Where Are the Women in First-Episode Studies of Schizophrenia?

by William G. Iacono and Morton Belser

Abstract

Almost all investigations of first-episode schizophrenia uncover more male than female subjects. Two possible explanations for this observation are (1) first-episode investigations suffer more or less consistent methodologic biases or (2) the incidence of schizophrenia is higher in men than in women. Data from the markers and predictors of schizophrenia (MAP) project, a community-based first-episode study, permitted an investigation of the two alternatives. The results suggest that neither recruitment nor diagnostic vagaries explain the excess of males. Instead, the MAP results, consistent with other recent investigations, suggest that the incidence of schizophrenia is lower in women than in men. The findings are consistent with the literature on gender differences in schizophrenia, which indicates that schizophrenia in women is a less severe disorder than in men. The report includes recommendations for future first-episode investigations to ensure adequate representation of women.

Most studies of first-episode schizophrenia report a preponderance of males; in many instances the male to female ratio among study participants exceeds 3 to 1. There are two possible explanations for this observation. First, investigations of first-episode schizophrenia may suffer more or less consistent methodologic biases. Alternatively, the long-held assumption that the incidence of schizophrenia in males and females is equal may be incorrect. In this article, we focus on the methods and findings of the markers and predictors of schizophrenia (MAP) project in order to investigate the two alternatives. Because schizophrenia is a rare occurrence, a true community incidence study will probably never be possible. The MAP study, using an "administrative incidence" approach, avoids some of the biases inherent in using a single class of facilities such as public hospitals, which may be more likely to attract males, or of reliance only on institutionalized patients who are more likely to have severe forms of disorder. This methodologic advance over older studies offers advantages in the investigation of gender differences in incidence.

The MAP Project

Identifying Cases. For approximately 2 years, beginning in 1982, we attempted to recruit every resident aged 15 to 54 in a catchment area centered on Vancouver, British Columbia (approximate population = 480,000) who experienced a first episode of functional psychosis. To avoid the possible bias associated with recruiting patients from a single facility (Cohen and Cohen 1984), we spread a wide recruitment net. The referral network comprised the agencies at which individuals experiencing a first episode of psychosis might appear. Included were psychiatric hospitals, community mental health centers, university and college counseling services, psychiatrists in private practice, social service agencies, and a random sample of one-sixth of the general practitioners in the catchment area. About 18 percent of the referrals were from sources other than inpatient hospital services, in-
including 2 percent from hospital outpatient services, 9 percent from community mental health centers, and 7 percent from private practitioners and community agencies. The subject recruitment strategy and the basic design of the project were similar to those used in the World Health Organization (WHO) Collaborative Study on Determinants of Outcome of Severe Mental Disorders (Sartorious et al. 1986).

To ensure that all potentially psychotic subjects were identified, we supplied our referral sources with a purposely broad definition of psychotic behavior (experiencing hallucinations or delusions; displaying grossly disorganized behavior; showing marked loss of drive, social withdrawal, severe excitement, overwhelming anxiety or fear, or gross self-neglect). All prospective subjects, including doubtful cases, were given a thorough clinical assessment that included administration of the Present State Examination (PSE; Wing et al. 1974), review of clinical charts, and interviews with family members and friends. These data were pooled at case conferences attended by project support staff to arrive at a “best estimate” diagnosis (Leckman et al. 1982).

We used five different diagnostic systems to classify participants: DSM–III (American Psychiatric Association 1980), ICD–9 (World Health Organization 1978), Research Diagnostic Criteria (RDC; Spitzer et al. 1978), the 12-point flexible system of Carpenter and colleagues (1973) with a score of 6 or greater defining schizophrenia, and the Washington University criteria (Feighner et al. 1972). To optimize accurate diagnostic assignment, the individual diagnostic criteria and symptoms associated with the psychotic disorders listed in each system were reviewed for each patient to ascertain whether or not each was present or satisfied. Then the diagnostic rules specified for each system were used to generate a diagnosis. In order to adapt the loosely characterized ICD–9 psychotic disorders to this system, we used a checklist of symptoms and diagnostic criteria derived from the ICD clinical constructs and followed the diagnostic guidelines described in the ICD–9 manual.

