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First Onset and Early Symptomatology of Schizophrenia

A Chapter of Epidemiological and Neurobiological Research into Age and Sex Differences

Heinz Häfner, Anita Riecher-Rössler, Kurt Maurer, Brigitte Fätkenheuer, Walter Löffler

Central Institute of Mental Health, W-Mannheim, Federal Republic of Germany

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Abstract. In the frame of the ABC (Age, Beginning and Course) Schizophrenia Project we studied the influence of age and sex on first-ever onset, symptom manifestation and early course up to first admission in schizophrenia by using a large, representative sample of first-admitted schizophrenic patients. The results showed that the two variables had suprisingly little bearing upon the core symptoms, particularly on negative and other most frequent symptoms and on first-rank symptoms. In 70% of the cases schizophrenia started solely with negative symptoms, in 20% with negative and positive and in 10% with positive symptoms only. In most of the cases symptoms accumulated exponentially up to the first acute episode with positive symptoms appearing considerably later. The age differences observed concerned secondary phenomena associated with developmental factors. Such phenomena, i.e. anxiety, depression and the cognitive formation of delusions, can be interpreted as responses to the psychosis. Also the sex differences, which culminated in far more frequent socially negative disease behaviour in males, were limited to secondary phenomena. This positive and negative core symptomatology of schizophrenia seems to be astonishingly uniform and fairly independent of age and sex at this early stage of the disease. The only remarkable difference was a three to four years higher mean age of onset in females. We were able to show in animal experiments and to confirm in a clinical study that this finding is attributable to a neuromodulatory effect of estrogens on the sensitivity of D_2 receptors in the brain. Apparently, estrogens raise the vulnerability threshold until menopause and have a slight neuroleptic-like effect on the symptomatology in acute schizophrenic episodes.

Key words: Schizophrenia, first onset, early symptomatology, early course, age and gender, illness behaviour, paranoid delusions

Correspondence to: H. Häfner

Introduction

The investigation of age and sex in connection with schizophrenia offers some advantages. Unlike complex and mutable variables such as social status and family atmosphere, they are simple and immutable so that we can assess or measure them precisely, understand what we are examining and interpret our findings. We also have to test causal relationships in one direction only: from age and sex to the disease and not vice versa.

We will concentrate on the beginning of schizophrenia, because at this early stage symptomatology and course are likely to be determined mainly by the disease process itself, whereas the effect of external factors like personality and environment will become stronger with increasing duration of the disease.

Two age-related topics are of particular relevance, i.e. *1. The influence of the definition of onset, e.g. by first onset of symptoms, on the age distribution and mean age at onset and 2. the influence of age at onset on symptoms and on the time pattern of their manifestation.*

It has been known for a long time that the maximum number of onsets of schizophrenia is observed during early adult age. Kraepelin (1909–1915) already reported that in Bavaria among 644 first admissions with a diagnosis of dementia praecox women had been admitted on average 5 to 10 years later than men.

Since then the gender difference in age at first admission was validated in more than 50 studies (Angermeyer and Kühn 1988). Together with E. Strömgren and P. Munk-Jørgensen (Häfner et al. 1989) we replicated this result in a systematic transnational comparison of case register data from Denmark and Mannheim and demonstrated a significant age difference of 4 to 5 years. Further evidence for the transnational stability of this finding was provided also by an analysis of the transnational WHO Determinants of Outcome data, recently carried out by Hambrecht et al. (1992) from our research group.

