Schizophrenia: do men and women suffer from the same disease?

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ABSTRACT

This article reviews the literature on normal brain development and behavioural development in men and women as well as on aetiological risk factors for schizophrenia, such as pre-, peri- and postnatal complications.

The male-female comparisons of age and type of onset, symptomatology, course and outcome were based on a population-based sample of 232 first illness episodes – the ABC Schizophrenia Study sample. The probands were assessed using the IRAOS interview and other instruments retrospectively at first admission and prospectively at six cross sections over five years after first contact. A representative subsample of 130 first admissions or 115 first illness episodes were compared with 130 controls, matched by age, sex and area of residence.

Women, 3 to 4 years older than men at illness onset, showed a second peak of onsets in age group 45 to 50 years. After animal experiments and a controlled clinical study this finding was explained by a protective effect of oestrogen persisting until menopause. The underlying neurobiological mechanism consisted in a sensitivity reducing effect of oestrogen on D2 receptors in the brain. The effect of oestrogen, meanwhile confirmed in randomised control trials, also includes genomic effects as well as interactions with free-radical detoxifying systems, thus demonstrating the neuroprotective capabilities of oestrogen.

Postmenopausal schizophrenia was more frequent and more severe in women. Men fell ill more frequently and more severely at young age and less frequently and more mildly later in life. Illness course, too, was more unfavourable in postmenopausal women than in their male peers.

The protective effect of oestrogen in women depended on the degree of their predisposition to the illness: the higher the familial load for schizophrenia, the weaker the protection by oestrogen. The more favourable illness course in premenopausal women resulted from their higher level of social development at illness onset – determined by their higher age at onset – and from their socially more adaptive behaviour. The illness behaviour of young men showed a significant excess of socially negative behaviours with an unfavourable impact on their early illness course. In contrast, older men were socially better adjusted. With genetic and morphological findings considered the subtypes of schizophrenia did not differ between men and women.

Gender differences in symptomatology and course of schizophrenia obviously are not explained by differences in the disease process. They seem to be determined by a complex pattern of interaction between disease variables, hormonal and behavioural differences and their consequences for age at onset and illness course.

Keywords: Schizophrenia; Risk factors; Gender; Oestrogen

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Introduction

Nearly one hundred years ago Kraepelin (1909-1915) pointed to women's several years higher age at first admission for dementia praecox compared to men's. Since then the finding has been replicated in more than 50 studies (for a review see Angermeyer and Kühn, 1988). Discrepant findings have been reported mainly from India (Murthy et al., 1998; Gangadhar et al., 2002). But systematic empirical research into various aspects of gender differences in schizophrenia has been pursued for only about 15 years. According to Moldin (2000) robust gender differences in major disease variables "may have important implications both in future research on the pathophysiology and aetiology of schizophrenia and in clinical practice".

Gender differences in schizophrenia can be studied in various domains:

1. Diagnoses, types of onset, subtypes of the disorder and symptoms.
2. Lifetime risk for psychosis and distribution of onset over the life-cycle.
3. Distant (genetic, pre- and perinatal) and proxy (antecedent) risk factors.
4. Premorbid functioning, determinants and consequences of the gender difference in age at onset.
5. Gender-specific illness behaviour versus illness-specific deficits and symptoms.
6. Course and outcome.
7. Brain development, structure and functioning.
8. Treatment and care.

I will discuss these eight domains, as far as we have informative data available.

Proceeding particularly from the sex difference in age at first admission – a fairly robust finding reported from allover the world – in 1986 we launched a systematic study into sex differences and other aspects of schizophrenia. The study has been funded continuously for 16 years by grants from the German Research Association (DFG). We hoped that studying this robust variable would yield us information on causal determinants of the first emergence of the disorder and, hence, some insight into pathophysiological processes underlying its symptomatology and course. For this reason, the study was designed as consisting of three levels – epidemiological, clinical and biological. As the study progressed, new hypotheses were continuously formulated on the basis of the results gained.

I am particularly happy to be able to present results from this study at the invitation of my longtime research partner and friend Wagner Gattaz. It was with him that we planned the biological part, especially the animal experiments, of the study.

A large part of our analyses will be based on a *population-based* sample of 232 first illness episodes of a broad diagnosis of schizophrenia (ICD-9: 295, 297, 298.3), =84 % of first admissions from a semi-urban, semi-rural German population of about 1.5 million. The patients, aged 12 to 59 years, were assessed with the PSE (Wing et al. 1974), the SANS (Andreasen, 1983), the PIRS (Biehl et al., 1989), the DAS (World Health Organization 1988, Jung et al. 1989) immediately upon hospitalisation in the first psychotic episode. Individual premorbid development, *onset and early course* were assessed retrospectively using the IRAOS interview (Häfner et al., 1992, 1999) 4 to 6 weeks later in order to keep memory distortions to a minimum. A subsample of 130 cases was compared with the corresponding data for 130 "healthy" population controls and 130 first-admission cases with a diagnosis of a depressive episode, both matched for age, sex and area of residence (Figure 1).
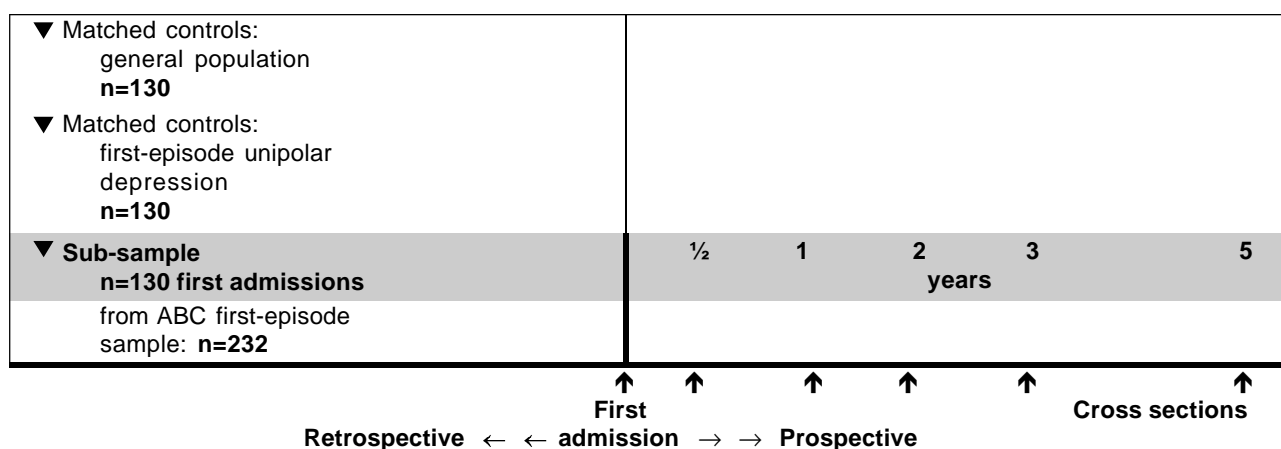

Figure 1 ABC Schizophrenia Study: design for early and medium-term course of schizophrenia spectrum disorder (ICD 295, 297, 298.3, 298.4) from onset to 5 years after first admission.

Illness course from first admission on was assessed prospectively over 5 years in a subsample of 115 first episodes of schizophrenia using the same instruments and additonally the FU-HSD (WHO, 1980) and over 15 years in another representative sample of 70 first admissions.

Domain 1: diagnoses, subtypes, symptoms, type of course

Most studies report a greater frequency of positive and affective symptoms for women and more negative symptoms and insidious types of onset for men (Castle et al., 1993; Castle, 1999). But there are also several reports of men showing a greater frequency of positive symptoms compared with women (Goldstein and Link, 1988; Bardenstein and McGlashan, 1990; Lewis, 1992). Still other studies have failed to find comparable gender differences (Fennig et al., 1995; Kendler and Walsh, 1995; Moldin, 2000). For testing these diverging results we compared diagnoses, subtypes, symptoms and types of onset or early course at the same stages of illness: (1) in the first psychotic episode with maximum symptom presentation, (2) at illness onset with minimum symptom presentation and (3) cumulatively in the early course from onset to first admission.

As shown in table 1, significant differences were found in none of the clinical or the operationalised diagnoses, scores or syndromes in the psychotic episode. Nor did the 10 most frequent initial symptoms, i.e. at illness onset – defined by the emergence of the first sign of mental disorder – show significant gender differences, except one item, which was significantly more frequent in women: worrying. But the frequency of this item is specific to female gender rather than to the disorder (Häfner et al., 1995) (Table 2).

The results of comparative neuropsychological studies, too, are inconsistent (Goldstein and Lewine 2000; Fitzgerald and Seeman, 2000). Goldberg et al. (1995) for example studied four independent cohorts of men and women with schizophrenia using a large test battery, but did not find any substantial neuropsychological gender differences (Albus et al., 1996). Most authors compared samples that differed in the durations of their illness.

To compare *clinical subtypes* we analysed symptomatology, type of illness onset and course from the first sign to the climax of the first episode. The three types of onset: acute, subacute and chronic and three categories of initial symptoms: positive, negative and unspecific, did not show any significant gender

Table 1 Comparison of clinical and operationalised diagnoses and CATEGO subclasses, scores and index of definition at first admission (= in the first psychotic episode) between men and women – ABC study sample of 232 first-episode cases (= 84% of 276 first admissions)

Diagnosis (%)[*]	females n=124	males n=108	p
Schizophrenia broad definition (ICD-9: 295, 297, 298.3/4)	100%	100%	
Schizophrenia ICD 295	87.1%	88.0%	n.s
Operationalised diagnosis:			
CATEGO ICD 295	79.0%	73.1%	n.s
CATEGO class S+	73.4%	67.6%	n.s
CATEGO: affective psychosis	13.7%	13.0%	n.s
Scores (mean values)[**]			
PSE: Index of definition	7.47	7.49	n.s
CATEGO: total score	40.67	41.44	n.s
CATEGO subscores:			
DAH (delusions, hallucinations)	10.83	10.01	n.s
BSO (behaviour, speech)	8.04	7.85	n.s
SNR (specific neurotic syndrome)	7.11	7.68	n.s
NSN (non-specific neurotic syndrome)	14.69	15.91	n.s

[*] chi²-tests
[**] t-tests

Table 2 Percentages of men and women presenting the ten most frequent earliest signs of schizophrenia reported by the patients[1] – ABC first-episode sample n=232

	Total (n=232) %	Men (n=108) %	Women (n=124) %	p
Restlessness	19	15	22	
Depression	19	15	22	
Anxiety	18	17	19	
Trouble with thinking and concentration	16	19	14	
Worrying	15	9	20	*
Lack of self-confidence	13	10	15	
Lack of energy, slowness	12	8	15	
Poor work performance	11	12	10	
Social withdrawal, distrust	10	8	12	
Social withdrawal, communication	10	8	12	

[1] Based on closed questions in the IRAOS interview, multiple counting possible.

All items tested for sex differences; *: p ≤ 0.05

Source: Häfner et al., 1995, modified.

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differences (Table 3). Nor did the six *symptom clusters* – representing empirical subtypes – derived from the psychotic prephase of a mean duration of 1.3 years – differ significantly between men and women either in mean age of onset or in frequency (Table 4).

These findings indicate that the proxy characteristics of schizophrenia – symptoms, psychopathological subtypes, types of onset and early illness course – show no major differences between men and women. Accounting for this result maybe the homogeneous stage of illness (first psychotic episode), representativeness, size and the wide age range of 12 to 59 years of the sample. This result provides support for the assumption that the inconsistency in the literature might be a result of methodological shortcomings rather than a reflection of true gender differences.