Although all studies of first-episode schizophrenia must grapple with what constitutes a first occurrence of the disorder, few investigators clearly specify their operational definition of first episode. Often it means the first time a patient has been hospitalized with a diagnosis of schizophrenia, but this definition leaves open the possibility of a past psychiatric hospitalization with some other diagnosis or of previous outpatient care with the same or a different diagnosis. Under these circumstances, a question can be raised about whether the identified episode is truly the first occurrence of schizophrenia or an exacerbation of schizophrenia already expressed. To circumvent this problem requires reliance on retrospectively collected data of questionable quality to determine whether current difficulties actually constitute the beginning of a schizophrenic psychosis. Also, studies that rely on a hospital diagnosis of schizophrenia to identify cases make false positive errors and miss outpatient cases and patients who are experiencing a first episode of schizophrenia but who are diagnosed at the source as having a different disorder.

It quickly became apparent to us that it was difficult to determine whether a patient’s current problems constituted a first episode and that we could be missing first-episode patients who had schizophrenia but who were misdiagnosed. We handled these problems by recruiting all individuals showing psychotic behavior, regardless of their diagnosis at the referral source.

In addition, our definition of first episode required that our subjects have no past history of treatment with antipsychotic, anomic, or antidepressant medications. Past pharmacotherapy can be determined objectively but has the disadvantage that, because some potential participants may have received these drugs for problems unrelated to their current psychosis, they would be excluded from the study even though their current symptoms reflect first expression of a psychotic disorder. As indicated below, it does not appear that our results were seriously affected by the exclusion of such cases.

Characterization of the Sample. We identified a total of 318 potential study participants, 193 of whom consented to a PSE interview. Of this group, 18 were eliminated from the study because they were judged to be either nonpsychotic or not in their first episode. The study sample thus contained 175 subjects. Of the 125 individuals who did not consent to a PSE, 31 terminated contact with their referral source before we could contact them. These were individuals who, for example, kept one outpatient appointment but never returned or who were admitted to the hospital but left against medical advice after a few days. Such persons would not be available for study at any site to any group of investigators conducting an incidence study. The remaining 94 individuals refused to be interviewed and thus would be also unavailable for study at any site where it was necessary to obtain informed consent from research partici-
pants. It is not possible to compare our refusal rate with that of other investigators because refusal rates are not reported in the relevant literature. Although the 125 nonparticipants were not evaluated by our research staff, we were able to obtain their age, sex, and referral source diagnosis.

**Distribution of Males and Females Across Diagnostic Groups.** Table 1 indicates the number of participants and percent male by diagnosis and diagnostic system (see also lacono and Beiser, in press). The diagnostic systems are ordered in the table so that the largest number of schizophrenia-related subjects is identified by the system on the left and the smallest number by the one on the right. As the table illustrates, there was an excess of males with schizophrenia and schizophrenia-related diagnoses, and the proportion in excess was about the same for all the classification systems regardless of the method used to classify subjects. For this table, schizophrenia-related diagnoses (schizoaffective and schizophreniform disorder) were combined with schizophrenia. However, the proportion of males with these related disorders did not differ from that among those with schizophrenia alone. Likewise, for mood disorders the sex distribution did not differ across bipolar manic and psychotically depressed patients.

At first glance, the mood disorder data may seem unusual in that major depression is much more common in women than men. We did not replicate this finding here. However, to the best of our knowledge, our study is the first to focus on mood disorder cases whose very first expression of the disorder was accompanied by psychotic features. Individuals with a history of nonpsychotic mood disorder who developed their first psychotic symptoms in a later episode would be excluded from our study, as would those with first episodes of mania or depression that were not psychotic. We are not aware of any data indicating what sex ratio to expect in first-episode psychotic mood disorder as we have defined it.

Another way to evaluate the sex distribution data is to calculate the incidence of schizophrenia and other disorders in the study sample. Catchment area residents between the ages of 15 and 54 constituted the population at risk which, according to Canadian census figures, consists of 241,217 males and 239,185 females. The number of cases of disorder per year was computed by dividing the number of cases by the number of years over which cases were recruited. This result was divided by the number of people at risk to yield an estimate of 1-year incidence per 100,000 population. The results of this analysis for the schizophrenia-related disorders is presented in figure 1. These data are consistent with those presented in table 1: Regardless of which classification system was used, the incidence of schizophrenia was greater in males than in females.

