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Sex and Schizophrenia: Effects of Diagnostic Stringency, and Associations with Premorbid Variables

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In a case-record study, all first-contact patients with non-affective functional psychosis from a defined area over 20 years were diagnosed according to operational criteria of varying stringency and emphasis, and incidence rates for each set of criteria determined by sex and age at onset; data on premorbid adjustment were also analysed by sex and age at onset. The overall first-contact incidence of non-affective functional psychosis was approximately equal in men and women; however, the ratio of male to female incidence rates rose progressively when RDC (1.2), DSM-III-R (1.3), DSM-III (2.2), and Feighner (2.5) criteria for schizophrenia were applied. Schizophrenia was most common in young males and least common in older males, with females occupying an intermediate position. Schizophrenia in young males, particularly when stringently defined, was especially likely to be associated with single status, poor work and social adjustment, and premorbid personality disorder. The results suggest that schizophrenia syndrome is heterogeneous, and young males are especially prone to a severe neurodevelopmental form of illness associated with premorbid deficits.

In recent years, considerable attention has been focused on gender differences in the epidemiology, clinical expression, and outcome of schizophrenia (Seeman, 1982; Lewine, 1988; Goldstein & Tsuang, 1990). The best-replicated finding is that males have a tendency to an earlier onset of illness than females (Lewine, 1981; Angermeyer & Kuhn, 1988; Lewine *et al*, 1981). This finding is independent of diagnostic system (Shimizu *et al*, 1988; Goldstein *et al*, 1989), and is true irrespective of how onset of illness is defined (Loranger, 1984; Riecher *et al*, 1989).

It is widely held that the preponderance of females among later-onset schizophrenic patients compensates for the larger number of males among earlier-onset cases, and results in an overall equal sex ratio of prevalence rates (Rosenthal, 1970; Dohrenwend & Dohrenwend, 1976; Flor-Henry, 1985; Hafner, 1987). Some recent data (see Castle & Murray, 1991) suggest that the male excess is maintained overall, but this has not been a universal finding (see Lewine, 1988). What is consistent, however, is that the application of criteria which define a severe form of schizophrenia exclude more females, and result in an overall male excess (Lewine, 1988; Lewine *et al*, 1984; Katschnig & Lenz, 1988).

However, most studies of gender differences in schizophrenia have been confined to hospital admissions, often including readmissions, and thus biased the sample examined towards more severely ill or more chronic patients. As males tend to have more severe illnesses, with higher readmission rates (Angermeyer *et al*, 1989, 1990), the apparent male excess may be a consequence of the confounding effects of severity. Furthermore, studies have not specifically examined the effect of age at onset on gender differences. For example, in the study by Lewine *et al* (1984) the diagnostic criteria which resulted in the highest male:female ratio were those of Feighner *et al* (1972), which have a cut-off for age at onset at 40 years; the effect of an age-at-onset stipulation in less stringently defined schizophrenia was not determined.

There are two main explanations for the gender differences in schizophrenia. Firstly, it could be that males and females have the same disorder, but some factor(s) associated with femininity both ameliorates and delays the onset of the symptoms. Secondly, heterogeneity might exist, with a higher proportion of males than females suffering from a subtype of the disorder which has early onset and poor outcome. For example, we (Castle & Murray, 1991) have suggested that males are particularly prone to a severe neurodevelopmental form of the illness.

We investigated gender differences and their origins in a representative sample of schizophrenic individuals, ascertained without preselection according to either admission or age at onset. This is the first study to determine gender differences in the incidence of operationally defined schizophrenia in a defined area over a long period.

Method

The method has been described in full elsewhere (Castle *et al*, 1991). Briefly, we ascertained all non-organic, non-affective psychotic patients on the Camberwell Cumulative Psychiatric Case Register (Wing & Hailey, 1972); 'schizo-affective' and 'atypical' psychoses were included. The

Register provides a comprehensive list of all persons from the area of Camberwell in south London, who had their first contact with the psychiatric services between 1965 and 1984.

The case records of each patient were obtained from the appropriate hospital or clinic, and all medical, nursing, social work, and occupational therapy notes were scrutinised, as well as all correspondence and accessory information. The quality of the written notes was high, and in most cases a semi-standardised case summary was also available. Patients who had had contact with the psychiatric services before 1965 were excluded from further analysis, as were patients in whom there was an obvious organic basis to the illness.

