC*</td>
<td>22.4*</td>
</tr>
<tr>
<td>Denmark, Ireland, Hawaii, Russia, Japan, UK, Czech Republic, USA (industrialized countries, IC)</td>
<td>25.5*</td>
<td>30.7*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Szymanski et al. (1995) USA, 1986-89</td>
<td>29</td>
<td>25</td>
<td>16-40</td>
<td>First hospitalization</td>
<td>RDC</td>
<td>22.0</td>
</tr>
<tr>
<td>Vazquez-Barquero et al. (1995a,b) Spain, 1989-90</td>
<td>43</td>
<td>43</td>
<td>15-54</td>
<td>First contact with psychiatric services</td>
<td>ICD-9 DSM-III-R</td>
<td>24.0</td>
</tr>
</tbody>
</table>

* 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 symptomatic features 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 symptomatic features (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.

NnNullain 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 preceding 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, Hafner 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 slightly 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

<table>
<thead>
<tr>
<th>Author</th>
<th>Country, time</th>
<th>Population (N) Age</th>
<th>Diagnostic criteria</th>
<th>Incidence rates (rate/100,000/year)</th>
<th>Male-to-female sex ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bland (1977)</td>
<td>Canada, 1972</td>
<td>21.9 million (t)</td>
<td>ICD-8 (c1,re)</td>
<td>29.0 26.0</td>
<td>1.12</td>
</tr>
<tr>
<td>Goldstein et al. (1984)</td>
<td>Australia, 1974-77</td>
<td>4.3 million (r) 0 - 54</td>
<td>DSM-III (c1,br)</td>
<td>23.9 20.3</td>
<td>1.18</td>
</tr>
<tr>
<td>NiNuallain et al. (1987)</td>
<td>Ireland, 1973-75</td>
<td>150,000 (t) 15 - 64</td>
<td>CATEGO/ICD-9 (op,re)</td>
<td>20.6 15.8</td>
<td>1.30</td>
</tr>
<tr>
<td>Hänfner et al. (1989)</td>
<td>Denmark, 1976</td>
<td>5.6 million (t) 12 - 59</td>
<td>ICD-8 (c1,re)</td>
<td>10.7 8.1</td>
<td>1.32</td>
</tr>
<tr>
<td>Germany, 1978-80</td>
<td></td>
<td>307,000 (t) 12 - 59</td>
<td>ICD-8 (c1,re)</td>
<td>32.1 32.3</td>
<td>0.99</td>
</tr>
<tr>
<td>Denmark, 1976</td>
<td></td>
<td>5.6 million (t) 12 - 59</td>
<td>ICD-8 (c1,br)</td>
<td>21.0 25.1</td>
<td>0.84</td>
</tr>
<tr>
<td>Germany, 1978-80</td>
<td></td>
<td>307,000 (t) 12 - 59</td>
<td>ICD-8 (c1,br)</td>
<td>35.9 36.9</td>
<td>0.97</td>
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<tr>
<td>Folinovgic et al. (1990a)</td>
<td>Croatia, 1980-84</td>
<td>4.6 million (t) no age limits</td>
<td>ICD-8 (c1,br)</td>
<td>23.0 21.0</td>
<td>1.10</td>
</tr>
<tr>
<td>Sartorius et al. (1986)</td>
<td>Denmark, 1978</td>
<td>314,344 (r) 15 - 54</td>
<td>ICD-9 (c1,br)</td>
<td>18.0 13.0</td>
<td>1.39</td>
</tr>
<tr>
<td>Jablensky et al. (1986)</td>
<td>India, rural, 1978</td>
<td>61,642 (r) 15 - 54</td>
<td>ICD-9 (c1,br)</td>
<td>37.0 48.0</td>
<td>0.77</td>
</tr>
<tr>
<td>India, urban, 1978</td>
<td></td>
<td>205,786 (r) 15 - 54</td>
<td>ICD-9 (c1,br)</td>
<td>34.0 35.0</td>
<td>0.97</td>
</tr>
<tr>
<td>Ireland, 1978</td>
<td></td>
<td>149,879 (r) 15 - 54</td>
<td>ICD-9 (c1,br)</td>
<td>23.0 21.0</td>
<td>1.10</td>
</tr>
<tr>
<td>Hawaii, 1978</td>
<td></td>
<td>210,020 (r) 15 - 54</td>
<td>ICD-9 (c1,br)</td>
<td>18.0 14.0</td>
<td>1.29</td>
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<tr>
<td>Japan, 1978</td>
<td></td>
<td>267,149 (r) 15 - 54</td>
<td>ICD-9 (c1,br)</td>
<td>23.0 18.0</td>
<td>1.28</td>
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<tr>
<td>UK, 1978</td>
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<td>202,214 (r) 15 - 54</td>
<td>ICD-9 (c1,br)</td>
<td>28.0 15.0</td>
<td>1.87</td>
</tr>
<tr>
<td>Russia, 1978</td>
<td></td>
<td>231,866 (r) 18 - 54</td>
<td>ICD-9 (c1,br)</td>
<td>25.0 31.0</td>
<td>0.81</td>
</tr>
</tbody>
</table>
Table XII - following