The interaction of symptom presentation and gender with age – a frequent further source for error in comparative studies – was not taken into account in this first analysis, based on mean values of the total age of risk range of 12 to 59 years in both sexes. Focusing on the validity of the findings, Jablensky (1995) summed up the results reported in the literature on sex differences in the symptom expression of schizophrenia as follows: "There is no unequivocal evidence of consistent sex differences in the symptom profiles of schizophrenia and particularly in the frequency of positive and negative symptoms".

Table 3 Type of onset and type of initial symptoms of schizophrenia – ABC first-episode sample n=232

	Total n=232	Men n=108	Women n=124
Type of onset*			
Acute (≤ 1 month)	18%	19%	17%
Subacute (> 1 month ≤ 1 year)	15%	11%	18%
Insidious or chronic (> 1 year)	68%	70%	65%
Type of first symptoms*			
Negative or non-specific	73%	70%	76%
Positive	7%	7%	6%
Both	20%	22%	19%

* The variables listed, except "worrying", showed no significant sex differences.

Source: Häfner et al., 1995, modified.

Table 4 Age at first admission and frequency of symptom clusters in the psychotic prephase (from first positive symptom to first admission) of the first psychotic episode in men and women with schizophrenia

Cluster	Non-specific, negative, depressive	Delusional	Psychotic thought disorder	Auditory hallucinations, substance abuse	Disorganisation/ psycotic thought disorder	Low values on all dimensions
Sex:						
males (%)	49.2	45.2	40.6	48.4	50.0	42.3
females (%)	50.8	54.8	59.4	51.6	50.0	57.7
$Chi^2 = 1.1$, df: 5; p=0.95						
Age at first admission (years) (both sexes)	31.1	29.8	29.9	29.3	30.3	31.4
F=0.293, df=5; p=0.91						

Source: Häfner, 2000.

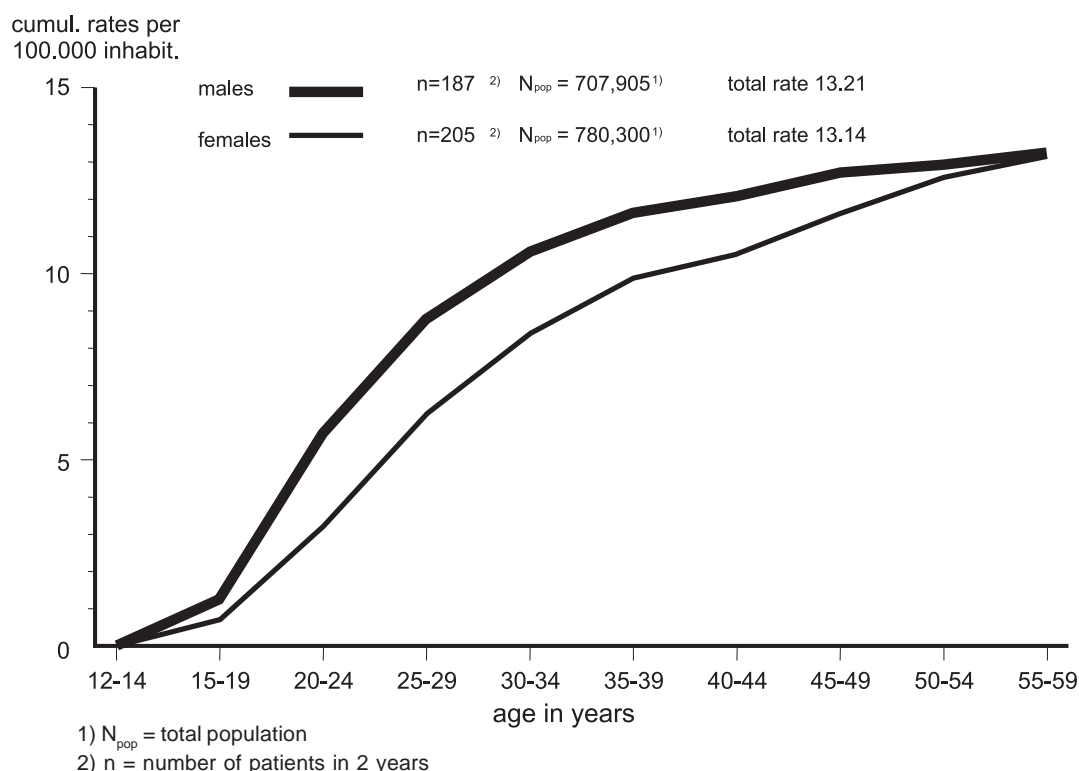## Gender difference in the morbid risk (Domain 2)

The male-female ratio of the incidence rates and lifetime risk of schizophrenia varies considerably in the literature. According to Hambrecht et al. (1994) the male-female ratio of annual incidence rates ranges from 0.70 to 3.47/10,000 population. Because of the unevenness of the male and female age distributions in the numerator (e.g. late-onset in women) and the denominator (e.g. population at risk) it is very difficult to calculate sex-specific risks correctly. The male predominance in the majority of the studies (Lewine, 1988; Castle et al., 1993; Goldstein and Lewine, 2000; see also Häfner and an der Heiden, 1997) are accounted for by an overrepresentation of young males and an underrepresentation of female late-onset cases in many of the samples studied, particularly those with age cut-offs of 45 (DSM-III) (Iacono and Beiser, 1992). Other limitations are small catchment areas, small and/or non-representative populations, restricted diagnostic or screening criteria, non-use of standardised assessment techniques (Hambrecht et al., 1992).

The rare studies which try to avoid these methodological pitfalls show a trend towards convergence in the male-female lifetime prevalence rates for schizophrenia of a broad, but sufficiently precise diagnostic definition (e.g. Jablensky et al., 1992; Häfner and an der Heiden, 1997). But the same does not apply to rates based on diagnoses requiring a 6-month symptom persistence or social decline prior to first contact, as for example do DSM-III-R and – IV diagnoses of schizophrenia (APA, 1987; 1994). In addition, it is not clear whether the rates would converge if schizophrenia-like delusional disorders of old age (late paraphrenia etc.), which show markedly higher incidence rates for women, were included (Castle and Murray 1993; van Os et al., 1995; Häfner et al., 2001b).

We calculated cumulative incidence rates – a good indicator of the lifetime risk – as based on five-year age bands of the population studied, from age band 12 to 14 years to age band 54 to 59 years at first admission.

As figure 2 shows, men consumed their lifetime risk until age-band 30 to 35 years more rapidly than women did. From that age on, however, women caught up with men, finally reaching almost the same lifetime rate at about 13/100,000. The shape of the curves also clearly shows that lower age cut-offs are bound to lead to a male predominance in the risk ratios. This result provided further support for the hypothesis that the disorder as such is essentially the same in men and women.

cumul. rates per 100.000 inhabit.

males — n=187 [2] N_{pop} = 707,905 [1] total rate 13.21
females — n=205 [2] N_{pop} = 780,300 [1] total rate 13.14

age in years

1) N_{pop} = total population
2) n = number of patients in 2 years

Source of data: a representative first-admission sample (1987/89) n=392
Catchment area: Mannheim, Heidelberg, Rhine-Neckar-District, Eastern Palatinate

Figure 2 Cumulative incidence rates for schizophrenia, broad definition (ICD 295, 297, 298.3 and .4). Source: Häfner et al., 1991.

Childhood and youth antecedents of schizophrenia (Domain 3)

Normal early childhood development (Richman et al., 1982; Earls, 1987) differs very little between the sexes. In late childhood, boys exhibit more externalising behaviours and a slightly higher frequency of attention deficits and girls more anxiety (Anderson et al., 1987; Campball, 1990; Cohen et al., 1993; Gomez et al., 1999). From puberty on, the mental health risks of males and females follow different lines, males showing a greater frequency of hyperactivity, attention deficit disorder, dissocial behaviour, aggressiveness and antisocial personality disorder and females a greater frequency of anxiety and affective disorders. Rosenfield (2000) distinguished between externalising disorders including antisocial behaviour and substance abuse, more frequent in men, and internalising disorder including anxiety and depression, more frequent in women. These different age- and sex- specific behavioural trends have to be taken into account in schizophrenia, too.

As shown in studies based on teachers, 'and parents' reports (Watt et al., 1984), on offpsring of schizophrenic mothers (Erlenmeyer-Kimling et al., 1993; Cannon et al., 1993, Cannon & Mednick, 1993; Parnas et al., 1993), on two British (Jones et al., 1995) and one North-Finnish (Isohanni et al., 1998a, b) population birth cohort, adult-onset schizophrenia is preceded by mild neuromotor, cognitive and behavioural anomalies.

The minor early-childhood deficits in neuromotor and speech development as antecedents of schizophrenia seem to occur at the same frequency in boys and girls. From school age on behavioural anomalies manifest themselves several years later in girls than in boys (Crow et al., 1995). These anomalies are particularly severe in children of mothers with schizophrenia, boys clearly scoring higher than girls on cognitive impairment (Erlenmeyer-Kimling et al., 1984; Castle, 2000). Walker et al. (1995) compared private childhood video clips of siblings discordant for schizophrenia. They also showed that premorbid behavioural signs manifest themselves somewhat later in girls than in boys (Figure 3). But, similarly to the behavioural patterns of normal children, boys exhibit primarily externalising behaviours (e.g. hyperactivity, physical and verbal aggression, failure of behavioural inhibition), whereas girls manifest mainly "internalising" behaviours, e.g. shyness, social withdrawal, depressive mood and social anxiety.

Promorbid functioning (Domain 4)

Follow-back studies of school records, retrospective studies with patients and prospective studies of children of mothers suffering from schizophrenia have consistently found a greater frequency of premorbid deficits in social and occupational functioning for men than women (McGlashan and Bardenstein, 1990; Mueser et al., 1990a; Moldin, 2000). This was also shown by
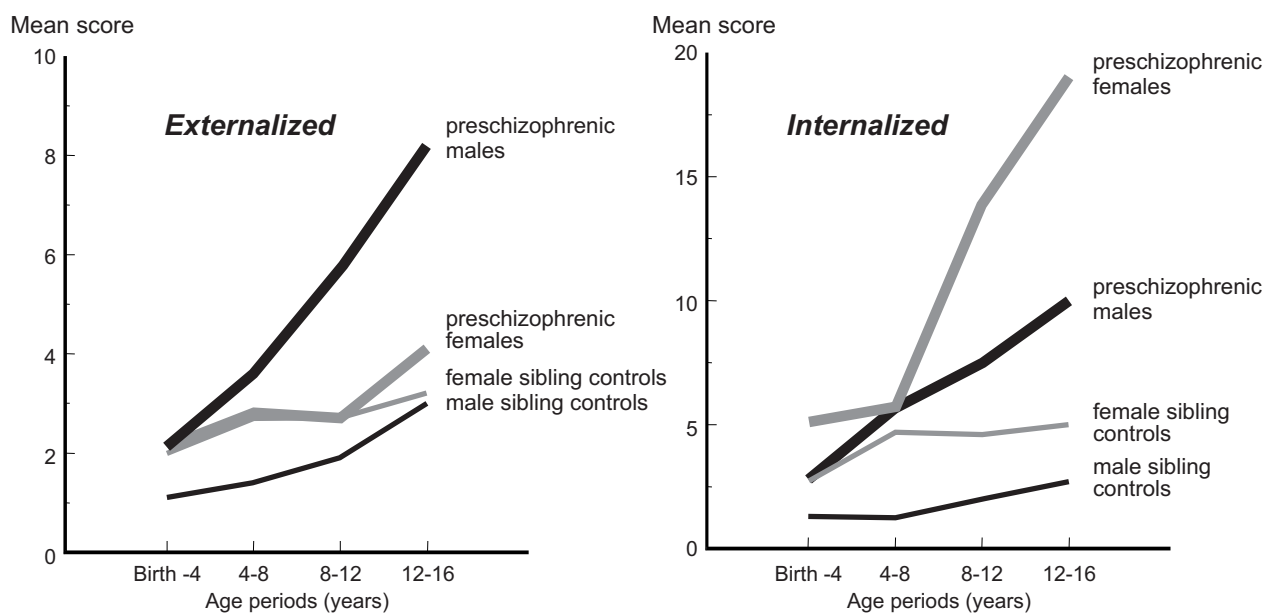

Figure 3 Antecedents of schizophrenia in childhood and youth: comparison of pre-schizophrenic and control siblings, mean externalized/internalized behaviour problem scores by age period and sex.
Source: Walker et al., 1995, modified.

the Israeli conscript study among probands aged 16 to 17 years (Weiser et al., 2000). In view of the normal behavioural gender differences in childhood and adolescence and the three to four years later onset of the prodromal stage of several years' duration in women (Häfner et al., 1993a; 1999b) the question arises when these premorbid dysfunctions come about and end. It is a fact that numerous studies in which illness onset was defined by first admission, first contact or psychosis onset have found gender differences in premorbid functioning that have been contaminated with the prodromal stage of the disorder. The prodrome, characterised by negative symptoms, functional impairment and social disability, has an earlier onset in men. The overlap between premorbid dysfunctioning and the prodromal stage should not be ignored (Castle, 2000). It is also conceivable that the normal behavioural differences between males and females discussed above translate into the differences in premorbid social functioning.