Table 1. Mean age at onset – 4 different definitions – based on the assessments of patient, relative and research psychiatrist

	Patient (years)	Relative (years)	Research psychiatrist (years)	*P*
Earliest sign of mental disorder	25.4	25.4	25.9	0.85
First psychotic symptom	27.9	28.8	28.9	0.30
Beginning of index episode	29.4	29.0	29.4	0.61
First admission for schizophrenia	30.0	30.0	30.0	

Source: Häfner et al. 1992a

Methodological Requirements

Our first step was to test the hypothesis that the gender difference in age at first admission is due to a gender difference in real age at onset, but this topic needs some methodological considerations: A valid analysis of the impact of age has to fulfil some requirements, 1. a sufficiently large sample of all new cases covering the whole age range of onsets from a truly representative population and 2. a clear definition and reliable assessment of symptoms in temporal order from their first occurrence until first hospitalization.

Because of the low incidence rate of approximately 10 per 100,000 annually, large onset samples of schizophrenics cannot be collected in population studies, but only by means of enrichment and screening of presumed cases from large populations. The usual way to do this is to take all hospital admissions in a given period of time with a clinical diagnosis of schizophrenia or non-affective functional psychoses from a defined population. Precondition to this method is that schizophrenics have a nearly 100% lifetime chance of being hospitalized, as Weyerer and Dilling (1978) found in a population study for southern Germany. This result, however, depending as it is on a particular cultural pattern of helpseeking behaviour and free access to a well-developed system of mental health care, is certainly not applicable to all countries and cultures.

In first admission samples the systematic assessment of first onset and course prior to first admission has to be carried out retrospectively. For this purpose we developed a standardized, semi-structured interview, IRAOS, on the basis of internationally approved instruments for measuring psychopathology, social disability and indicators of psychosocial changes (Häfner et al. 1992b). The IRAOS was administered by experienced psychiatrists and psychologists. The timing of each piece of information is ascertained by means of anchor events. We used three independent sources of information, 1. the patient, 2. a close relative, and 3. case notes and other records. The interrater reliability was found to be satisfactory with kappa values varying between 0.62 and 1.0. A comparison of the age values at three different definitions of onset from these three sources (Table 1) shows no significant differences but remarkable similarity of the values. The mean differences to the patients' estimations were 5 months at most, except for the first psychotic symptom, which was noticed by the relatives and documented in the case records some twelve months later than by patients. The reason for this is presumably that whereas 90% of cases begin with negative and thus socially perceptible first signs of the disorder, the first psychotic symptoms. e.g. hallucinations or delusions, are subjectively experienced symptoms and hence not easily perceived by others.

The ABC Study Sample

We interviewed a comprehensive sample of 276 first admissions with a broad diagnosis of schizophrenia (ICD-9: 295, 297, 298.3, 298.4) out of a population of 1.5 million in West Germany (Rhine-Neckar-District, cities of Heidelberg and Mannheim, eastern Palatinate) with the PSE during the first two weeks after first admission. Exclusion criteria were organic brain disease and severe mental retardation. 267 patients (127 men and 140 women) were able to perform the complete IRAOS interview (for details see Häfner et al. 1992a), which was administered about 4 to 6 weeks after admission when the acute symptoms had remitted.

Results

Age at First Onset

Based on our interview sample of 267 cases Fig. 1 shows the mean ages for four different definitions of onset. The age difference by sex, which varies between 3.2 and 4.1 years, is significant at least at the 0.05 level for each definition. Under these conditions, the gender difference in age at first admission must therefore be almost completely due to a real age difference at the onset of the disease.

The mean period of time elapsing between the first sign of a mental disorder and first admission was 4.5 years (4.2 years in females and 4.9 years in males). The maximum time difference between first sign and first admission was 31.5 years in one case.