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

<sup>a</sup> first ever contacts  
<sup>b</sup> first admissions  
<sup>c</sup> any admission  
<sup>d</sup> any contact  
<br> = broad  
<sub>cl=clinical  op=operational  r=risk  re=restrictive  t=total</sub>
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>
<thead>
<tr>
<th>Author</th>
<th>Population (N)</th>
<th>Diagnostic criteria</th>
<th>Incidence rates (rate/100,000/year)</th>
<th>Male-to-female sex ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age</td>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>Munk-Jørgensen (1986)</td>
<td>3.9 millions (r)</td>
<td>ICD-8 (cl,re)</td>
<td>19.3</td>
<td>10.8</td>
</tr>
<tr>
<td>Denmark, 1972</td>
<td>&gt; 14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooper et al. (1987)</td>
<td>202,214 (r)</td>
<td>ICD-9 (cl,br)</td>
<td>28.0</td>
<td>14.0</td>
</tr>
<tr>
<td>UK, 1978-80</td>
<td>15 - 54</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iacono &amp; Beiser (1992)</td>
<td>757,510 (r)</td>
<td>DSM-III (cl,re)</td>
<td>6.8</td>
<td>2.0</td>
</tr>
<tr>
<td>Canada, 1982-84</td>
<td>15 - 54</td>
<td>ICD-9 (cl,re)</td>
<td>10.9</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RDC (cl,re)</td>
<td>7.6</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feighner (cl,re)</td>
<td>5.6</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carpenter (cl,re)</td>
<td>6.8</td>
<td>2.5</td>
</tr>
<tr>
<td>Nicole et al. (1992)</td>
<td>338,300 (t)</td>
<td>DSM-III-R</td>
<td>12.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Canada, 1983-87</td>
<td>no age limit</td>
<td>ICD-9 (br)</td>
<td>39.8</td>
<td>22.4</td>
</tr>
<tr>
<td>Castle et al. (1993)</td>
<td>171,000 (t) (1965)</td>
<td>ICD-9 (cl,br)</td>
<td>&lt;45 years</td>
<td>25.2</td>
</tr>
<tr>
<td>England, 1965 and 1984</td>
<td>118,000 (t) (1984)</td>
<td></td>
<td>&gt;45 years</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>total</td>
<td>19.2</td>
<td>17.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RDC (op,re)</td>
<td>&lt;45 years</td>
<td>16.4</td>
</tr>
<tr>
<td></td>
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<td>&gt;45 years</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>total</td>
<td>13.7</td>
<td>11.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DSM-III-R (op,re)</td>
<td>&lt;45 years</td>
<td>11.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;45 years</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>total</td>
<td>9.0</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DSM-III (op,re)</td>
<td>&lt;45 years</td>
<td>13.9</td>
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<td></td>
<td></td>
<td>Feighner (op,re)</td>
<td>&lt;40 years</td>
<td>14.8</td>
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<tr>
<td>Lynge &amp; Jacobsen (1995)</td>
<td>not reported</td>
<td>ICD-8 (cl,re)</td>
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<tr>
<td>Greenland, 1980-83</td>
<td>&gt;14</td>
<td></td>
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<tr>
<td>Hickling &amp; Rodgers-Johnson (1995)</td>
<td>2.46 millions (t)</td>
<td>ICD-8 (op,re)</td>
<td>30.4</td>
<td>16.6</td>
</tr>
<tr>
<td>Jamaica, 1992</td>
<td>15-54</td>
<td></td>
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</table>