The gender difference in age at onset and its consequences (Domain 5)

The gender difference in age at first admission, which, as mentioned at the outset, was already known to Kraepelin, is a hallmark of the disorder, as Lewine (1980), Seeman (1982), Angermeyer and Kühn (1988) and others have pointed out. Underlying this difference seems to be an analogous difference in age at illness onset (Häfner et al. 1995). The pooled data of the World Health Organization ten-country "Determinants of Outcome" study (Jablensky et al., 1992) revealed a 3.4 years higher mean age of onset for women than men (Hambrecht et al., 1994).

In the ABC first-episode sample with a broad definition of schizophrenia, illness onset and the consecutive milestones of the early course were dated by means of the IRAOS interview conducted with the patients, their relatives and applied to available records (Häfner et al., 1992; 1999a). Mean age at the emergence of the first sign of the disorder, first negative and first positive symptom and at the climax of the first episode – defined by the maximum of positive symptoms – ranged from 22.5 to 28.2 years for males (Figure 4). Women's mean age at all these milestones, ranging from 25.4 to 32.2 years, was 2.9 to 4.0 years higher than that of men's. As a result, it seems well established that the disorder manifests itself clearly later in women than men.

Looking at the distribution of onsets in five-year age bands over the entire age range, we found an early

and steep increase with a maximum between 15 and 25 years for men and after that a monotonous decrease to a very low level (Figure 5). In women the rate of onsets rose slightly less steeply and reached a lower and broader peak in age band 15 to 30 years. After a decline female onsets reached a second, somewhat smaller peak in age group 45 to 50 years around premenopause with a significant difference to men. The same pattern also emerged in Castle et al.'s (1993) study, based on the Camberwell case register, and in our analysis of all first admissions for a diagnosis of schizophrenia from the Danish case register (Löffler et al., 1994).

A few studies have failed to find any gender difference in age at onset. Three studies conducted in India and based on service utilisation samples (Eaton et al., 1995, Murthy et al., 1998, Gangadhar et al. 2002) and a Japanese study (Shimizu et al., 1988) found no significant gender difference in age at onset, nor did a case-register study in Croatia (Folnegovic and Folnegovic-Smalc, 1994) in a sample of 679 patients. In the Indian and Japanese samples culture-dependent and age-specific utilisations of psychiaric services probably have influenced the result. In the Croatian study emigration waves of primarily young men had swept over the catchment area (Folnegovic and Folnegovic-Smalc, 1994), and they might have affected the age and sex distribution of the population at risk. Addington et al.'s study (1996) of 113 patients in Canada, in which, too, no age difference was found, might have been biased by the exclusion of older age groups, in which women with schizophrenia are overrepresented.

Testing the oestrogen hypothesis at different levels (Domain 5)

The age distribution of onsets in women suggested an explanation by oestrogen secretion across the female life-cycle. A protective effect of oestrogen had previously been suggested by Mendelson et al. (1977), Seeman (1981), Loranger (1984), Häfner (1987), Lewine (1988), and Seeman (1996). A neuroleptic-like effect of short-term oestrogen applications in animals had been shown by DiPaolo and Falardieu (1985), Fields and Gordon (1982) and Hruska (1986).

As mentioned at the outset, the design of the animal experiments for testing the oestrogen hypotheses was planned with Wagner Gattaz: after a four-week oestrogen treatment of ovariectomised rats we found a significant attenuation of apomorphine-stimulated dopaminergic behaviour compared with two control groups (the one sterilised and with placebo treatment, the other sham-operated and with placebo treatment). In a post-mortem
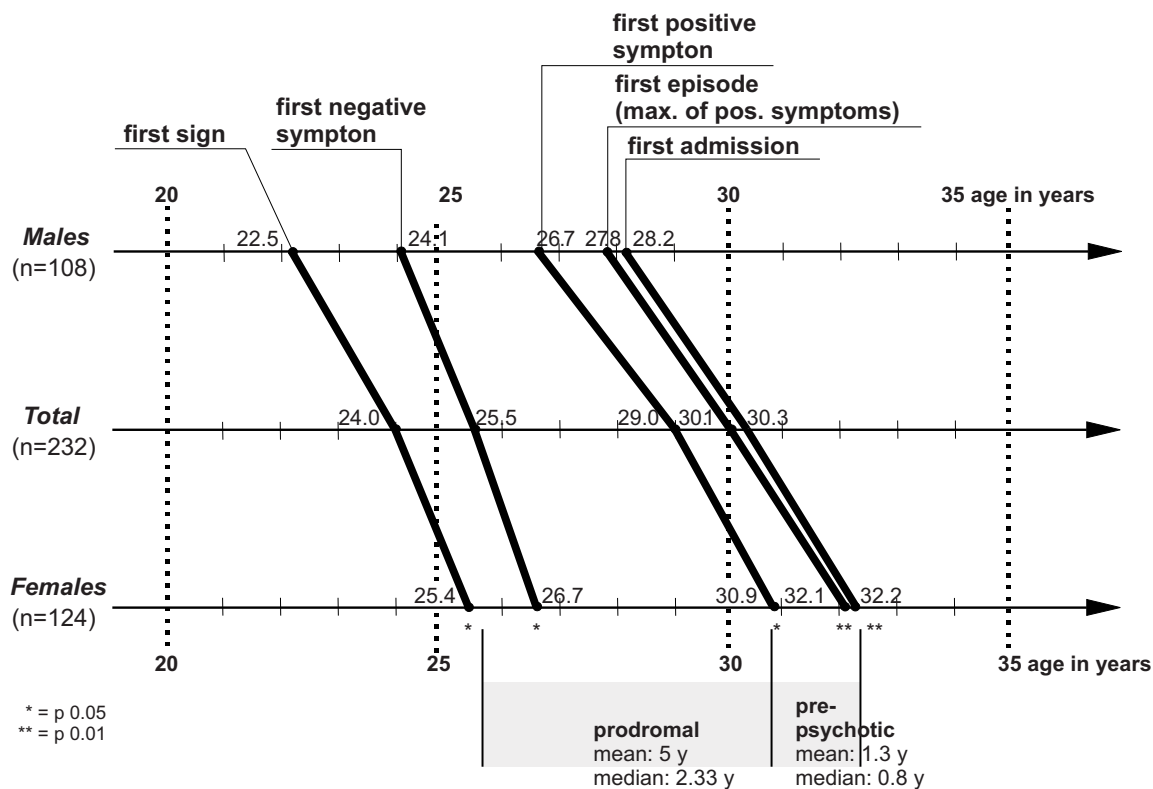
Figure 4 Mean age values at five definitions of onset until first admission, first-episode sample of schizophrenia, broad definition (n=232). Source: Häfner, 1996.
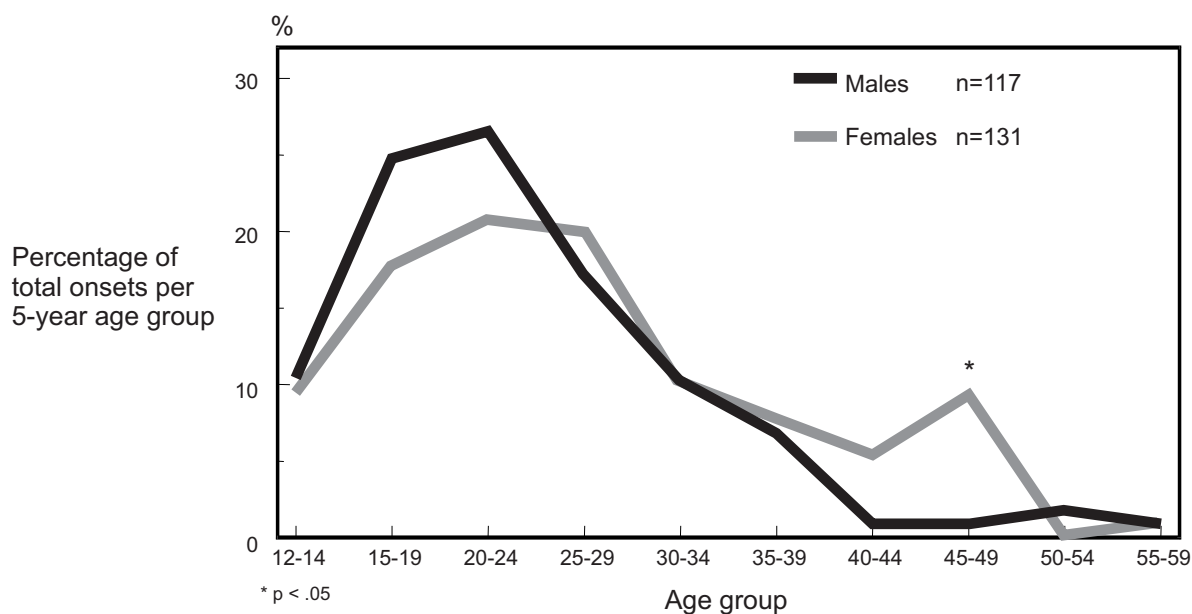

Figure 5 Distribution of age at onset of schizophrenia (first ever sign of mental disorder) by sex, ICD 9: 295, 297, 298.3 and .4), ABC Schizophrenia Study.
Source: Häfner et al., 1993b.

analysis we could demonstrate that oestrogen reduces the sensitivity of D2 receptors (Gattaz et al., 1992). This effect seems to be responsible for the suppression or lower probability of symptom production. The effects were at their highest in young animals.

A decade of experimental oestrogen studies has shown that the sex hormone has potent neuromodulatory effects and beneficial functions in both health and disease (Kulkarni and Fink, 2000). The basic neurobiological mechanisms include genomic and nongenomic effects as well as interactions with free radical detoxifying systems and the inhibition of the cellular liquid peroxidation (McEwen et al., 1981, Woolley and McEwen, 1994, Sumner and Fink, 1995, Shughrue et al., 1997, Fink et al., 1998, Sumner et al., 1999, Behl, 2002). The protective effect in schizophrenia, as shown in our study, is based on a sensitivity reducing effect on central D2 receptors and the inducement of a significant increase in $5HT_{3A}$ receptors and a serotonine transporter (SERT). The reduction of D2 sensitivity is presumably responsible for attenuating positive symptoms, and the increase in $5HT_{2A}$ receptors might protect against depressive and negative symptoms (Fink, 1995).