Manifestation of Symptoms Prior to First Admission

To examine the influence of age on patterns of the early course of schizophrenia, we chose the two most frequently used symptom dimensions of schizophrenia. We selected from the IRAOS based on PSE symptoms 13 items attributed to the negative and 17 items of the positive syndrome and recorded the mean values of the first manifestation by months prior to first admission. With

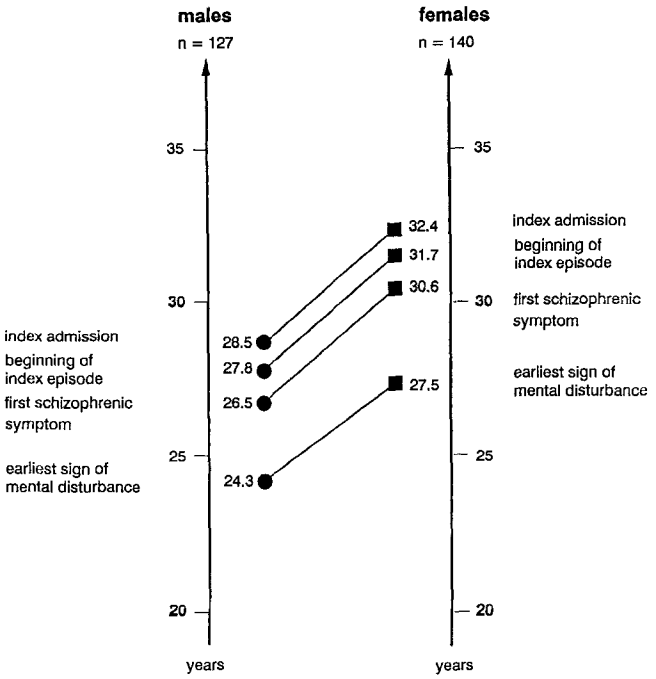

Fig. 1. Mean age for various operationalized definitions of first-ever onset of the disorder (ICD 9-295, 297, 298.3, 298.4). Mannheim, Heidelberg, Rhine-Neckar-County, Eastern Palatinate (Source: Häfner et al. 1991a)

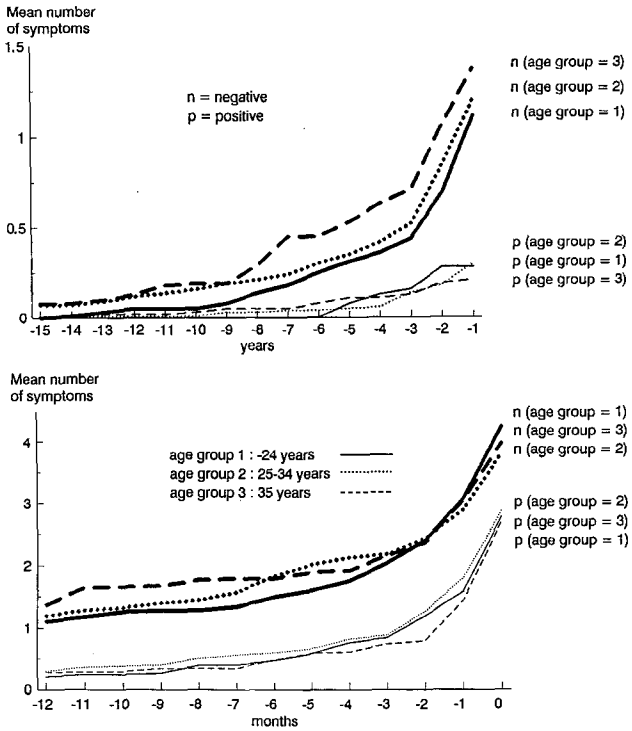

Fig. 2. Cumulative values of positive and negative symptoms until first hospital admission for schizophrenia by age group (Source: Häfner et al. 1991b)

the exception of disturbed speech, which contains a positive as well as a negative component, the mean values of the first occurrence for all positive symptoms were observed within two years, those of the negative symptoms, however, more than two years prior to first admission. In 70% of cases schizophrenia began with only negative, in 20% with both negative as well as positive symptoms. Only in 10% of all cases positive symptoms clearly occurred first.