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 (Strömgren, 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, Strömgren (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, Strömgren and collaborators (Strömgren, 1938; Bøjholm & Strömgren, 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 form 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

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

* 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>f</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 Portoguaro, 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

<table>
<thead>
<tr>
<th>Author Country</th>
<th>Sample (N)</th>
<th>Diagnostic criteria</th>
<th>Length of follow-up</th>
<th>Outcome criteria</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td>(years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jablensky et al. (1986) Colombia, Czechoslovakia, Denmark, India, Ireland, Japan, Nigeria, UK, USA, USSR</td>
<td>1,078 (total)</td>
<td>1,078 (total)</td>
<td>ICD-9 CATEGO</td>
<td>2</td>
<td>- 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.</td>
</tr>
<tr>
<td></td>
<td>first-ever contacts</td>
<td>first-ever contacts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hambrecht et al. (1992a) Bulgaria, Croatia, Germany, Netherlands, Sudan, Switzerland, Turkey</td>
<td>277</td>
<td>233</td>
<td>ICD-9</td>
<td>2</td>
<td>Mental, working and treatment status were rated jointly to assign each patient to a single outcome category</td>
</tr>
<tr>
<td></td>
<td>onset within 24 months</td>
<td>onset within 24 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scottish Schizophrenia Research Group (1988; 1992) Scotland</td>
<td>49 (total)</td>
<td>49 (total)</td>
<td>Clinical</td>
<td>2</td>
<td>Readmissions and/or positive/negative symptom, Readmissions and/or positive/negative symptom,</td>
</tr>
<tr>
<td></td>
<td>first admissions</td>
<td>first admissions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watt et al. (1983) Shepherd et al. (1985) UK</td>
<td>61</td>
<td>60</td>
<td>PSE/ICD-8</td>
<td>5</td>
<td>Clinical outcome according to PSE</td>
</tr>
<tr>
<td></td>
<td>48 first admissions</td>
<td>48 first admissions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO (1979) China, Colombia, Czechoslovakia, Denmark, India, Nigeria, UK, USA, USSR</td>
<td>543 (total)</td>
<td>543 (total)</td>
<td>ICD-9 CATEGO</td>
<td>2</td>
<td>Time spent in psychotic episode</td>
</tr>
<tr>
<td></td>
<td>consecutive admissions or referrals</td>
<td>consecutive admissions or referrals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leff et al. (1992) Colombia, Czechoslovakia, Denmark, India, Nigeria, UK, USA, USSR</td>
<td>270</td>
<td>261</td>
<td>ICD-9 CATEGO</td>
<td>5</td>
<td>Time spent in psychotic episode</td>
</tr>
<tr>
<td></td>
<td>consecutive admissions or referrals</td>
<td>consecutive admissions or referrals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thara &amp; Rajkumar (1992) India</td>
<td>36</td>
<td>31</td>
<td>Feighner</td>
<td>5</td>