Oestrogen also acts receptor independently as a potent neuroprotective factor. Acting on various sites of the brain, especially the basic forebrain, the hypothalamus, but also the spinal cord, oestrogen seems to improve synaptic connectivity, neurotrophic signalling, dendritic plasticity and cholinergic activity (Fink, 1995). Via these mechanisms oestrogen is capable of improving cognitive functioning and memory not only at the early stages of Alzheimer's disease, but also throughout life. Whether this neuroprotective property of oestrogen could also be harnessed for preventive or restitutive purposes in schizophrenia is not yet known.

The applicability of the results of our animal experiments to human schizophrenia was shown by Riecher-Rössler et al. (1994a, b). Comparing 32 women with schizophrenic and 29 women with depressive episodes, both with normal menstrual cycles, we found significant negative correlations of increasing oestrogen plasma levels with schizophrenia symptom scores in both groups of women, but no correlation with depressive symptom scores in either group. From this we concluded that oestrogen also has a weak neuroleptic-like effect on schizophrenic symptoms. An analogous variation in symptom severity over the menstrual cycle was also reported by Hallonquist et al. (1993), and similar clinical observations had previously been published by Dalton (1959) and Endo et al. (1978).

Seeman and Cohen (1999), early proponents of the oestrogen hypothesis, tested the hypothesis that an earlier onset of functional oestrogen secretion with puberty might be associated with a later onset of schizophrenia in women. In line with the hypothesis, they found a significantly negative correlation between age at puberty and age at schizophrenia onset in women, but no correlation in men.

Age difference in severity of illness between men and women (interaction of age and gender) (Domain 5)

Assuming that a greater severity of illness is associated with an early outbreak of the illness, men, lacking the protective effect of oestrogen, would be expected to develop the most severe forms of the disorder fairly early and, with increasing age, increasingly milder forms. In women, as long as oestrogen remains effective, the disease should be slightly milder, and a certain proportion of schizophrenias should not become manifest until menopause. From premenopause on, with decreasing oestrogen secretion, women should not only show higher incidence rates, as depicted in table 5, but also present more severe forms of the disorder.

A comparison of PSE-CATEGO symptom scores in early- and late-onset schizophrenia (age at onset 20 years or younger versus 40 years or older) by gender yielded different age trends for men and women (Table 6). Four out of eight symptom scores were significantly lower for late-onset men than for their early-onset counterparts. In contrast, in late-onset women not a single symptom score was significantly lower and one, the SANS global score denoting negative symptomatology, was significantly higher compared with early-onset cases. This means that the milder symptomatology of late-onset schizophrenia is accounted for by men alone. These gender-different age trends in the severity of first psychotic episodes support our hypothesis of an age-dependent protective effect of oestrogen: men develop relatively severe first episodes at young age, whereas young women present slightly milder cases on average. But later in life, severity of first episodes decreases in men and increases slightly in postmenopausal women.

In clear agreement with our results at the symptom level, Lewine et al. (1997), who studied the interaction of sex and age of onset of schizophrenia, found a worse cognitive outcome for early-onset males (<25 years) compared with late-onset males and a poorer outcome for late-onset females compared with early-onset females.

Also in line with our hypothesis are the results of several long-term studies showing that schizophrenia of an early onset, too, has a poorer outcome from menopause on in women than in men (Opjordsmoen, 1991).

Table 5 Onset of schizophrenia by age and sex – ABC first-episode sample n=232

Age at first psychotic symptom	n	Men	Women	m/f ratio
12 - 20 yrs.	49	57%	43%	1.33
21 - 35	136	48%	52%	0.92
36 - 59	47	32%	68%	0.47*

* Odds ratio = 2.16 (sex ratio in the age group against the sex ratio in the remaining age groups); p < .05

m/f = male/female

Source: Häfner and Nowotny, 1995.

Table 6 Symptomatology at onset: young and old in comparison (age at first psychotic symptom < 21 years vs. > 40 years)

Symptomatology	Men			Women		
	Young n=28	Vs. Wilcoxon	Old n=9	Young n=21	Vs. Wilcoxon	Old n=24
DAS	12.1	.02*	⁻5.7	10.0	.95	10.5
BSO	8.6	.29	7.3	8.9	.44	7.9
SNR	10.7	.11	7.3	8.2	.42	7.1
NSN	18.9	.03*	⁻11.4	13.0	.58	13.8
Total score	50.3	.02*	⁻31.8	40.0	.80	39.2
SANS	9.3	.29	6.6	6.7	.08t	- 9.5
PIRS	10.7	.29	8.4	9.8	.73	10.5
DAS-M	3.0	.06t	⁻1.8	1.9	.61	1.8

Source: Häfner et al., 1998a.

The antagonism between the strength of predisposition to the illness and the protective effect of oestrogen (Domain 5)

Leboyer et al. (1992), DeLisi et al. (1994), Kendler and Walsh (1995) and Albus & Maier (1995) showed that there is no major gender difference in age at onset in familial schizophrenia. In contrast, the definitely non-familial cases of Albus and Maier's sample had a gender difference as pronounced as 5.7 years. In our replication study of the ABC first-episode sample the gender difference in age at psychosis onset did indeed fall in cases with at least one first-degree relative with schizophrenia from 4.2 in the total sample to 1.6 years and, thus, below the level of signifigance (Könnecke et al., 2000) (Figure 6). In sporadic cases (i.e. proband has no relative with any type of mental disorder) the gender difference was a highly significant 4.9 years. As predicted by the oestrogen hypothesis, the age at onset difference between familial and non-familial cases was almost entirely limited to women, whereas men showed no significant difference in age at onset between familial and non-familial cases.

These results supported Albus & Maier's hypothesis: the stronger the patients' genetic liability, the weaker the effect of delay that oestrogen has on schizophrenia onset (Albus and Maier, 1995).

We then tested whether the other risk factor of aetiological relevance for schizophrenia, pre- and perinatal complications, too, weakens the protective effect of oestrogen. And it indeed does, though to a somewhat smaller extent than familial load (Figure 7). Hence, oestrogen is capable of warding off schizophrenia onset the more strongly, the weaker individuals' vulnerability or strength of predisposition.

Support for the oestrogen hypothesis from intervention studies (Domain 5)

Reliable evidence for causal effects can be obtained from intervention studies varying the presumed causal factors. Kulkarni et al. (1999), conducting a systematic study with two different dosages of oestradiol as an adjunct to neuroleptic medication in psychosis, found significant dose-related improvement in positive and
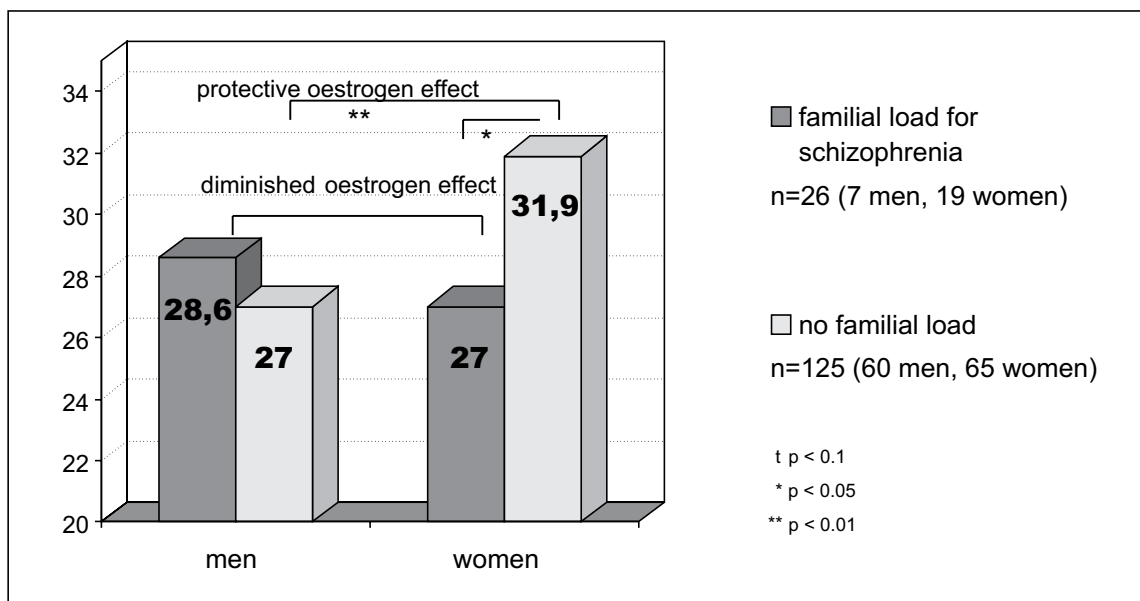
Figure 6 Age at first psychotic symptom by gender and familial load (ABC first-episode sample n=232).
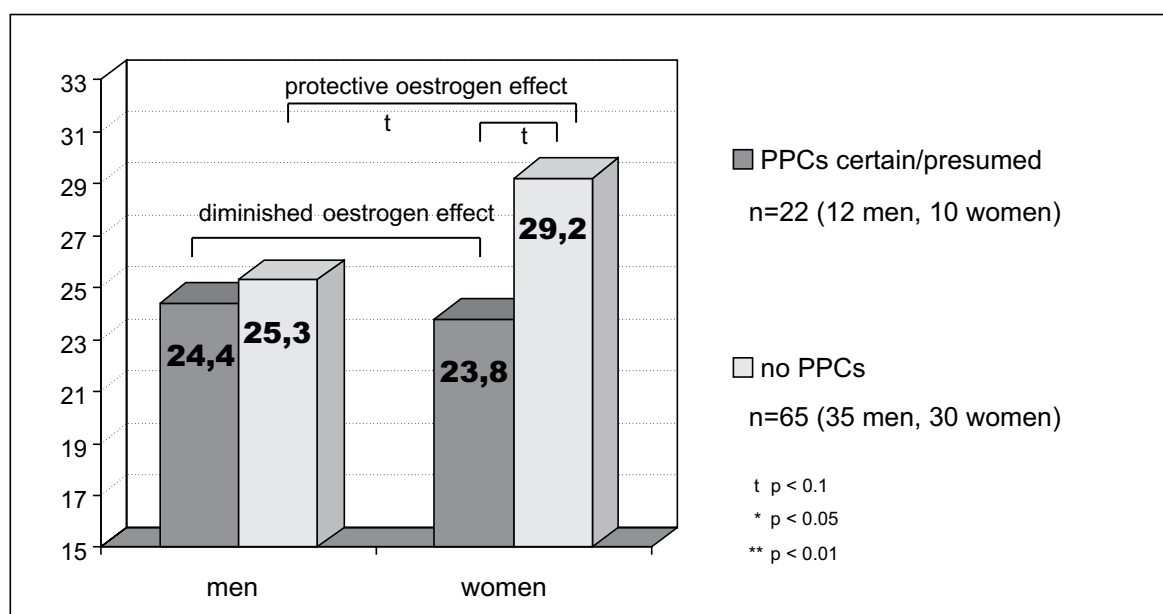Source: Könnecke et al., 2000.

Figure 7 Age at first psychotic symptom by gender and presence/absence of pre- and perinatal complications (PPC) (ABC first-episode subsample n=87).
Source: Könnecke et al., 2000.

negative symptoms (Kulkarni et al., 1999). In two pilot studies, one with male patients suffering from schizophrenia, Kulkarni et al. (1996a, b, 2002) also found significant short-term antipsychotic effects of adjunctive oestradiol treatment. Improvement in psychotic symptoms has also been reported to occur with the addition of a combined oestrogen-progesterone oral contraceptive (Felthous et al., 1980).