**Possible Limitations to the MAP Findings.**

Noninclusion of females. Could our findings be due to the fact that nonparticipants were more likely than participants to be females with schizophrenia? To answer this question, we identified all the nonparticipants with a referral source diagnosis of schizophrenia-related disorder and calculated the incidence separately for males and females. As the rightmost bar in figure 1 indicates, the incidence for males was again substantially greater than that for females. Figure 1 shows that the ratio of males to females among nonparticipants diagnosed with a schizo-

### Table 1. Number of subjects and percent male by diagnostic category within each diagnostic system

<table>
<thead>
<tr>
<th>Disorder</th>
<th>RDC</th>
<th>ICD-9</th>
<th>DSM-III</th>
<th>12-Point</th>
<th>Feighner</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>118</td>
<td>73(^1)</td>
<td>114</td>
<td>75(^1)</td>
<td>91</td>
</tr>
<tr>
<td>Mood psychosis</td>
<td>45</td>
<td>56</td>
<td>51</td>
<td>53</td>
<td>73</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
<td>67</td>
<td>10</td>
<td>70</td>
<td>11</td>
</tr>
</tbody>
</table>

Note.—RDC = Research Diagnostic Criteria (Spitzer et al. 1978); ICD-9 = International Classification of Diseases (World Health Organization 1978); DSM-III = Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 1980); 12-Point = flexible system of Carpenter et al. 1978; Feighner = Washington University Criteria (Feighner et al. 1972). Proportion of males differs significantly from proportion of females at \(^1p < 0.001\), \(^2p < 0.01\), and \(^3p < 0.05\). Schizophrenia includes schizoaffective and schizophreniform disorder; Mood psychosis includes bipolar disorder and major depression (manic-depression in ICD-9); and Other includes delusional and reactive psychoses for ICD-9 and DSM-III and unspecified psychosis for the RDC, 12-point, and Feighner systems.
Figure 1. The incidence of schizophrenia-related disorders as a function of classification approach

Incidence per 100,000

RDC  ICD-9  DSM-III  12-pt  Felghner  Nonpart

<table>
<thead>
<tr>
<th>Classification Approach</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDC</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>ICD-9</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>DSM-III</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>12-pt</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Felghner</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

RDC = Research Diagnostic Criteria (Spitzer et al. 1978); ICD-9 = International Classification of Diseases (World Health Organization 1978); DSM-III = Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 1980); 12-pt = 12-point flexible system of Carpenter et al. 1973; Felghner = Washington University Criteria (Felghner et al. 1972); Nonpart = nonparticipants given a clinical diagnosis of schizophrenia at the referral source.

The incidence of schizophrenia-like disorder was smaller than that for participants. However, there was no statistically significant difference between the proportion of males and females among these nonparticipants and the proportions among participants diagnosed as having schizophrenia using any of the five diagnostic approaches.

These referral source diagnoses are no doubt less reliable than the MAP research diagnoses, but there is no reason to believe that they would be differentially accurate across the sexes. Because both ICD-9 and DSM-III were in use in Canada during the early 1980s, we can add these cases to the project participants identified as having schizophrenia by these classification systems to estimate the incidence of schizophrenia for this study. Adding the nonparticipants with schizophrenia-related diagnoses to the participants with corresponding DSM-III diagnoses yields incidence figures of 15.76 for males and 7.26 for females. Doing the same for ICD-9 yields rates of 19.85 and 9.42, respectively. In either case, the male:female risk ratio (RR) exceeds 2.0, indicating that the incidence of schizophrenia is more than twice as high in the male population.