The Operational Criteria Checklist for Psychotic Illness (OCCPI; McGuffin *et al*, 1991) was completed for each individual. The check-list provides a simple, reliable method of applying multiple operational diagnostic criteria in studies of psychotic illness. ICD-9 diagnoses (World Health Organization, 1978) were taken as akin to a Register diagnosis of schizophrenia (ICD-9 codes 295.0–295.9), schizoaffective disorder (295.7), paraphrenia (297.2), or other non-organic psychosis (298.1–298.9), while Research Diagnostic Criteria (RDC; Spitzer *et al*, 1978), DSM-III and DSM-III-R (American Psychiatric Association, 1980, 1987), and Feighner (Feighner *et al*, 1972) diagnoses were computed using the OPCRIT computer program, designed to analyse the OCCPI. OPCRIT treats missing values as zero.

Two independent workers (DJC and SW) rated the records. SW was blind to the fact that the study was addressing gender issues in schizophrenia. Inter-rater reliability was computed on a random subset of 50 case notes which were rated by both workers; kappa was 0.82 for RDC diagnoses and 0.76, 0.74, and 0.76 for DSM-III, DSM-III-R, and Feighner diagnoses, respectively.

Age at onset was recorded as the earliest age at which medical advice was sought for psychiatric reasons, or at which symptoms began to cause subjective distress or impair functioning (as in OCCPI). Inter-rater reliability for age at onset (dating to five-year bands) was excellent (kappa = 0.93). Information relating to marital/cohabiting status at time of contact, and to premorbid social and work adjustment and premorbid personality traits were also rated, in accordance with the criteria laid down in the OCCPI. 'Premorbid' refers to the period before the onset of illness, as defined above. The criteria for poor premorbid work adjustment take account of academic work or performance as a housewife if the patient had not entered full-time employment. For the premorbid variables, inter-rater reliabilities were: single status, 1.0; premorbid work adjustment, 0.65; premorbid social adjustment, 0.64; and personality disorder, 0.60.

Incidence figures were determined using data supplied by the Office for Population Censuses and Surveys (OPCS). Data from the 1961, 1971 and 1981 censuses (100% samples) were used, with appropriate interpolations for the intermediate years. Incidence rate ratios were calculated using person-time data; approximate 95% confidence limits were calculated according to the method described by Rothman (1986). Hypothesis testing of the differences between two rate ratios was derived from the formulae for the mean and variance of the number of cases in a binomial distribution; test statistics were translated into *P* values using the tables for the standard normal distribution (Rothman, 1986).

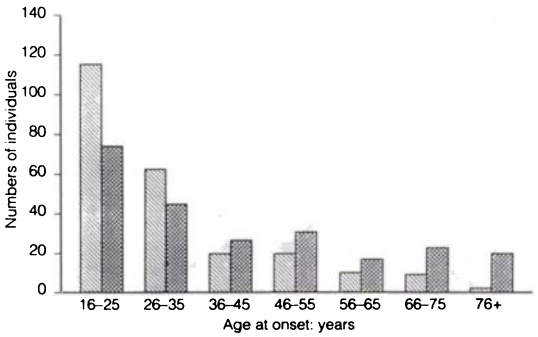

Fig. 1 Age-at-onset distribution for all non-affective, non-organic psychotic individuals (▨ men; ▩ women).

Results

In total, the case records of 470 patients were rated. The records of a further 55 patients (10% of the total) had been lost or destroyed owing to lack of storage space at one of the local hospitals. There is no reason to suspect that the patients for whom notes were missing differed in any significant way from the rest; specifically, the proportion of males did not differ, and the age structure was similar. Thus, analyses of sex ratios were confined to the 470 rated patients. For the determination of incidence rates an allowance was made for missing notes, as outlined elsewhere (Castle *et al*, 1991).

Figure 1 shows the age-at-onset distribution for all non-affective, non-organic psychotic patients. Mean age at onset was 31.2 years for men and 41.1 years for women. Males exceeded females in those patients with an onset of less than 35 years, whereafter a female preponderance was seen.