<td>Time spent in psychotic state and pattern of course as classified in the Psychiatric and Personal History Schedule</td>
</tr>
<tr>
<td></td>
<td>first admissions</td>
<td>first admissions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breier et al. (1992) U.S.A</td>
<td>30</td>
<td>28</td>
<td>not specified</td>
<td>6 (mean)</td>
<td>Positive/negative symptoms, neuroleptic exposure, suicide attempt, disorders as major depression, alcoholism, substance abuse</td>
</tr>
<tr>
<td></td>
<td>chronic patients</td>
<td>chronic patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lynge &amp; Jacobsen (1995) Greenland</td>
<td>24</td>
<td>13</td>
<td>ICD-8</td>
<td>7</td>
<td>Presence and severity of mental symptoms, neurotic or personality disfunction</td>
</tr>
<tr>
<td></td>
<td>first admissions</td>
<td>first admissions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salokangas (1983) Finland</td>
<td>39</td>
<td>61</td>
<td>Clinical</td>
<td>7.5</td>
<td>Neurotic and psychotic symptoms</td>
</tr>
<tr>
<td></td>
<td>first admissions</td>
<td>first admissions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>53</td>
<td>31</td>
<td>Clinical</td>
<td>8</td>
<td>Neurotic and psychotic symptoms</td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>M</td>
<td>Scale</td>
<td>T Score</td>
<td>Indicator</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----</td>
<td>----</td>
<td>--------</td>
<td>---------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Tsai &amp; Kue (1992) China</td>
<td>234</td>
<td>172</td>
<td>Clinical</td>
<td>10</td>
<td>Psychiatric symptoms (mood, thought processes, delusions, hallucinations, cognitive functions)</td>
</tr>
<tr>
<td>Thara et al. (1994) India</td>
<td>40</td>
<td>36</td>
<td>ICD-9</td>
<td>10</td>
<td>PSE symptoms, percentage of time spent in psychotic state</td>
</tr>
<tr>
<td>Tsai &amp; Wong (1991) China</td>
<td>189</td>
<td>141</td>
<td>ICD-9</td>
<td>5</td>
<td>Psychiatric symptoms (thought disorder, affective blunting, depression, delusions, hallucinations)</td>
</tr>
<tr>
<td>Affleck (1976) Scotland</td>
<td>86</td>
<td>67</td>
<td>Clinical</td>
<td>12 (mean)</td>
<td>Clinical status and drug regime</td>
</tr>
<tr>
<td>Bland &amp; Orn (1978) Canada</td>
<td>22</td>
<td>21</td>
<td>ICD-9</td>
<td>14</td>
<td>Psychiatric condition and intellectual deficit</td>
</tr>
<tr>
<td>Schmid et al. (1991) Germany</td>
<td>209</td>
<td>293</td>
<td>Clinical</td>
<td>22.4 (mean)</td>
<td>Psychopathological remission</td>
</tr>
<tr>
<td>Harding et al. (1987a,b) USA</td>
<td>81</td>
<td>87</td>
<td>DSM-III</td>
<td>32 (mean)</td>
<td>Clinical status according to the Global Assessment Scale</td>
</tr>
<tr>
<td>Ciompi (1980) Switzerland</td>
<td>92</td>
<td>197</td>
<td>Clinical</td>
<td>39.6 (median)</td>
<td>Clinical 'end state' (indifference, motor stereotypes, affective withdrawal, thought disturbances, abulia, hypocondria, mutism, negativism)</td>
</tr>
<tr>
<td>Loyd et al. (1985) USA</td>
<td>103</td>
<td>97</td>
<td>Feighner</td>
<td>2.4 35-40</td>
<td>Psychiatric symptoms</td>
</tr>
</tbody>
</table>