Noninclusion of older subjects. Various researchers have shown that males are more likely than females to succumb to schizophrenia at an early age (e.g., Angermeyer and Kühn 1988; Loranger 1984). Usually the incidence of schizophrenia is characterized as higher in males under 30 and in females over 40, so that over the lifespan the incidence of schizophrenia in females eventually matches that of males (Flor-Henry 1985). Because an age ceiling of 54 was imposed on recruitment, we may have eliminated older women with a first episode of schizophrenia. Although we cannot rule out this possibility, the data do not support this notion. Contrary to DSM-III and Feighner criteria, we did not adopt an age limit beyond which schizophrenia was not diagnosed. Nevertheless, no patient in this study with a diagnosis of schizophrenia under any system was over the age of 45. Using the DSM-III, RDC, or Feighner classification systems, there was no schizophrenic patient over the age of 37. It seemed unlikely that there would be an age gap from 9 (for ICD-9) to 19 years (for RDC and Feighner) containing no first-episode schizophrenic patients but that after the age of 54 the rate would suddenly pick up, yielding a substantial number of older women. It could also be the case that older psychotic women were identified, but that they were disproportionately represented as nonparticipants. To evaluate this possibility, we compared the average age of participating and nonparticipating women. The results showed little evidence that more older women were nonparticipants. Participating women had a mean age of 25.7 (standard deviation [SD] = 8.9) while nonparticipants were on average only about 1 year older (mean = 27.1, SD = 9.0).

It should be noted that investigations showing the incidence of schizophrenia to be high in women over 40 tend to include individuals with delusional disorders in their count. Because these psychoses have a peak age of onset over 40 and are more common in women (Kendler 1982; Widerlov et al. 1989), the inclusion of delusional patients will
artificially boost the number of older persons, especially women, who are counted as having schizophrenia. It is also the case that older women diagnosed with schizophrenia express more delusional symptomatology than either men or younger women (Forrest and Hay 1971; Harris and Jeste 1988), a fact that raises the possibility that many older women might be better classified as having delusional psychosis. Danish data presented by Häfner and colleagues (1989) illustrate how adding paranoid patients to the schizophrenia tally can affect incidence sex ratios. The male:female RR for ICD-defined schizophrenia was 1.32. If paranoid states and reactions are added to the total, the resulting RR becomes 0.86. Given that the diagnosis of schizophrenia in older people, especially women, is unsettled and historically controversial (Kay 1975; Harris and Jeste 1988) and that most incidence studies count paranoid disorders as instances of schizophrenia, it is not clear to what extent older females should be represented in the MAP schizophrenia sample.

Exclusion due to prior pharmacotherapy. Our operational definition of a first psychotic episode led to the exclusion of individuals who had been treated with antipsychotic, antidepressant, or antimanic drugs. Perhaps some of our potential female participants were experiencing their first episode but were disqualified because they received these medications at some earlier point in their lives for an unrelated psychiatric problem. If this were the case, we would expect a more balanced sex ratio among the nonparticipants because, although these individuals were judged by the referral source to be making their first contact for psychotic symptoms, they were not screened for prior drug treatment. That the male:female ratio was still about 2:1 for all the nonparticipants renders this explanation unlikely.

More males at risk than females. Regardless of the diagnostic system we used, at least 71 percent of the subjects considered to have schizophrenia were under the age of 26 at the time of their first episode; this suggests that the 16- to 25-year-olds were at greatest risk for schizophrenia. If 16 to 25 years before the initiation of the MAP project there was a “baby boom,” then the at-risk population could have a disproportionately large sample of individuals entering the age of greatest risk. Because the age of onset for schizophrenia is earlier for males than for females and because we recruited cases over only a 2-year period, we could have identified many of the males, who are at greater risk during this time, while missing many of the females who would have entered their greatest risk period after our recruitment of patients was completed. However, data from the 1981 Canadian census revealed that there were actually 4 percent fewer Vancouver residents in this age group than in the 25- to 34-year-old population. Thus, if the age of the population introduced a bias, it was one that might have led to our identifying more females than males as having schizophrenia.