Table 1 shows the numbers of patients fulfilling increasingly stringent criteria for schizophrenia, by sex; sex ratios are also shown. Following DSM-III-R criteria, we analysed the data in two groups according to age at onset:

Table 1
Numbers of patients fulfilling various criteria for schizophrenia, by sex and age at onset

Criteria	Onset: years	Male[1]	Female[1]	M:F ratio
ICD	<45	195	141	1.4:1
	>45	44	90	0.5:1
RDC	<45	127 (65%)	82 (58%)	1.6:1
	>45	37 (84%)	75 (83%)	0.5:1
DSM-III	<45	108 (55%)	50 (35%)	2.2:1
DSM-III-R	<45	86 (44%)	41 (29%)	2.1:1
	>45	22 (50%)	47 (52%)	0.5:1
Feighner	<40	96 (50%)	39 (29%)	2.5:1

1. Percentages in parentheses reflect proportion of non-affective psychotic individuals (ICD 'schizophrenia', 'atypical psychosis' and 'paraphrenia') fulfilling various criteria for schizophrenia.

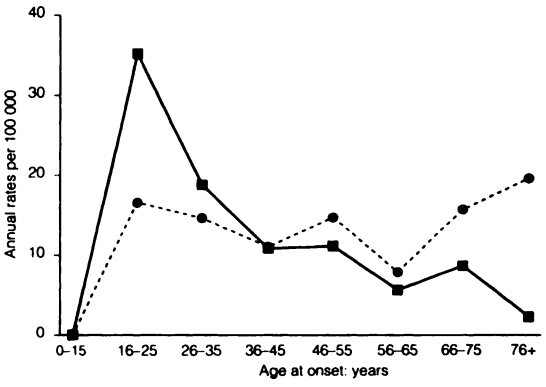

Fig. 2 Rates for DSM-III-R schizophrenia per 100 000 population (—■— male; --●-- female).

less than 45 years, and 45 years and over. Surprisingly, a higher proportion of older than younger patients met the various operational criteria. In the group with age at onset under 45 years, increasing the stringency of diagnosis resulted in a more emphatic male preponderance. This was particularly so for those criteria stipulating a six-month duration, namely DSM-III, DSM-III-R and Feighner criteria. In contrast, the male:female ratio in the later-onset group was far less affected by increasing stringency of diagnosis.

Rates of schizophrenia by gender were determined across the study period. The male:female ratio of the general population of Camberwell was fairly uniform throughout the period under study, showing a slight female preponderance. The male:female rate ratios were much the same over the 20 years, and the results shown are based on rates calculated using the entire 20-year period in the denominator. Figure 2 shows annual incidence rates for DSM-III-R schizophrenia, by sex and age at onset. It will be noted that the distribution for males peaks in the under-25s, while for females the distribution is far more even.

To explore these findings further, we calculated rates for schizophrenia as defined by a range of different criteria, and analysed the incidence rate ratios with and without an age-at-onset stipulation (Table 2). For those criteria with no age-at-onset stipulation (i.e. not the DSM-III and Feighner criteria), overall rate ratios for the two sexes showed a slight male excess, significant only for DSM-III-R criteria. The rate ratios were similar to the sex ratios shown in Table 1; in the younger group increasing stringency of diagnosis resulted in much higher male:female ratios, while little difference was made to the rate ratios in the older group. In consequence, whenever an age-at-onset stipulation was made (45 years for all criteria other than those of Feighner, where it was 40 years), the incidence of schizophrenia was higher in the resulting young males than young females; for the older-onset groups, the reverse was the case.

Data relating to personality disorder, marital status, and premorbid social and work adjustment for all non-affective psychotic patients are shown in Table 3 (upper half). In the early-onset group, males were significantly more likely to be single, to have poor premorbid social and work adjustment, and to have a premorbid personality disorder (the OCCPI criteria for personality disorder are broad, including schizoid, schizotypal and paranoid types). None of these premorbid parameters distinguished males from females in the later-onset group.

Comparison of the early- and late-onset non-affective psychotic patients by sex in terms of premorbid dysfunction revealed that, for both sexes, the younger group were more likely to be unmarried (males $\chi^2=32.32$, $P<0.001$; females $\chi^2=7.35$, $P<0.01$) and to have a poor work record (males $\chi^2=29.70$, $P<0.001$; females $\chi^2=15.70$, $P<0.01$). However, only for males were the younger group significantly more likely to have had poor premorbid social adjustment ($\chi^2=13.30$, $P<0.001$), and to have had premorbid personality disorder ($\chi^2=6.71$, $P<0.01$).