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**

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

<table>
<thead>
<tr>
<th>Author Country</th>
<th>Sample (N)</th>
<th>Diagnostic criteria</th>
<th>Length of follow-up (years)</th>
<th>Outcome criteria</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sample selection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jablensky et al. (1985) Colombia, Czechoslovakia Denmark, India, Ireland Japan, Nigeria, UK, USA, USSR</td>
<td>1,078 (total)</td>
<td>First-ever contacts</td>
<td>ICD-9 CATEGO</td>
<td>2</td>
<td>Time in hospital</td>
</tr>
<tr>
<td>Test et al. (1990) U.S.A</td>
<td>82</td>
<td>40</td>
<td>&lt; 12 months in psychiatric and penal institutions</td>
<td>RDC DSM-III</td>
<td>2</td>
</tr>
<tr>
<td>Watt et al. (1983) UK</td>
<td>61</td>
<td>60</td>
<td>48 first admissions</td>
<td>PSE/ICD-8</td>
<td>5</td>
</tr>
<tr>
<td>Breier et al. (1992) U.S.A</td>
<td>30</td>
<td>28</td>
<td>chronic patients</td>
<td>not specified</td>
<td>6</td>
</tr>
<tr>
<td>Number of admissions</td>
<td>F equal to M</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saikokangas (1983) Finland</td>
<td>39</td>
<td>61</td>
<td>first admissions</td>
<td>Clinical</td>
<td>7.5</td>
</tr>
<tr>
<td>53</td>
<td>31</td>
<td>first admissions</td>
<td>Clinical</td>
<td>8</td>
<td>Time in hospital</td>
</tr>
<tr>
<td>Angermeyer et al. (1990) Germany</td>
<td>137</td>
<td>141</td>
<td>first admissions</td>
<td>DSM-III-R</td>
<td>6-11</td>
</tr>
</tbody>
</table>
Gender Differences in the Epidemiology of Affective Disorders and Schizophrenia

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Diagnosis</th>
<th>Follow-Up</th>
<th>Outcome 1</th>
<th>Outcome 2</th>
<th>Outcome 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein (1988) USA</td>
<td>58</td>
<td>32 early phase of the disorder</td>
<td>DSM-III</td>
<td>10</td>
<td>Number of hospitalizations</td>
<td>F better than M</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Length of hospital stay</td>
<td>F better than M</td>
<td></td>
</tr>
<tr>
<td>Riecher et al. (1990) Denmark</td>
<td>527</td>
<td>642 first admissions</td>
<td>ICD-8</td>
<td>10</td>
<td>Number of readmissions</td>
<td>F equal to M</td>
</tr>
<tr>
<td>Tsai &amp; Kua (1992) China</td>
<td>234</td>
<td>172 first admissions</td>
<td>Clinical</td>
<td>10</td>
<td>Number of readmissions</td>
<td>F equal to M</td>
</tr>
<tr>
<td>Munk-Jørgensen (1986) Denmark</td>
<td>370</td>
<td>217 first admissions</td>
<td>ICD-8</td>
<td>10,7-11,7</td>
<td>Time spent in in- or day-patient settings</td>
<td>F better than M</td>
</tr>
<tr>
<td>Tsai &amp; Wong (1991) China</td>
<td>189</td>
<td>141 first admissions</td>
<td>ICD-9</td>
<td>5</td>
<td>Number of rehospitalizations</td>
<td>F equal to M</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>Number of rehospitalizations</td>
<td>F equal to M</td>
</tr>
<tr>
<td>Afteck (1976) Scotland</td>
<td>86</td>
<td>67 chronic patients</td>
<td>Clinical</td>
<td>12</td>
<td>Number of rehospitalizations</td>
<td>F equal to M</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eaton et al. (1992) Australia</td>
<td>7,271 total</td>
<td>ICD-8</td>
<td>20</td>
<td>Risk of rehospitalization</td>
<td>F equal to M</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>13,870 total</td>
<td>DSM-</td>
<td>7.5</td>
<td>Risk of rehospitalization</td>
<td>F equal to M</td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>9,250 total</td>
<td>ICD-8</td>
<td>20</td>
<td>Risk of rehospitalization</td>
<td>F equal to M</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>532 total</td>
<td>ICD-8</td>
<td>20</td>
<td>Risk of rehospitalization</td>
<td>F equal to M</td>
<td></td>
</tr>
</tbody>
</table>

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; Amaddeo 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 psychophysio-
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 pathophysiological 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 or contact with psychiatric services, since previous psychotic episodes and institutionalization 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 prepon-
derance, 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 psycho-
pathological syndromes, such as psychopathy and sexual deviations, as well as the excess of females

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 schizo-
phrenia. 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 fac-
tors 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 distribu-
tions 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, exogeneous 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.
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120
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