Definition of schizophrenia excludes females. Lewine and colleagues (1984) compared the male:female ratio when six different sets of criteria were used to diagnose schizophrenia. They found schizophrenia to be approximately equal in men and women when the disorder was broadly defined, but when the 12-point, RDC, and Feighner systems were used, more males than females had a diagnosis of schizophrenia. Although our findings were similar to those of Lewine and colleagues (1984) for these three classification systems, when we used broad criteria for schizophrenia (i.e., ICD-9), which identified almost three times as many schizophrenic subjects as the Feighner criteria (see table 1), schizophrenia remained a disorder affecting mostly males. Hence, it seems unlikely that we found an excess of males with schizophrenia simply because our diagnostic approach was overly narrow. Other recent investigations that have examined either the incidence of schizophrenia (Cooper et al. 1987; NiNullain et al. 1987) or the diagnosis of schizophrenia generally (Copolov et al. 1990) as a function of diagnostic breadth have also failed to find that narrowing the criteria necessarily leads to an excess of males. In their eight-center incidence study, Sartorius and colleagues (1986) also did not find such an effect. Comparing the restrictive research definition of schizophrenia to the broad, “clinical” ICD-9 definition reveals no pattern indicating that the narrower criteria differentially reduced the number of female cases. The average RRs across centers were the same (about 1.2) under the broad and narrow definitions.

Summary. In any one study, we can never be certain that case finding is complete and unbiased. In the MAP project, for instance, it is conceivable that there were some physicians in private practice treating first-episode psychotic women who neither became part of the mental health care system nor were referred to the project. It is also possible that some women in the catchment area had a mild, nondebilitating first episode of psychosis but that these women never came into contact with the health care system. Such cases would have been unavailable to us.
However, because they would also presumably be unavailable to any investigation, their possible existence would not seem to be a major deficiency peculiar to our project. As best we can determine, we were able to identify virtually everyone, whether or not they became MAP participants, who made a first contact with the helping agencies and individuals in our referral network. There is little evidence that we missed a large number of prospective female participants. Our results thus suggest that the incidence of schizophrenia is substantially higher in men than women.

Incidence of Schizophrenia in Males and Females

Problems With Incidence Studies.

The notion that schizophrenia affects both sexes equally is derived mostly from pre-1975, European studies with no consistent pattern of sex differences (Dohrenwend et al. 1980; Babigian 1985; Jablensky 1986; Hafner 1987). Most of these studies relied on first-hospital-admission statistics, which, as noted above when discussing what constitutes a first episode, can be problematic. They may also be unsatisfactory because they miss noninstitutionalized cases, are dependent on regional factors such as what constitutes the need for hospitalization and the availability of beds, and can count itinerant cases more than once, a phenomenon that has been used to argue that the high rate of schizophrenia observed in Ireland is an artifact of how first-admission statistics are kept (Cabot 1990). Another limitation, noted previously, is that these studies count delusional disorders as schizophrenia.

In general, there is wide variability even among neighboring European countries in what constitutes a clinical diagnosis of schizophrenia (Saugstad 1985; Jablensky 1986), a fact that makes it difficult to evaluate European first-admission statistics. It is not clear how patients diagnosed 15 or more years ago would be classified today or how the results of these investigations would differ had structured interviews and operationalized diagnostic rules been used. The decline in the incidence of schizophrenia reported by several investigators (see Der et al. 1990 for a review), could indicate that schizophrenia is becoming less common. However, these observations could also reflect changes in the administration of mental health care services (Weeke et al. 1986), such as the increased use of community care resources and other factors that affect the case count, and changes in diagnostic practices (Munk-Jorgensen 1987), including the greater likelihood that first-episode cases will be diagnosed as having affective psychoses (Saugstad 1989). Whatever the reason for the drop in the rate of schizophrenia, the fact that it has dropped suggests that we should be wary of using old data to estimate the incidence of schizophrenia in males and females today. Given this background, it is not surprising that Sartorius and colleagues (1986) stated that the question about the rates of occurrence of schizophrenia in "different age groups and in the two sexes . . . has not been answered satisfactorily" (p. 909).

Recent Studies. There is ample evidence from a wide variety of sources indicating that the incidence of schizophrenia may be higher in males, with male:female RRs often exceeding 1.5. The most recent report from the United States (Babigian 1985) found higher rates for males in New York State in both 1970 (RR = 1.51) and 1975 (RR = 1.74). Bland (1984) has reported a similar RR (RR = 1.41) in Canada for 1978.