To show the effect of increasing diagnostic stringency on premorbid characteristics, we analysed these parameters in patients fulfilling DSM-III-R criteria; these criteria define a severe form of schizophrenia, but do not have an age-of-onset stipulation, allowing comparison of early- and late-onset groups (Table 3; lower half). In comparison with the broad group of non-affective psychotics, the DSM-III-R group were more likely to have had poor premorbid functioning irrespective of sex or age at onset; however,

Table 2
Rates and rate ratios of schizophrenia per 100 000 population, by sex

Criteria	Onset: years	Male	Female	IRR[1] (95% CI)	χ^2 statistic; P value
ICD	<45	25.2	17.8	1.41 (1.13-1.75)	3.86; $P<0.001$
	>45	10.4	17.1	0.50 (0.34-0.71)	2.76; $P=0.002$
	all ages	19.2	17.6	1.13 (0.94-1.35)	1.37; NS
RDC	<45	16.4	10.4	1.58 (1.20-2.08)	3.26; $P<0.001$
	>45	8.7	14.3	0.61 (0.41-0.90)	2.48; $P=0.006$
	all ages	13.7	11.9	1.16 (0.92-1.42)	1.29; NS
DSM-III	<45	13.9	6.3	2.20 (1.57-3.07)	4.73; $P<0.001$
DSM-III-R	<45	11.1	5.2	2.14 (1.47-3.10)	4.10; $P<0.001$
	>45	5.2	9.0	0.58 (0.35-0.96)	2.14; $P=0.016$
	all ages	9.0	6.7	1.34 (1.01-1.78)	2.07; $P=0.020$
Feighner	<40	14.8	6.0	2.49 (1.72-3.61)	4.98; $P<0.001$

1. Incidence rate ratio, male:female.

Table 3
Premorbid social and occupational adjustment by sex and age at onset

Parameter	Onset: years	Male	Female	χ^2 statistic; P value
All non-affective psychotics				
Single[1]	<45	147 (75%)	76 (53%)	16.92; $P<0.001$
	>45	14 (31%)	33 (35%)	0.18; NS
Poor work adjustment	<45	107 (55%)	62 (44%)	3.93; $P<0.05$
	>45	4 (9%)	16 (18%)	0.54; NS
Poor social adjustment	<45	103 (53%)	41 (29%)	18.87; $P<0.001$
	>45	10 (23%)	19 (21%)	0.01; NS
Personality disorder	<45	53 (27%)	19 (13%)	9.17; $P<0.01$
	>45	4 (9%)	7 (8%)	0.01; NS
DSM-III-R schizophrenics only				
Single[1]	<45	70 (82%)	23 (56%)	9.86; $P<0.01$
	>45	7 (32%)	21 (45%)	0.77; NS
Poor work adjustment	<45	53 (62%)	24 (58%)	0.17; NS
	>45	3 (14%)	11 (23%)	0.74; NS
Poor social adjustment	<45	54 (64%)	11 (27%)	14.91; $P<0.001$
	>45	7 (32%)	16 (34%)	0.03; NS
Personality disorder	<45	30 (35%)	8 (20%)	3.27; NS
	>45	2 (9%)	7 (15%)	0.36; NS

1. Never married or cohabited.

differences were not statistically significant. Among early-onset patients, the levels of significance of the gender differences in premorbid parameters were lower for the DSM-III-R group than for the broad group. In the later-onset group, males and females did not differ significantly in terms of any of the premorbid parameters.

Comparison of early- and late-onset individuals with DSM-III-R schizophrenia showed early-onset males were more likely than their later-onset counterparts to be single ($\chi^2=19.68$, $P<0.001$), and to show poor premorbid social adjustment ($\chi^2=7.17$, $P<0.01$) and work adjustment ($\chi^2=13.74$, $P<0.001$), and personality disorder ($\chi^2=5.72$, $P<0.05$); however, the levels of significance were lower than when a similar comparison was made by age at onset for all non-affective psychotic patients (see above). For females, the early- and late-onset DSM-III-R groups differed significantly only in terms of work adjustment ($\chi^2=11.2$, $P<0.001$).

Figure 1 shows that there is a particular excess of males among those with an onset below the age of 25. The application of stringent criteria dramatically increased the male:female ratio in this group (from 1.6:1 for all non-organic, non-affective psychoses, to 3.4:1 for DSM-III-R schizophrenia). Incidence rates for the broadly defined group were 25.5 per 100 000 for males and 16.1 per 100 000 for females (rate ratio 1.58, 95% confidence intervals 1.18–2.12; $\chi^2=3.15$, $P=0.008$); for the DSM-III-R defined group, the rates were 12.0 per 100 000 for males and 3.4 per 100 000 for females (rate ratio 3.53, 95% confidence intervals 2.04–6.20; $\chi^2=4.79$, $P<0.001$).