Premorbid hypooestrogenism (Domain 4)

In a historical review Riecher-Rössler and Häfner (1993) showed that the early psychiatric writers, for example E. Kraepelin and E. Kretschmer, had already noticed that persons with schizophrenia show deficits in the maturation of primary and secondary sex characteristics more frequently than their healthy peers.

As a consequence, it was also early speculated that the risk for schizophrenia might be associated with gonadal hypofunctioning. Recently, several authors have fairly consistently reported subnormal oestrogen blood levels in women with first-onset schizophrenia not yet treated with psychotropic drugs (Riecher-Rössler, 2002). The temptation is now great to regard gonadal hypofunction as a risk factor amenable to preventive action. But we are still a long way off from this goal, especially since the specificity and positive predictive power of hypooestrogenism for schizophrenia onset have not yet been demonstrated and are presumably rather low. Under these circumstances they do not justify any intervention involving risks.

An unresolved question is whether the finding might be attributable to secondary, environmental, causes at least to some extent: The early deficits in communicability and mating behaviour of pre-schizophrenic individuals presumably result in a lower stimulation of the gonadal function due to a sexually less stimulating environment. Last but not least, the equal lifetime risk of men and women for schizophrenia hardly speaks for a lifetime risk factor specific to the female gender. Nothing is known yet on hypogonadism as a risk factor for schizophrenia in men.

Abnormalities in brain development and morphology (Domain 9)

The female brain matures more rapidly than the male brain. Hence, it might be less vulnerable to pre- and perinatal and childhood insults. Castle and Murray (1991) assumed that the gender difference in age at onset might be caused by a preponderance of men with pre- and perinatal complications and an early illness onset. This hypothesis did not find support in methodologically sound studies (Geddes and Lawrie, 1995; Jones et al., 1998; Könnecke et al., 2000).

Castle (2000) explains the female preponderance of schizophrenia and delusional disorders of old age with a difference in the aging of male and female brains. According to him the loss of dopamine receptors in women begins earlier in life, but shows a relative excess compared with men in later life. This differential process of loss of D2 receptors might also account for the higher frequency of tardive dyskinesia in elderly women after a lengthy treatment with neuroleptics.

We do not know yet whether the sex differences in brain maturation cause substantial differences in disease variables in a stricter sense. At any rate the sex-specific behavioural patterns which become evident in childhood and youth, for example the highly different social behaviour, have very different impacts on illness behaviour and social outcome in male and female patients. Castle (2000) puts this as follows: "... understanding differences between women and men in terms of biological, psychological and social domains can inform our understanding of gender differences in schizophrenia, but more broadly schizophrenia as a disorder." Gender differences in cognitive functioning of the mature brain seem to play a minor role in schizophrenia (cf. P. 5; Goldberg et al., 1995). The basis in brain morphology is a greater bihemispheric presentation of functions in female and a more pronounced lateralisation in males (McGlone, 1980; Witelson, 1989). Crow (1994) took the gender differences in cerebral lateralisation as a basis for speculations: a delay in maturation and an increase in brain size evolved the capacity for a high degree of communication and social interaction. Schizophrenia is seen by Crow as a defect of cerebral lateralisation tied to the emergence of language: "Schizophrenia is the price (humans) pay for language. The sex difference in the rate of hemispheric differentiation could account for the sex difference in age at onset...". But these are just hypotheses of minor plausibility still awaiting to be validated.

A series of neuroanatomical and neuroimaging studies on gender differences in structural brain abnormalities have shown more pathology in male than female patients (Andreasen et al., 1990; Bogerts et al., 1990; Castle and Murray, 1991; Lewine and Seeman, 1995; Goldstein, 1996). But there are also several studies that have found no exaggeration of the normal gender dimorphism of the brain in schizophrenia (Flaum et al., 1995). The reasons for this inconsistency may have something to do with the methodologies of these studies (Goldstein, 1993; 1995a, b; Lauriello et al., 1997; Goldstein and Lewine, 2000), with the small sample sizes in particular (Moldin, 2000). For example, sMRI studies have reported a preponderance of enlarged lateral ventricles (Andreasen et al. 1990) and a small hippocampal formation in males (Bogerts et al., 1990). A post-mortem study (Crow et al., 1989) found a larger planum temporale in male but not in female patients with schizophrenia. A few studies have reported ventricular enlargement in women, but not in men (Nasrallah et al., 1990; Gur et al., 1991). Despite increasing controlling for confounding factors, like IQ, ethnicity and social class, it is still too early to pass a definitive judgement on the role of these factors.

But comparative analysis based on functional imaging (e.g. Gur and Gur, 1990; Gur et al., 1995) and neurophysiological paradigms (EP etc., Reite et al., 1989; 1993), have equally failed to provide a definitive answer to sex differences in schizophrenia. For this reason

especially the case on the effects of steroid hormones on brain development and brain functioning and their implications for the risk of schizophrenia (Seeman, 1989a; Seeman and Lang, 1990; Behl, 2002) cannot be closed yet.

Gender differences in illness behaviour (Domain 6)

The "normal" sex differences in social and coping behaviour in adolescence and early adulthood led us to investigate them in schizophrenia, too. To analyse sex differences in the first illness episode in greater detail we compared all the 303 single items from the instruments we used for measuring symptoms, functional impairment and social disability (PSE, SANS, PIRS, DAS and IRAOS) in the first episode. Controlling for multiple testing we found no significant gender differences in the positive and negative core symptoms, except for some contents of delusions, such as delusions of pregnancy, which were – quite understandably – more frequent in women.

The most pronounced gender difference emerged with socially adverse behavioural items, such as self-neglect, reduced interest in a job, social withdrawal and deficits of communication, which were all significantly more frequent in men in the first psychotic episode (Table 7). Only one – socially favourable – behavioural item was significantly more frequent in women: overadaptiveness/conformity. The cumulative prevalence of drug and alcohol abuse, too, was significantly more

frequent in men, as shown by several other studies (Mueser et al., 1990b, 1992; Soyka, 1994; Kessler et al., 1994; Jenkins et al., 1997; Kandel, 2000). Restlessness was the only further item that showed a significantly higher frequency in women.

But these findings are presumably not specific to schizophrenia, considering the behavioural gender differences in normal development mentioned above. In view of the consistent reports of a higher frequency of conduct disorders, disruptive, antisocial and violent behaviour and of alcohol and substance abuse among young men in comparison with their female counterparts from population studies (Choquet and Ledoux, 1994; Döpfner et al., 1997), we are here probably dealing with a reflection of normal gender- and age-specific behaviour. The normal psychology of behavioural gender differences, reviewed for example by Maccoby and Jacklin (1974), has shown that boys and young men exhibit a higher frequency of aggressive behaviour, in particular antisocial aggression, than girls and young women do, who display more prosocial aggression or aggressive inhibition and a greater acceptance of authority.

But this socially adverse illness behaviour of men with schizophrenia is strongly age-dependent, showing the highest frequency before age 30 (Figure 8). With increasing age men's illness behaviour in schizophrenia becomes socially more favourable indicating improved adjustment and, as a result, probably also reducing the male disadvantage in the social course of schizophrenia.

Table 7 Behavioural items with significant sex differences (from a total of 303 PSE, PIRS, SANS, DAS and IRAOS items)* – ABC first-episode sample, n=232

More frequent in women:	More frequent in men:
a) cumulative until first admission	
■ restlessness	■ drug abuse
	■ alcohol abuse
b) cross-sectional: at first admission	
■ overadaptiveness/ conformity	■ self-neglect
	■ reduced interest in a job
	■ social inattentiveness
	■ deficits of free time activities
	■ deficits of communication
	■ social disability (overall estimate)
	■ loss of interests
	■ deficits of personal hygiene

* Validated by split-half method for Â-correction
Source: Häfner, 1998.

Mean score

* Self-neglect; Deficits of free time activities; Deficits of communication
Reduced interest in a job; social disability (overall estimate); loss of interests;
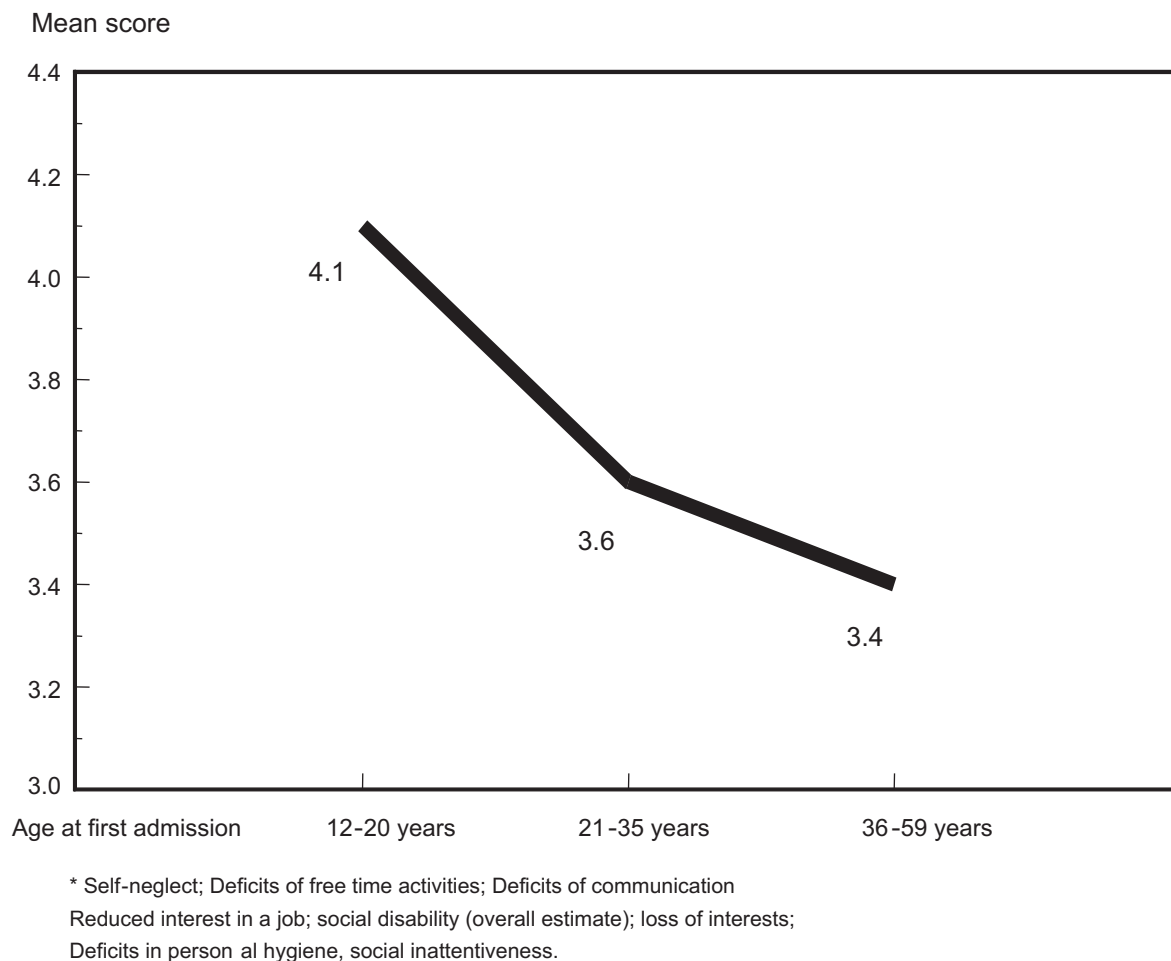Deficits in person al hygiene, social inattentiveness.

Figure 8 Socially negative behaviour* of men (significantly different to women's) at first admission by age (ABC first-episode sample n=232).
Source: Häfner, 2000.