Various European studies, all published since 1986, indicate a greater male risk for schizophrenia. These studies all use first-admission data and were likely to count instances of delusional disorder as schizophrenia. Munk-Jorgensen's (1986) Danish incidence data yielded a RR of 2.29. Reporting Danish as well as German data, Hafner and colleagues (1989) found a higher incidence of schizophrenia in Danish (RR = 1.32) but not German (RR = 0.99) men. Strømgren (1987) noted that despite a decrease in the overall incidence of schizophrenia in Denmark from 1970 to 1984, the number of males succumbing to schizophrenia was consistently higher than the number of females during each calendar year. Based on Croatian first-admission statistics covering 1980 to 1984, Folnegovic and colleagues (1990) reported a slightly higher incidence rate for men (RR = 1.10). NiNulain and colleagues (1987) reported first-admission data for all of Ireland for 1983 indicating a high male incidence rate (RR = 1.50). In Great Britain, Orbell and colleagues (1990) found a higher male incidence rate in Northern Ireland (RR = 1.56), Scotland (RR = 1.44), and England (RR = 1.43). Other investigators from the United Kingdom have generated similar results, using first-admission data for England in 1984 (RR = 1.29; Castle and Murray 1991) or for Birmingham from 1980 to 1983 (RR = 1.49; McGovern and Cope 1987).

Several recent investigations, rather than relying on hospital diagnoses, have interviewed prospective cases to determine incidence rates. Wattie and Kedward (1985) relied on the RDC to classify cases and found that 60 percent of their sample from...
four Canadian provinces was male. NiNULLain and colleagues (1987) interviewed patients in three Irish counties using the PSE and found, depending on the breadth of the diagnostic criteria, that 59 to 68 percent of their cases were male. In Nottingham, Cooper and colleagues' (1987) incidence data for DSM-III schizophrenia yielded a RR of 2.43.

Also in Nottingham, in a study of the incidence of schizophrenia in Afro-Caribbeans, Harrison and colleagues (1988) and Chen and colleagues (1991) found that males made up from 57 to 60 percent of their samples, a finding that was similar to that of McGovern and Cope (1987), who also found a high incidence of schizophrenia among men in this ethnic group. Finally, Sartorius and colleagues (1986) reported higher male incidence rates in six of eight sites when restrictive diagnostic criteria were applied, with RRs at those six sites ranging from 1.22 to 1.80.

Summary. While older investigations have not indicated a consistent difference in the incidence of schizophrenia in males and females, the vast majority of recent studies concur with the MAP findings that males appear to be more prone to schizophrenia. Incidence studies based on first-admission statistics have yielded RRs ranging from 0.99 to 2.76 (median = 1.47). Those investigations in which research staff interviewed patients and assigned research diagnoses show similar RRs; the sole study that applied DSM-III criteria showed a RR of 2.43. In those investigations that do not report incidence figures, it is evident that about 60 percent of the first-episode cases are male. These findings suggest that males are more likely to develop schizophrenia than females. This conclusion, in turn, indicates that first-episode studies can be expected to contain a preponderance of males.

Gender and Schizophrenia

There are many ways in which men and women with schizophrenia differ. In general, women seem to have a more benign, less deteriorated form of schizophrenia. The age at onset is later in women (Angermeyer and Kühn 1988; Häfner et al. 1989), and women are more likely to display affective symptoms and persecutory delusions (Goldstein and Link 1988; Goldstein et al. 1990). By contrast, men are more apt to have negative symptoms (Pogue-Geile and Zubin 1988; Salokangas and Stengård 1990). The course of schizophrenia is likely to be milder in women. They show less premorbid impairment (Zigler and Glick 1986) and a better outcome (Goldstein 1988), including shorter hospital stays (Angermeyer et al. 1990) and a better response to neuroleptics (Seeman 1986).

Although findings indicating sex differences for biological variables related to schizophrenia are less consistent than those regarding clinical characteristics, it may also be the case that men and women with schizophrenia tend to be biologically different, with men having a more neurological, less genetic form of schizophrenia. For example, men with schizophrenia have been found to have more morphological deviations on magnetic resonance imaging and computed tomographic scans (Andreasen et al. 1990; Lewine et al. 1990; Gur et al. 1991), more birth-related problems (Foerster et al. 1991), and a lower family morbidity risk for schizophrenia (Goldstein et al. 1990).