Table 4 (upper half) shows that in terms of premorbid functioning, those with onset before 25 years were severely impaired; on all parameters they showed more abnormality than the total group with age at onset less than 45 (see Table 3; upper half). Males fared worse than females in terms of social and occupational adjustment.

Table 4
Premorbid social and occupational adjustment by sex

Parameter	Male	Female	χ^2 statistic; P value
Non-affective psychotics (<25 years age at onset only)			
Single[1]	106 (91%)	56 (76%)	7.84; $P<0.01$
Poor work adjustment	74 (63%)	35 (47%)	4.71; $P<0.05$
Poor social adjustment	69 (59%)	27 (37%)	9.17; $P<0.01$
Personality disorder	36 (31%)	15 (20%)	2.55; NS
DSM-III-R schizophrenics (<25 years age at onset only)			
Single	60 (94%)	24 (92%)	0.06; NS
Poor work adjustment	47 (73%)	12 (47%)	6.09; $P<0.05$
Poor social adjustment	43 (67%)	10 (39%)	6.30; $P<0.05$
Personality disorder	24 (38%)	7 (27%)	0.92; NS

1. Never married or cohabited.

When premorbid functioning was analysed in only those very-early-onset patients fulfilling DSM-III-R criteria for schizophrenia, both males and females showed more impairment than for the broadly defined very-early-onset group (Table 4; lower half). Furthermore, the differences between the sexes were less marked for the very-early-onset DSM-III-R schizophrenic patients than for the whole group with onset before age 25.

Discussion

We assessed a first-contact sample, thus precluding any bias from admission and readmission practices.

The sample included all non-affective, non-organic psychotic patients, irrespective of age, thus avoiding conclusions being drawn about a sample which had already been partly selected according to age of onset. In the past, there has been a tendency to presume that schizophrenia can commence only at a young age (e.g. less than 45 years in DSM-III). Recently, there has been a resurgence of interest in the late-onset non-affective functional psychotics, and it is clear that such patients often manifest phenomenology similar to that of their early-onset counterparts (Pearlson *et al*, 1984; Rabins *et al*, 1984). Studies of gender differences in schizophrenia have seldom included later-onset patients; in particular, very-late-onset patients (>60 years), among whom there is an emphatic female preponderance (Harris & Jeste, 1988; Castle & Howard, 1992), have generally been excluded.

The study was catchment area based, and therefore can be expected to be representative of all schizophrenics in Camberwell. The study examined a 20-year period, and the demography of the area changed considerably. The total population declined from 171 000 in 1965 to 118 000 in 1984. However, the proportion of females remained stable (52% in both 1965 and 1984). Furthermore, there has been remarkably little change in the age structure of the population. In 1965, 38% of males and 35% of females were under 25, and 66% of males and 61% of females under 45. The comparable figures for 1984 were: 37% of males and 35% of females under 25, and 65% of males and 61% of females under 45. National figures for England and Wales are similar; for example, the 1981 census shows that 38% of males and 34% of females were under the age of 25, and 65% and 60%, respectively, under the age of 45.

The Camberwell catchment area is a deprived inner-city area with a significant minority of Afro-Caribbean persons. We have shown elsewhere (Castle *et al*, 1991; Wessely *et al*, 1991) that Afro-Caribbeans in Camberwell have a peculiar susceptibility to schizophrenia; indeed, around 20% of our sample were born in the Caribbean, four to six times the proportion in the general population of Camberwell over the period of the study. The Afro-Caribbean population of Camberwell are generally younger than their UK-born counterparts. This is reflected in the fact that in our sample, the mean age at onset for this group (28.3 years for males, 31.2 years for females) was lower than for the Caucasians (33.7 years for males, 46.2 years for females). To investigate any bias arising from this maldistribution, we analysed the Afro-Caribbean and Caucasian groups independently. Aside from the low number of late-onset Afro-Caribbean cases, the gender differences were much the same as for the group as a whole.

Case-note studies are not ideal for rating premorbid functioning, but the quality of the notes was high, and almost all contained sufficient details for a judgement to be made in this regard. Inter-rater reliability for the premorbid variables was good. Inevitably, some false negatives would have occurred, but there is no reason to suspect systematic bias by sex. It is probable that ratings of personality disorder were underestimates, particularly given the low rates in the late-onset group compared with other studies (Harris & Jeste, 1988).

