Sampling Biases in Studies of Gender and Schizophrenia

by Elaine F. Walker and Richard R.J. Lewine

Abstract

Gender differences in schizophrenia are of great interest to researchers, and some have recently concluded that female patients suffer from a more benign form of the illness. However, the research findings do not support this conclusion consistently, and some reports suggest greater impairment in female patients. In this article, we discuss the potential effects of sampling biases on the findings from studies that compare male and female patients. More specifically, we assume that females do manifest a less severe schizophrenic illness than males, and we propose that sex differences in severity thresholds for voluntary and involuntary treatment are contributing to inconsistencies in the research findings. Some other sources of sampling bias that may influence findings on gender differences are also discussed.

Gender differences in schizophrenia are receiving increasing attention from researchers; a recent edition of Schizophrenia Bulletin (Vol. 16, No. 2, 1990) was devoted solely to this topic. Many investigators believe that gender differences in the course and phenomenology of schizophrenia may hold important clues to the etiology of the disorder (Lewine 1981; Seeman and Lang 1990). However, although certain gender differences are found consistently, others are not. In this article, we offer a model to explain how gender differences and sampling methods might interact to influence research findings. Several writers (e.g., Goldstein and Tsuang 1990; Nasrallah et al. 1990) have discussed the idea that sampling may account for the discrepancies among the findings on gender differences in schizophrenia. But so far no one has offered specific hypotheses about how this might occur.

There are three findings on gender differences in schizophrenia that are reported frequently and with such consistency that they are viewed as fact by most in the field. First, research has shown consistently that females have a later age of onset than males (see Lewine 1981, 1988). This later age holds for a variety of indices, including age at onset of symptoms, age at first diagnosis, and age at first hospitalization. Second, female schizophrenic patients are more likely than male patients to marry and have children (Walker et al. 1985; Pancheri et al. 1990; Test et al. 1990). Third, females show better premorbid adjustment than males (see Lewine 1981, 1988). It should be noted that these three findings are based on investigations that used large-population data bases, as well as small-sample studies.

Some other gender differences in schizophrenia, which have been studied less extensively, are also pertinent to our proposed model. One set of findings concerns sex differences in behavior. Male schizophrenic patients are more likely than females to show antisocial behavior (Haas et al. 1990) and to have police contact and criminal records (Test et al. 1990). Also, among patients classified as criminally insane, females have less extensive and less serious...
criminal histories than men (Zonana et al. 1990). Given these sex differences in patient behavior, it is not surprising that family members' perceptions of male and female patients differ. Relatives view female patients as more helpless, withdrawn, and depressed than male patients (Chu et al. 1989). In contrast, male patients are viewed by their families and treatment providers as more aggressive and threatening than female patients (Lewis et al. 1990).

As to patient's self-perceptions, there is evidence that female schizophrenic inpatients are more likely than male inpatients to view themselves as mentally ill, to acknowledge their symptoms, and to view themselves as needing treatment (Walker and Rossiter 1990). It has also been shown that female patients are more compliant with treatment, and there is evidence that they may be more responsive to neuroleptics (Seeman 1983; Zito et al. 1985). These findings are consistent with evidence that, across levels of illness severity, women are more likely than men to report psychological discomfort and to seek treatment (Weyerer and Dilling 1991). They are also consistent with the finding that females with psychotic disorders are less likely to be involuntarily committed than their male counterparts (Kastrup 1987).

However, there are several areas of controversy in the literature on sex differences in schizophrenia. Some researchers have found greater evidence of brain abnormalities in males than in females (Takahashi et al. 1981; Williams et al. 1985; Andreasen et al. 1986; Flaum et al. 1990; Lewine et al. 1990; Gur et al. 1991). Other studies have shown that males have greater impairment in cognitive performance (Haas et al. 1991) and a poorer long-term prognosis than females (Haas et al. 1990; McGlashan and Bardenstein 1990; Test et al. 1990). These findings are highly consistent with the demonstrated gender differences in age at onset, premorbid functioning, and postmorbid interpersonal functioning, in that they all suggest a more virulent form of the illness in males.

In contrast, other researchers have reported that female patients show more brain abnormalities (Nasrallah et al. 1990), greater neuropsychological deficit (Hoff et al. 1991; Perlick et al. 1991), and no advantage over males in long-term prognosis (see Angermeyer et al. 1990). A few studies have reported no gender differences in brain abnormalities (Weinberger et al. 1979; Golden et al. 1980; Jeste et al. 1982). With respect to symptoms, several investigators have found more negative symptoms in males than females (Haas et al. 1989; Goldstein et al. 1990), whereas others report no significant gender differences in symptoms (Josiassen et al. 1990).