Sex differences in the course and outcome of schizophrenia (Domain 7)

A wealth of studies have reported a poorer short- and medium-term course of schizophrenia for male compared with female patients. In a review of mainly short- and medium-term follow-up studies Angermeyer et al. (1990) found that about half of the studies showed a more favourable outcome in women, and this finding was statistically significant. When the dimensions of illness course and outcome have been looked at separately, the difference has turned out to be accounted for by the social and not the symptom-related course (Biehl et al., 1986; Salokangas et al., 1987; Häfner et al., 1999b).

In our study the symptom-related course over 5 years after first admission indeed showed no significant difference between men and women either in the CATEGO global scores or in the four subscores (Figure 9). The mean symptom scores from remission

of the first episode on indicated, rather than a trend to deterioration, absence of any significant change over time. By contrast, the social course of the disorder, indicated by the behavioural items with significant sex differences at first admission (cf. Table 7), was significantly poorer for men throughout the 5-year follow-up period studied (Figure 10). The same was true with social disability measured by the DAS (WHO, 1988). This result lends support to our hypothesis that men's socially unfavourable illness behaviour might contribute to their poorer social course and outcome, whereas women's higher tendency to prosocial behaviour, cooperativeness and compliance might influence the social course of schizophrenia favourably.

Real-life disadvantages are caused by deficits in social functioning. This leads to the question when and to what extent social disability, whatever its causes, emerges in the course of the disorder. We traced dysfunctional social roles and dysfunctional overall behaviour by means of the Disability Assessment
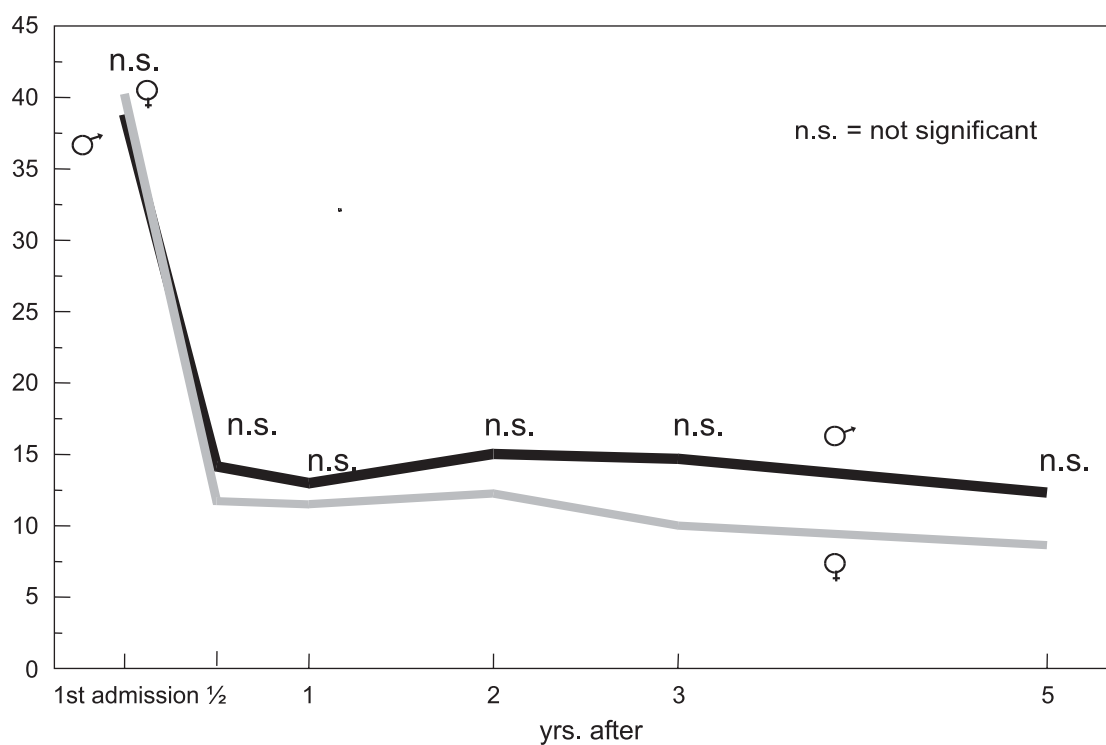
Figure 9 Five-year course of schizophrenia (from first admission – 6 cross sections) for men and women by the CATEGO total score (ABC first-episode follow-up subsample n=115).
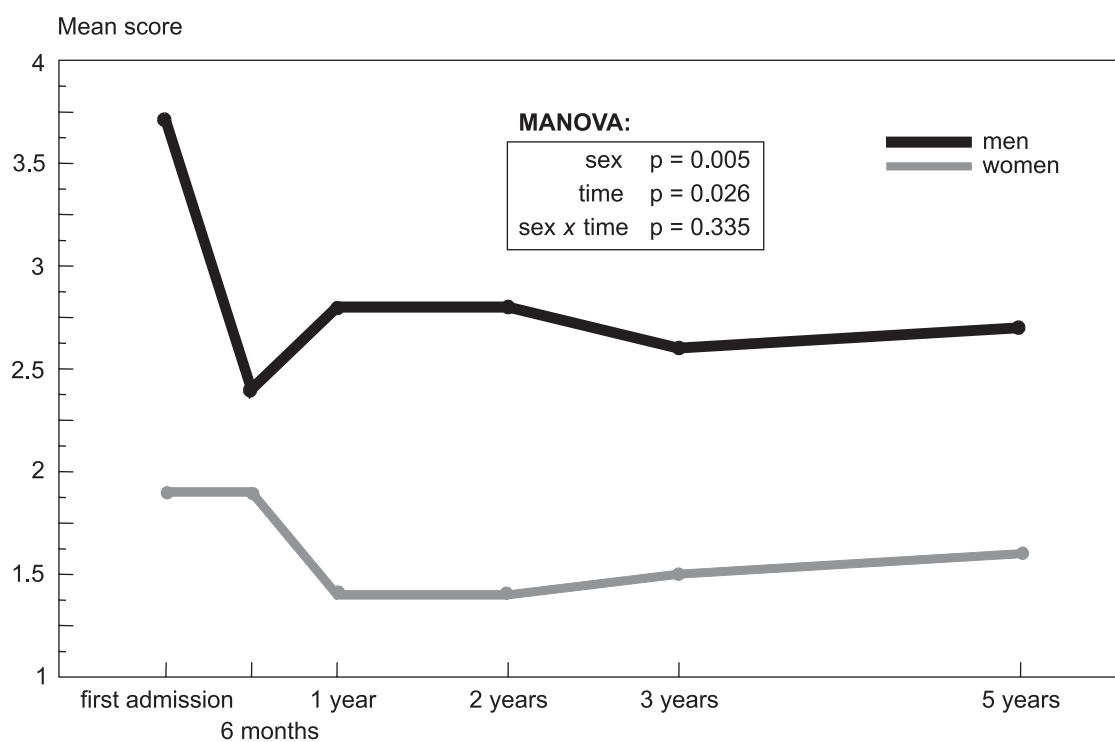
Source: Häfner, 1998.

Figure 10 Socially negative behaviour over five years after first admission for schizophrenia by sex (ABC first-episode follow-up subsample n=115).
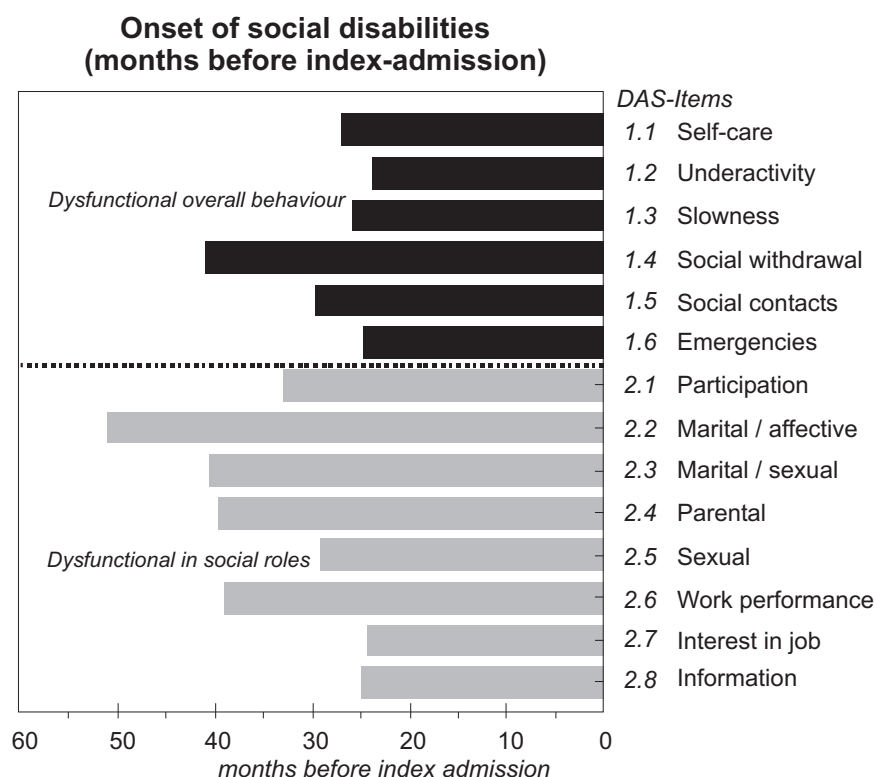
Source: Häfner et al., 1998b.

Schedule (WHO, 1988) retrospectively from first admission back. As figure 11 shows, the disabilities measured by the DAS items – dysfunctional social roles and behaviours – manifested themselves on average as early as 2 to 4 years before first admission. Hence, it was long before the first psychiatric contact that the patients with schizophrenia first exhibited deficits in social functioning.

For a reliable assessment of the social course and consequences of a disorder it is necessary to proceed from a baseline, the level of social development at the onset of the disorder. We chose six key social roles characteristic of the main period of risk for schizophrenia and compared them at age of illness onset in three age groups: 20 or younger, 21 to 35 years and 36 and older. The finding was trivial: large, significant age-differences in the six roles studied, i.e. school education, occupational training, employment, own income, own accommodation, marriage or stable partnership. These roles indicate the level of social development at illness onset: the older at onset, the higher the social status.

A comparison of social-role performance, as based on these six indicative roles, at illness onset between male and female patients revealed significant advantages for women in the domains of employment, own income and marriage or stable partnership in particular (Table 8). From these results we inferred that due to the disorder's three to four years earlier intrusion in men's social biographies it might be their lower baseline of social development at illness onset and their socially adverse illness behaviour that explain their more unfavourable social course compared with women's.

