

## **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 and 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**

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

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 Munich; 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

Author Country, time	Instruments Diagnostic criteria	Age range (years)	Sample (N)	Site	Mean age at onset	
					Males	Females
Weissman et al. (1988) USA, 1980-83	DIS DSM-III	18 and older	5,034	New Haven	22.4	20.3
			3,481	Baltimore	23.4	27.7
			3,004	St. Louis	19.6	19.7
			3,921	Piedmont	21.6	20.6
			3,132	Los Angeles	16.6	19.1
Bland et al. (1988c) Canada, 1980-83	DIS DSM-III	18 and older	3,258	Edmonton	20.5	20.0

## **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 Munich, 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.

### ***j) 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 & Girgus, 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 & Girgus (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 rhythms, and indeed there is some evidence that gonadal steroids may influence circadian rhythms 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 preparenthood 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 involitional 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).