In summary, the empirical data on age at onset of illness, premorbid history, marital functioning, and neuroleptic treatment response suggest that females suffer from a more benign schizophrenic syndrome than do males. This conclusion has led many investigators to predict that females will manifest other signs of a more benign syndrome, such as less negative symptomatology, brain abnormality, and cognitive deficit, and a better long-term prognosis. If it is true that female schizophrenic patients are, on average, less severely disturbed than males (i.e., if the distributions of illness severity differ in central tendency, as illustrated in figure 1), this sex difference should be apparent in most representative samples of patients. Further, the selection of samples of male and female patients based on a uniform severity cutoff criterion at any point on the continuum, from mild to extreme, should yield the same sex difference, although the sex ratio would be expected to vary as a function of the cutoff. Thus, we might expect females to show less impairment than males whether the sample is comprised solely of first-admission or chronic patients.

However, when gender comparisons are reported in the literature, the results do not consistently support the conclusion that male schizophrenic patients are more impaired than female patients. Although many studies reveal greater impairment in males, others find no sex differences, and some find greater impairment in females. Thus, sex differences are sometimes attenuated and, in other cases, reversed. The hypothetical model we propose here attempts to account for the discrepancies in the findings; specifically, we try to explain how sex differences might be attenuated or even reversed as a function of sampling procedure. It is assumed that the mean level of illness severity is indeed greater for males than females, but that sampling determines whether this difference is detected.

Our model makes the following basic assumptions about the provision of treatment. First, we assume that both the patient's self-perceptions and the perceptions of others partially determine whether, at any point in time, a patient is in treatment, particularly in an in-patient setting. It is important to emphasize that the term involuntary is used here to refer to treat-
Figure 1. Hypothesized frequency distributions of illness severity and thresholds for voluntary and involuntary treatment for male and female schizophrenic patients.

Severity of Disturbance Continuum

Treatment that results primarily from external pressure by others, with the most extreme case being commitment through the legal system. Thus, involuntary treatment or hospitalization occurs when others perceive the patient as unmanageable or dangerous to self or others. Self-referred or voluntary treatment results primarily from the patients' subjective feelings of distress, rather than external pressure. Although we make the general distinction between voluntary and involuntary treatment for purposes of explicating our model, we acknowledge that treatment often results from a combination of both external pressure and subjective distress, and sometimes results from factors unrelated to the psychopathology.

Of course, treatment facilities vary in the proportion of voluntary and involuntary patients they serve. In general, more restrictive settings will have a higher proportion of schizophrenic patients who are receiving involuntary treatment. Thus, State hospital inpatient wards serving chronic populations would be expected to have the highest proportion of involuntary patients, whereas private settings and outpatient settings would have the lowest proportion.

As previously stated, a gender difference has been found in the likelihood of involuntary treatment, especially hospitalization. The key assumption of our model is that this difference is due not only to differences in illness severity, but also is a function of real sex differences in behavioral and sociodemographic characteristics. Specifically, we propose that the severity of illness threshold for involuntary treatment is lower for male schizophrenic patients than for females. In other words, given a male patient and a female patient with comparable illness severity, the male will be more likely to undergo involuntary treatment. This is because males are viewed as more threatening and unmanageable, and they are less likely to be married and to have children. (It is assumed that mental health professionals will be less inclined to hospitalize patients who are married and have children.) On the other hand, we assume that the severity of illness threshold for voluntary treatment will be lower for females than for males because females are more likely than males to acknowledge and report their psychological distress and seek treatment.

The implications of these assumptions for sampling and research results are illustrated in figure 1. The frequency distributions for severity of illness in males and females are presumed to be overlapping, but males show a higher mean. However, because
the threshold for involuntary treatment is hypothesized to be much lower for males than for females, the mean level of illness severity for involuntarily treated females is higher than for their male counterparts. Consequently, as the proportion of involuntary patients in the study population increases, the likelihood that females will show greater impairment than males also increases. In contrast, because the threshold for self-referral is assumed to be lower for females than males, the mean level of illness severity for voluntary females will be lower than for their male counterparts. Thus, as the proportion of voluntary patients in the study population increases, the likelihood that the females will show less impairment than the males also increases. Contradictory patterns of findings can therefore be explained by positing sex differences in severity thresholds for treatment.

It should be noted that the only critical assumption made in figure 1 is that the mean severity of illness for males exceeds the mean for females. We have used a normal distribution of illness severity in our model solely as a convenience. It may be that the distribution of illness severity is skewed or multimodal for both sexes or that there are gender differences in the characteristics of the distribution. Gender differences in the skew or modality of the distribution of illness severity could exacerbate or mitigate the effects discussed here.

The proposed model also makes some predictions that have not yet been systematically tested. First, the ratio of male to female patients would be expected to increase as a function of the proportion of involuntarily treated patients in a study population. Second, the difference in illness severity between voluntary and involuntary patients should be greater for females than for males. Further, the nonrepresentativeness of a sample of female patients will be reflected in an earlier age-at-onset and lower rate of marriage than are characteristic of the general population of female schizophrenic patients. Testing these hypotheses will be relatively straightforward with large samples.