Earlier studies (Lewine *et al*, 1984; Katschnig & Lenz, 1988) have found that the application of stringent criteria to cohorts of schizophrenic hospital patients results in a marked excess of males. This study shows conclusively that this is a reflection of a higher incidence of severe schizophrenia in men. However, the incidence was higher only among those patients with an age at onset of less than 45; the effect was even more dramatic in those whose illness first manifested before the age of 25.

All the operationalised criteria used in this study exclude patients with a strong affective component to their illness. The RDC stipulate an illness duration of two weeks, while DSM-III, DSM-III-R, and Feighner criteria stipulate six months. Thus, males with an early age at onset (and particularly those with an onset before 25 years) appear to be particularly prone to a severe form of schizophrenia, characterised by long duration and lack of affective symptoms. Furthermore, these patients were more likely than their female counterparts to have remained single, to have poor premorbid social and employment records, and to exhibit premorbid personality disorder. These premorbid characteristics also differentiated early-onset from later-onset males.

We believe that these findings are incompatible with the notion that the relatively benign nature of schizophrenia in women is merely a reflection of later onset. Indeed, were that the case, early-onset male and female cases would be equally likely to fulfil stringent criteria for the illness. The fact that males with early-onset schizophrenia were particularly prone to a form of disease characterised by lack of affective symptoms, a long illness, and premorbid dysfunction, lends support to the hypothesis that men are particularly vulnerable to a subtype of schizophrenia consequent upon neurodevelopmental deviance (Castle & Murray, 1991). The fact that so many of the young males were single could merely reflect the demography of the general population, although criteria did not stipulate 'married'.

In the later-onset patients (>45 years), increasing the stringency of diagnosis had little effect on the sex ratio, which continued to show a female preponderance. Thus, among later-onset patients, males and females are proportionally equally likely to have a severe form of schizophrenia, without prominent affective features and of long duration. Although a higher proportion of late- than early-onset non-affective psychotics met RDC and DSM-III-R criteria, late-onset patients were less likely than their early-onset counterparts to be unmarried, or to be premorbidly occupationally or socially (for males only) compromised. Males and females in this group were equally unlikely to have exhibited premorbid social dysfunction or a poor work record. Personality disorder, despite being broadly defined in the OCCPI, distinguished between the early- and late-onset male cases; this did not hold for females. In short, later-onset patients tended not to show the premorbid deficits thought to be characteristic of neurodevelopmental schizophrenia. Of course, part of the explanation could lie in the later onset of illness *per se*.

The very-late-onset group are particularly interesting; many previous epidemiological studies of schizophrenia have not included such cases. Holden (1987) estimated the age-specific incidence of schizophrenia with onset after the age of 60 years to be between 17 and 26 per 100 000 per year, remarkably similar to the rate we found. Numerous studies have shown, like ours, that there is a marked female excess among these patients (see Harris & Jeste, 1988). The inclusion of this very-late-onset group caused the group mean age at onset to be higher than that reported in previous epidemiological studies of schizophrenia (e.g. Hafner, 1987), and is probably responsible for the large differential between males and females (usually reported as around five years; e.g. Loranger, 1984). The fact that so many very-late-onset patients met stringent criteria for schizophrenia reflects the florid symptoms and long illness in many such patients (see Castle & Howard, 1992).

Gender differences in premorbid functioning were less marked in those patients fulfilling stringent criteria for schizophrenia. This probably reflects the fact that stringent criteria define a form of illness inherently more likely to be associated with poor premorbid functioning. Thus, even though young males were more likely to fulfil such criteria, females who did meet the criteria were more likely to exhibit these premorbid characteristics than those who did not. Young schizophrenic females (DSM-III-R) though few in number, do show some of the deficits thought characteristic of neurodevelopmental schizophrenia.

Our results show that males under 45 years (and particularly those under 25 years) have a high incidence of a severe form of schizophrenia, characterised by poor premorbid functioning. These findings are reminiscent of Kraepelin's original conception (1896) of dementia praecox as a severe poor-outcome disorder predominantly affecting young men, and compatible with the possibility that young males are particularly prone to a severe form of illness consequent upon neurodevelopmental insult (Castle & Murray, 1991).

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