Such findings have led various investigators to posit that there may be differences in the etiology of schizophrenia for men and women. Because there is substantial overlap in the characteristics of men and women with schizophrenia, it would be unreasonable to assume that men and women have two different disorders. Rather, the prevalence of two different forms of schizophrenia may vary between the sexes (Goldstein et al. 1990). Saugstad (1989) has advanced a neurodevelopmental model of schizophrenia in which she argues that sex differences in schizophrenia are due in part to the late sexual maturation of males, placing them at greater risk for this disorder. In this model men and women express similar forms of schizophrenia because the sexes overlap in the onset and rate of maturation. Goldstein and colleagues (1990) interpreted their findings, some of which are summarized in the preceding paragraphs, as consistent with the notion that men are at higher risk for a neurodevelopmental form of schizophrenia. More recently, Castle and Murray (1991) have hypothesized that there are two separate schizophrenic disorders, one more common in young men, the other in older women. They postulate that more men than women have a form of schizophrenia that is due to a neurodevelopmental anomaly. Lewine (1981, 1988) has proposed that the later onset of schizophrenia in women could imply the influence of suppressor or protective factors that impede or mitigate schizophrenia. Seeman (1982) reached a similar conclusion and advanced a biological model in which female sex hormones are viewed as the protective factor mediating the expression of schizophrenia.

Whether sex differences in schizophrenia reflect differences in the
pathological processes underlying schizophrenia or reflect variations in disorder manifestation moderated by sex cannot be resolved here. However, if we are observing differences in the phenotypic expression of a single disorder, then it would be reasonable to expect the incidence of schizophrenia to be equal across the sexes. If a different pathophysiology were at work in men and women, an equal rate of expression would seem to require an unlikely coincidence. The data and hypotheses regarding sex differences reviewed above, indicating that women experience a milder form of schizophrenia, that women may be more neurologically vulnerable to the disorder, and that protective factors may diminish the likelihood of schizophrenia in women, all suggest that the incidence of schizophrenia should be lower in women. Hence, the findings that schizophrenia occurs at a lower rate in women are congruent with the literature on gender differences for this disorder and provide further evidence supporting neurodevelopmental hypotheses for gender differences.

Conclusions and Recommendations

There are special reasons for using first-episode patients in schizophrenia research. They allow us to address hypotheses concerning response to treatment, course, and outcome uncontaminated by the effects of chronicity. They also provide an opportunity to examine correlates of schizophrenia that are more likely to precede or be a manifestation of the disorder than to be a consequence of having been treated for and living with the disorder. As such, they provide an invaluable opportunity to address a wide variety of etiological hypotheses, some of which may help explain gender differences. Unfortunately, few of the studies of gender differences involve first-episode patients. Most involve chronic or mixed samples and retrospective data collection. Although there is a great need for first-episode investigations focused on sex effects, as this review indicates, tackling gender differences in first-episode studies may be complicated by a relative paucity of female participants. Various factors may combine to decrease the availability of women with schizophrenia. These include the possibilities that a narrow definition of schizophrenia lessens the probability that psychotic women qualify for this diagnosis, that women have a milder form of disorder that makes it less likely they will be available at institutions from which subjects are recruited, and that investigators may focus on younger subjects recruited during the age range when the RR clearly favors men. In addition, our MAP results and recent epidemiological investigations indicate that the incidence of schizophrenia may be lower in women. Those planning first-episode projects would be prudent to anticipate a lack of women, especially because gender is likely to be an independent variable of interest in their research. To convince critics that their study sample is representative of women with schizophrenia, investigators should note the demographic characteristics of referring and nonreferring agencies to determine whether their referral sites are representative with respect to this variable. It will also be important to keep track of potential recruits who decline participation to determine if there is a sex bias between refusers and participants. In an effort to obtain more women, investigators may extend the period of time during which women are taken into their study or target referral settings that may attract more female patients (e.g., private hospitals, outpatient clinics).

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