To demonstrate how schizophrenia affects social development between illness onset and first admission in men and women, we chose the most vulnerable social role: marriage or stable partnership. We compared 57 first-episode cases of schizophrenia from Mannheim with 57 controls matched for age-, sex- and place of residence. At illness onset there was no significant difference between patients and healthy controls, male or female (Figure 12). But, because of the age difference of 4 years and men's 2.5 years higher age of marrying in the general population at that time males and females showed a significant difference: during the period of 6 years the percentage of healthy men married or in a stable partnership gradually approached that of healthy women, whereas the figures for men and women with schizophrenia fell continuously after illness

Onset of social disabilities (months before index-admission)

months before index admission

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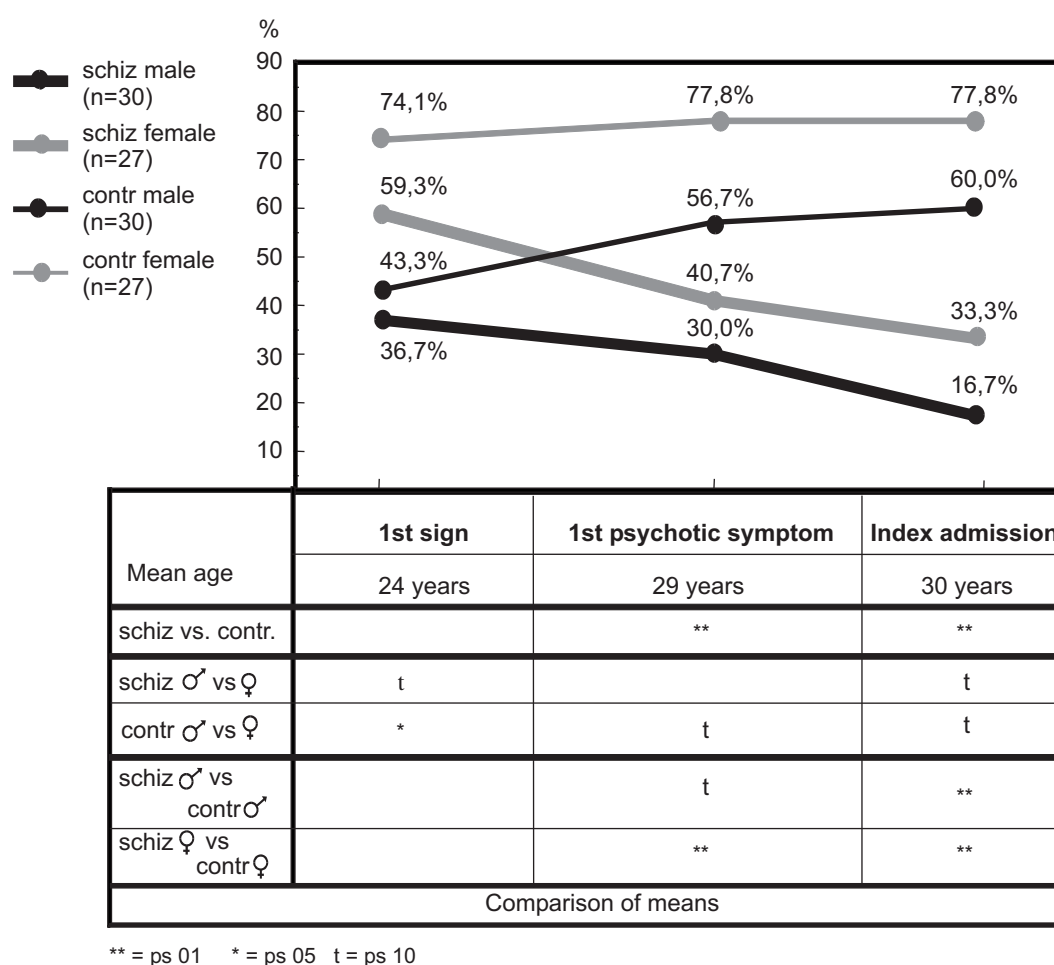**Figure 11** Onset of social disabilities (months before index admission).
Source: Häfner et al., 1996, modified.

Table 8 Social "baseline" at illness onset: social-role performance of men and women at the emergence of the first sign of mental disorder – ABC first-episode sample n=232

	Men n=108		Women n=124	Total n=232
Age (in years)	22.5		25.4	24.0
	%		%	%
School education	70		69	70
Occupational training	41	n.s.	38	39
Employment	37	*	52	45
Own income	44	n.s.	55	50
Own accommodation	39	*	54	47
Marriage or stable partnership	28	**	52	41

tp ≤ 0.1; * p ≤ 0.05; ** p ≤ 0.01; n.s. = not significant

Source: Häfner, 1996, modified

Mean age	1st sign 24 years	1st psychotic symptom 29 years	Index admission 30 years
schiz vs. contr.		**	**
schiz ♂ vs ♀	t		t
contr ♂ vs ♀	*	t	t
schiz ♂ vs contr ♂		t	**
schiz ♀ vs contr ♀		**	**
Comparison of means			

** = ps 01   * = ps 05   t = ps 10

Figure 12 Development of social-role performance in men and women with schizophrenia from illness onset to first admission: marriage or stable partnership (ABC first-episode sample n=232).

Source: Häfner et al., 1999b.

onset. Female patients, however, managed to retain their significant advantage over their male counterparts at first admission: at that time 33 % of the women with schizophrenia, but only 17 % of the male patients were living with a spouse or partner, compared with 78 % of the female and 60 % of the male controls.

Predicting five-year social outcome (after first admission) (Domain 7)

The next step was to test the predictive power of the two main variables of social course and outcome – level of social development at psychosis onset and socially adverse illness behaviour at first admission. Figure 13 illustrates two models: on the right a stepwise logistic regression including the two index variables and symptoms at first admission measured by the PSE, type of onset, age at first psychotic symptom and gender, and on the left a path-analytic model for analysing partial correlations of age at onset and gender with the two social variables. Significant predictors of 5-year social outcome, operationalised by the ability to earn one's living, were the number of non-fulfilled social roles at psychosis onset and the number of items of socially adverse illness behaviour at first admission. Symptomatology and type of onset had no effect, age and gender merely that mediated by the first two

variables. This is clearly shown in the pathanalytic model on the left, which revealed highly significant partial correlations of age at onset and gender with the two mediating variables: social development at illness onset and illness behaviour (Häfner et al., 2001b). This means that the sex difference in the social course of schizophrenia, instead of reflecting a gender-different illness, is basically a result of the protective effect of oestrogen in women, mediated by the higher stage of social development at illness onset, and an additional effect of the socially adverse illness behaviour of men.

Sex differences in the long-term course of schizophrenia (Domain 7)

There are only few methodologically high-standard follow-up studies of representative first-episode samples extending over 10 years or more. The studies by an der Heiden et al. (1995; 1996), Opjordsmoen (1991) and Goldstein (1988) showed that the gender differences in the early course of the disorder become diluted over long periods of follow-up. Harrison et al. (1996) reported a gender effect in a small first-admission sample sustained over a 13-year period after adjustment for sociodemographic variables and type of early course.

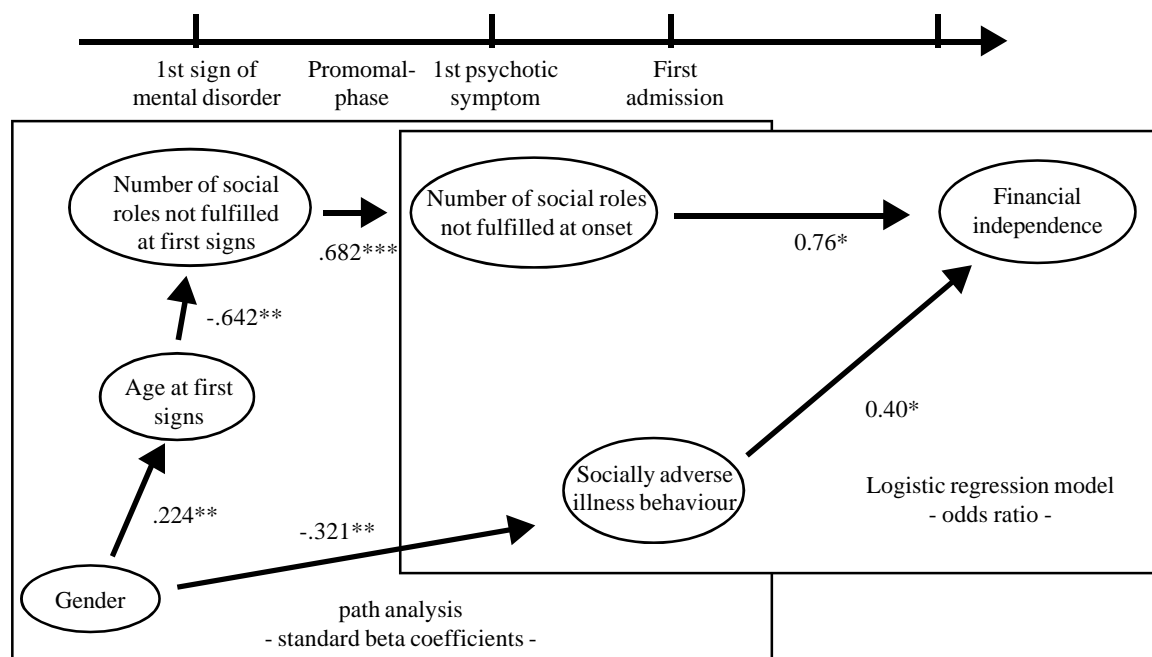The Mannheim first-admission cohort (an der Heiden et al., 1995; 1996) of the WHO Disability Study

Figure 13 Prediction of five-year social outcome in schizophrenia: analysis of direct and mediating causal factors (ABC first-episode follow-up subsample n=115).

Source: Häfner et al, 2001b.

was assessed at 10 cross sections over 15.6 years after first admission. The repeated single measurements, based on the PSE total score, demonstrated a relatively high degree of stability in the mean symptom scores over the long-term course (Figure 14). But women, showing significantly lower symptom scores only in the first 1.5 years after first admission primarily because of their shorter first episodes, attained the level of male scores in the long-term. From two to 15.6 years after first admission men and women showed almost equal symptom levels.

The gender differences in social disability, still present at the 5-year assessment after first admission, had disappeared at the later assessments, possibly as a result of the age-related decrease in socially negative male behaviour. During the last nine months before the 15.6-year assessment the percentages of good (no symptoms or disability present) and poor outcomes (suffering from at least one positive or negative core symptom or disability in the last 9 months) – 40% versus 60% – did not show any sex difference, as illustrated in figure 15.

But two thirds of the symptom-free women and only one tenth of the symptom-free men continued to be on antipsychotic drugs. We assume that this gender difference, too, resulted from sex-specific illness behaviour: women's generally better cooperativeness and compliance with treatment measures compared with men's. An alternative interpretation, which we are unable to refute, runs that men with schizophrenia who are doing well do not require as much antipsychotic treatment. The symptomatic group though did not show any significant gender difference in their use of neuroleptic drugs.

Inspite of the similar outcome measures in terms of symptom scores and social disability, there were considerable differences in marital status between men and women (Table 9): 71% of the male patients, but only 23% of the female patients had never married. Consequently, only 28% of the men, but 53% of the women were living with a spouse and 28% of the men, but only 5% of the women were living in a supervised apartment or home. Naturally, more than twice as many women as men had children. Interestingly, however, there was no significant sex difference in employment status, which coincided with the equal measures of social disability for men and women.