We should also note that there are other factors that might serve to distort findings on gender differences in schizophrenia. It has been shown that male patients have a higher mortality rate than female patients, especially from suicide (Johns et al. 1986; Test et al. 1990). If, as the findings of Test and colleagues (1990) suggest, the excess male mortality occurs more often in young patients who are at the upper end of the severity distribution, the male-to-female ratio at the upper end would be reduced. The effects of this selective loss on sampling would be to reduce the proportion of severely disturbed males in all patient populations, but particularly in those State inpatient facilities that house older, chronically ill patients. Also, the rate of incarceration is higher for male patients, and this further reduces the proportion of severely ill males in psychiatric facilities. Finally, several studies have shown that after index admission, female patients show a lower rate of rehospitalization than males (for a review, see Angermeyer et al. 1990). Thus, studies that draw samples from inpatient facilities may tend to include females at the more extreme end of the severity continuum for their sex.

Unfortunately, the vast majority of published studies on schizophrenia do not report either the characteristics of the population from which their sample is drawn or the determinants of treatment for subjects in their sample (e.g., proportion of voluntary versus involuntary patients). Consequently, we cannot subject our assumptions to direct, empirical tests. However, we believe it is reasonable to assume that samples drawn from State hospital inpatient facilities, especially the chronic wards, will contain a higher proportion of involuntary patients than will samples drawn from outpatient or private inpatient facilities. Given this assumption, the extant literature offers some support for our model.

Studies that find female patients to be more impaired than males, or not significantly different, tend to be based primarily on samples of chronic patients drawn from State hospital facilities (e.g., Israel and Johnson 1956; Lehrman 1960; Guggenheim and Babigian 1974; Weinberger et al. 1979; Golden et al. 1980; Jeste et al. 1982; Childers and Harding 1990; Hoff et al. 1991; Perlack et al. 1991). In contrast, studies that find males to be significantly more impaired draw samples primarily from outpatient populations or from private treatment facilities (e.g., Takahashi et al. 1981; Williams et al. 1985; Andreasen et al. 1986, 1990; Lewine et al. 1990; McGlashan and Bardenstein 1990; Test et al. 1990; Gur et al. 1991; Haas et al. 1991). The exceptions to these tendencies involve samples with characteristics that suggest they are nonrepresentative. For example, Nasrallah and coworkers (1990) conducted a magnetic resonance imaging (MRI) study of 41 male and 15 female schizophrenic outpatients and
found more brain abnormalities in the females. However, the sample showed no sex difference in age at onset of illness, and the females were significantly older than the males. The authors suggest that the sample may have been biased toward greater severity of illness in the female patients and less severity in the males.

Of course sampling biases do not arise solely from the nature of the population from which the sample is drawn. Another source of bias is the refusal of some patients to participate in the study. The demonstrated sex difference in treatment compliance suggests that there may be a sex difference in agreement to participate in research. Although we are not aware of any published data on this issue, these differential refusal rates could influence findings on gender differences in schizophrenia. Walker and Rossiter (1990) found that schizophrenic males were more likely than females to deny their illness, and this sex difference was most pronounced for the more severely disturbed patients. Thus, it may be that the refusal rate is highest for severely ill male patients, and that sex differences are attenuated in the resultant sample.

Inclusion and exclusion criteria for subject selection may also differentially influence male and female participation. Pharmacologic studies can be especially problematic in this regard. Consider first that many such studies exclude women who could get pregnant. Postmenopausal women or those with tubal ligation are eligible, but constitute an atypical sample. Second, some medication trials target patients who are “treatment refractory,” while others target individuals known to respond to standard antipsychotics. If there is, indeed, a gender difference in response to medication, with women responding better than men, then the ratio of men to women will vary considerably from one type of drug study to another. It is quite common for schizophrenia studies to be embedded in medication trials; unfortunately, it is also common to omit any details about drug trial inclusion and exclusion criteria. Interpretation of gender differences (or their absence) in such circumstances is difficult at best.

We have speculated on some potential sources of sampling bias that may account for inconsistencies among findings on gender differences in schizophrenia. It is anticipated that future research will shed light on the validity of the ideas put forward here. In the next generation of gender studies, it will be important for researchers to provide data on the demographic and clinical characteristics of their sample and the population from which it is drawn. Two elements are especially important with respect to the points raised here: the sex ratio of the population from which the sample is drawn and the sex ratio of the sample participating in the study. These two pieces of information will make it possible to determine the extent to which the study population is representative of the general population of schizophrenic patients and the extent to which the sample is representative of the study population. Under these circumstances, the generalizability of reported findings on gender differences can be evaluated, and we will be better able to separate sampling artifacts from gender phenomena.

References


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**The Authors**

Elaine F. Walker, Ph.D., is Professor of Psychology, Emory University, and Richard R.J. Lewine, Ph.D., is Professor of Psychiatry, Emory University School of Medicine, Atlanta, GA.