The fact that women fare better in real life than men is obviously accounted for by women's more favourable social conditions at illness onset and socially less adverse behaviour in the course of the illness. However, a high proportion of the female patients who had married before illness onset or in the subsequent 15-year course of illness were divorced and some had re-married. It seems that because of their more prosocial behaviour, presumably in conjunction with the traditional
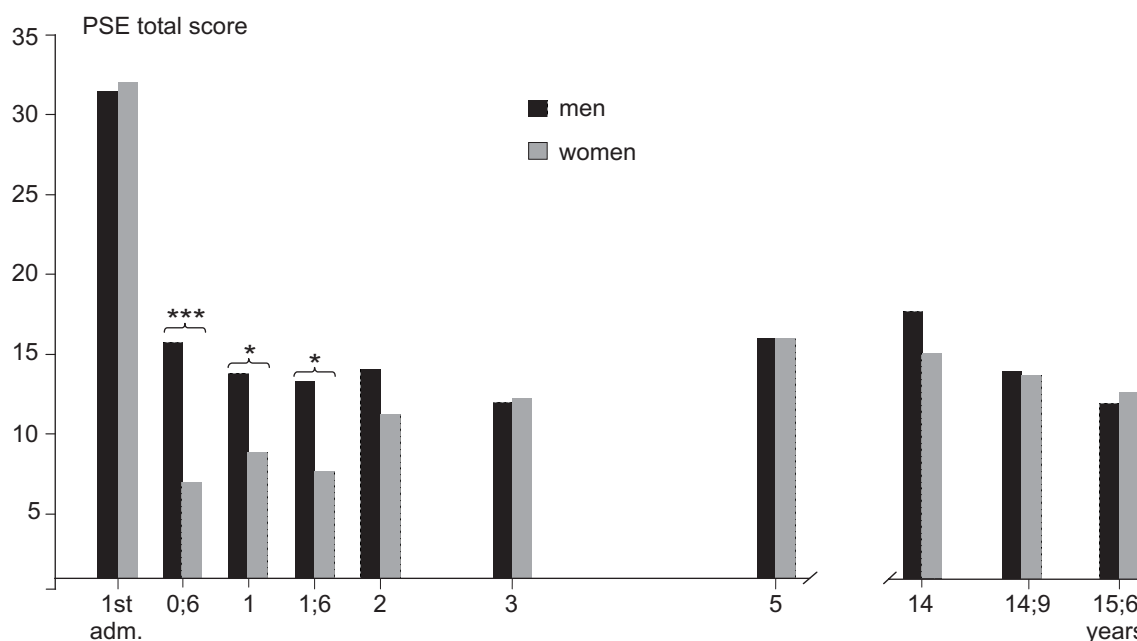

Figure 14 PSE total score over 15.6 years after first admission (9 cross sections) by sex (first-admission sample of the WHO "Disability Study" Mannheim cohort n=70).
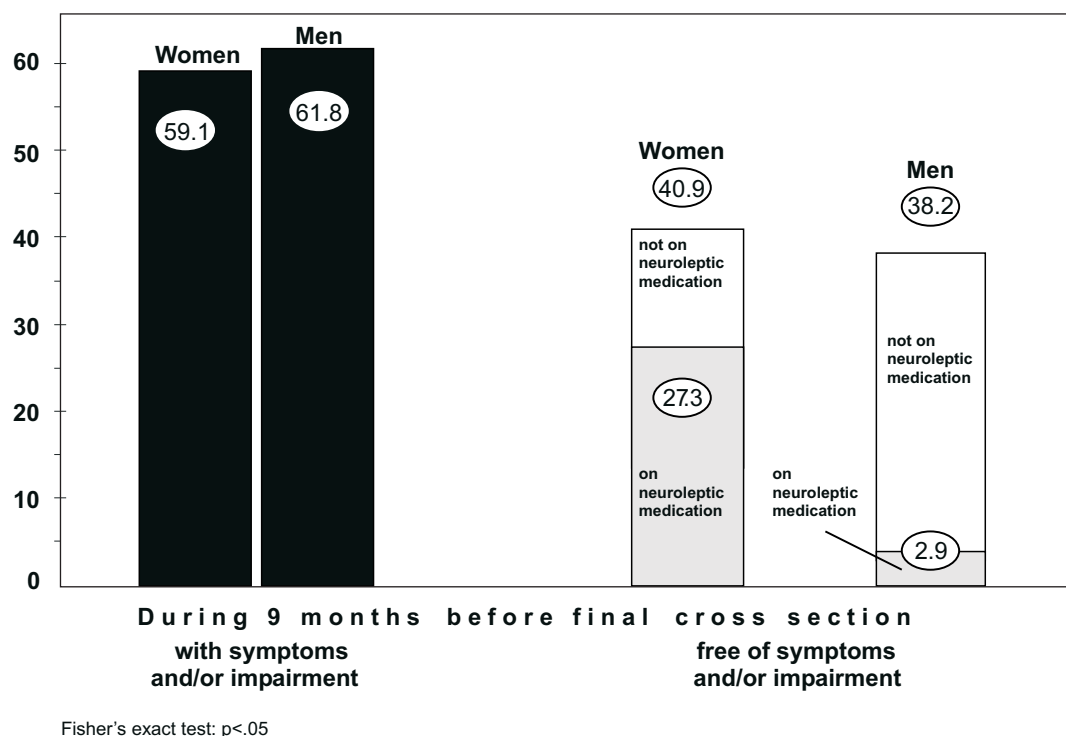Source: an der Heiden et al., 1995.

Figure 15 Two outcome groups 14 years after first admission by sex. Based on data from an der Heiden et al., 1996. Source: Häfner, 2000.

Table 9 Living situation of schizophrenic men and women 15.5 years after first admission – WHO "Disability Study" Mannheim cohort n=70 at inclusion in the study

	Women n = 22	Men n = 34	
Mean age[+]	44 years	41 years	n.s.
Outcome: symptoms or disability present	59%	62%	n.s.
Living situation:			
never married	23%	71%	**
married[+]	42%	19%	t
lives with a spouse/ partner[+]	53%	28%	*
lives in a home[+]	5%	28%	t
own children[+]	45%	26%	*
Employment status: has a regular job	26%	31%	n.s.

n.s.: not significant t: p < 0.1 *: p < 0.05 **: p ≤ 0.001
[+]n= 51 due to missing data
Source: an der Heiden, 2002

gender roles in society, women with persistent schizophrenia, more often than their male counterparts, manage to find a new partner after a failed marriage or to some extent also to maintain an existing partnership.

Response to neuroleptic treatment (Domain 8)

Because of the neuroleptic-like effect of oestrogen women with schizophrenia appear to respond more favourably than male patients to neuroleptics or require lower doses. In addition, post-menopausal women with their more severe illness seem to need higher doses of antipsychotic medications than their male counterparts do, who present milder illness in this period of age. Seeman and colleagues first reported this finding in 1983 (Seeman 1983) and have since then presented several results confirming the initial finding (e.g. Seeman, 1989b; Dickson et al., 2000). But not all the findings on the topic are consistent. Other carefully designed studies have failed to find gender differences in daily antipsychotic doses or treatment efficacy (Jeste et al., 1996). Moldin (2000) recently concluded that "more work is needed regarding gender differences ... in response to new therapeutic compounds". What seems to be clear is that men and women require specific treatment programmes not only because of the different effects of gonadal hormones, but also because of the differences in their behavioural predispositions, psychosocial situations, social course of the disorder and life courses (Seeman, 1983, 1989b).]

Coping with illness (Domain 5)

I. Weber (1996) from our group looked into cognitive coping with the illness and subjective life satisfaction in this fairly homogeneous cohort 15.5 years after first admission by using a life goal and satisfaction questionnaire (FNL: Fragebogen zur Lebenszielen und Lebenszufriedenzeit; Kraak and Nord-Rüdiger, 1989), based on Lehman's (1983a, b) interaction model. She assessed subjective importance of life goals, goal achievement and life domain-specific satisfaction and found no correlation between symptom measures and social disability on the one hand and overall life satisfaction on the other. But patients and controls showed significant differences: 82% of the control men and 84% of the control women reported a high degree of overall life satisfaction, whereas only 43% of the male and 58% of the female patients did so.

Many life goals were considered only slightly less important by patients with schizophrenia than by healthy controls, for example to be loved or to maintain stable relationships and self-esteem were almost equally important to both patients and healthy individuals (Figure 16). But only male patients considered sexual relationships and employment as important as did healthy controls. Women had significantly reduced their expectations in these life domains during the lengthy course of the disease obviously as a means of coping with their diminished capacities. As a consequence, women with schizophrenia were generally more satisfied than their male counterparts, whose goal achievement and satisfaction with current status differed more markedly from their high expectations and from those of healthy controls. Nonetheless, women managed to achieve, to a greater extent than male patients, some of their valued aspirations in the domain of interpersonal relationships. Again, it was their illness behaviour that contributed to the more favourable social situation and to their better coping with illness-related deficits and, as a result, to their slightly higher life satisfaction compared with men's.

Conclusions

The nuclear process of schizophrenia, irrespective of age effects, does not essentially differ between men and women. However, due to age-dependent neurohormonal and normal behavioural gender
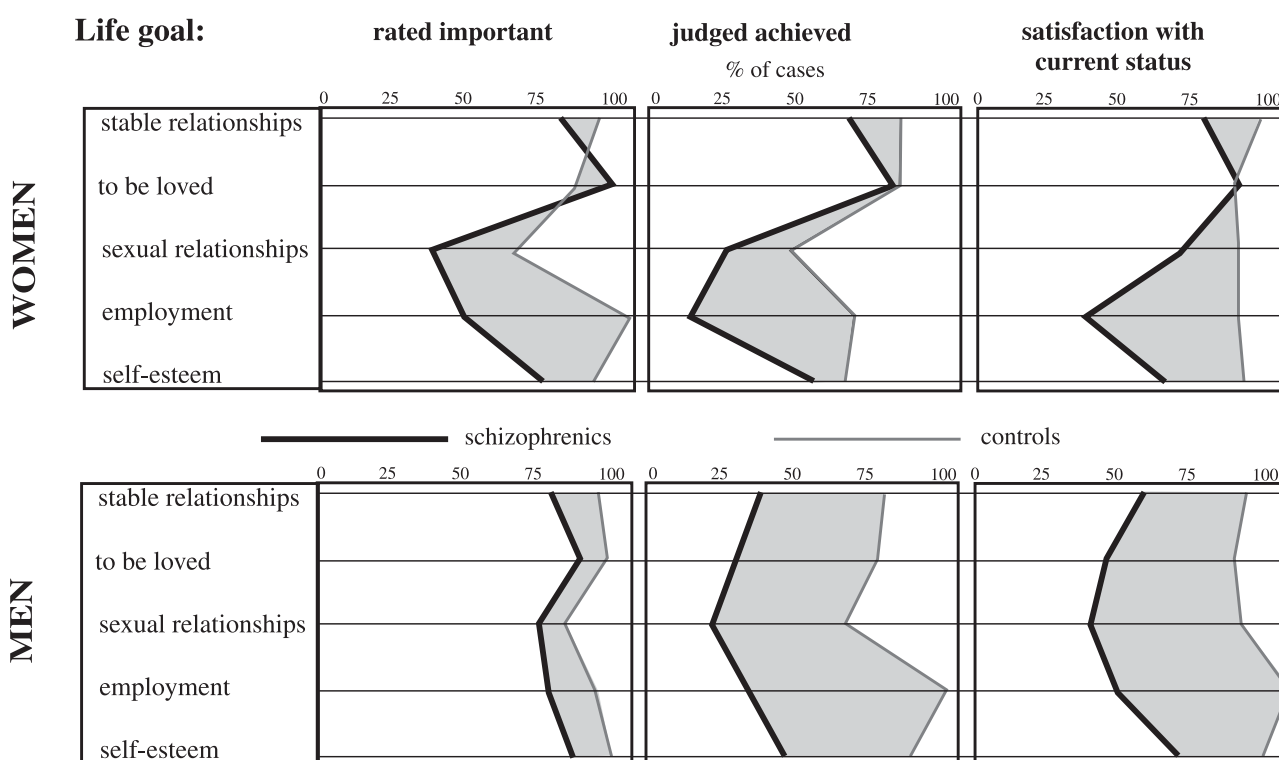

Figure 16 Life-goal importance, achievement and satisfaction of men (n=30) and women (n=18) with schizophrenia 15.5 years after first admission compared with age- and sex-matched controls (first-admission sample of the WHO "Disability Study" Mannheim cohort n= 70). Based on data from Weber 1996.

Source: Häfner, 2000.

differences, age as well as stage of social development at onset, the social course of the disorder and the severity of illness show considerable differences across the life-cycle: men fare particularly poorly at younger age, but significantly better at a later age, whereas women fare considerably better until the age of menopause, but worse afterwards. In the long-term, too, women cope with the illness better and, as a consequence, have better life satisfaction than men do. Oestrogen, which is responsible for a major part of these sex differences via its sensitivity-reducing effect on central D2 receptors, has meanwhile also been demonstrated to have therapeutic effects on both positive and negative symptoms in acute psychosis.

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