Modelling the Early Course

To model the early course of schizophrenia we divided the 236 patients who reported at least one positive and one negative symptom since onset into three age groups fairly equal in size, i.e. 12–24, 25–34 and 35–59 years of age, and listed the mean number of symptoms across all patients over a period of 15 years up to 1 year and separately over the last 12 months preceding first admission. Figure 2 shows an exponential increase in both symptom measures with a clear time lag of the positive syndrome. The comparison between the three age groups produced hardly any differences (Fig. 2).

An examination of the patterns of course for males and females separately yielded no essential differences in the total group, and the medium-age group (25 to 34 years) had a similar pattern as the total group. When the youngest group was contrasted with the oldest, reverse patterns of course emerged for males and females. In the youngest group negative symptoms started to increase disproportionately 8 years prior to first admission in males but in females only 5 years later (Fig. 3). In the oldest group, however, females showed a similar increase in negative symptoms 8 years prior to first admission whereas males did so only 4 years later.

In the youngest group the delayed increase in both negative and positive symptoms in females reflects the later but then slightly more acute onset of the disease as compared to males (Häfner et al. 1991b). Late-onset cases in females are in fact frequently characterized by an early accumulation and persistence of negative symptoms. This result fails to support Murray's model (Murray and Lewis 1987, Castle and Murray, 1991) of female late-onset schizophrenia as a benign, mainly affective disease without insidious outbreak and negative symptomatology. The early course of late-onset schizophrenia in women is very similar to the predominant course of schizophrenia at an early age.

We tested associations between the four variables age, sex, development of earliest positive and development of earliest negative symptoms by means of a log-linear model and found significant associations:

1. between positive and negative symptomatology. This finding indicates that the two syndromes are closely connected in the early stage of the disease and suggests that they might at least partly be of common origin (Häfner and Maurer 1991, Maurer and Häfner 1991).

2. between sex and age of onset. It is reflected in the significant sex difference in the mean age at onset;

3. between negative symptomatology and age of first onset. It is accounted for by a slightly increasing duration of the accumulation of negative symptoms before first admission with rising age.

Table 2. Symptoms showing significant differences between age groups, listed according to age-group maximum

Syndrome dimension	Symptom	Cases (%) with a positive rating of items
Age group 12–24 (n = 90):		
Anxiety	Anxiety on meeting people	31.2
	Specific phobias	19.0
	Avoidance of anxiety-provoking situations	38.3
	Situational anxiety[a]	43.0
Unspecific positive	Derealisation	42.4
	Depersonalisation[a]	51.2
	Simple delusions concerning appearance	17.4
Negative	Reduction of facial movements[b]	63.5
	Reduced quantity of expressive movements[b]	73.8
	Unchanging facial expression[c]	54.2
Age group 25–34 (n = 110):		
Depression	Early waking	35.9
	Delusions of guilt	16.3
Negative	Poor concentration	86.0
Positive	Visual hallucination	28.8
	Delusions of reference	74.3
	Delusions of reference[a]	84.1
	Delusional misinterpretation	64.4
Age group 35–59 (n = 76):		
Positive (paranoid)	Delusions of persecution	70.4
	Delusions of persecution[a]	68.7
Negative	Lack of humour[b]	32.1
	Relationship with friends and peers[c]	65.3
	Inattentiveness during testing	38.1

Items not marked are from the PSE, otherwise
[a] CATEGO-syndromes (derived from PSE-symptoms)
[b] Behavioural items (PIRS)
[c] Negative symptoms (SANS)

For positive symptoms neither a significant association was found between age at onset and the pattern of course nor any three-way interaction.

Cross Sectional Age Differences in Symptomatology at First Admission

We compared the three age groups at 4 levels of psychopathology at first admission: diagnoses, 4 CATEGO subscores, 38 CATEGO syndromes (Wing et al. 1974), 234 signs and symptoms including 15 social disability items assessed by PSE, PIRS, SANS and DAS.

We found hardly any differences with regard to the ICD diagnoses and the proportion of CATEGO class S+, which corresponds to the core syndrome. Regarding the four CATEGO subscores a significant difference was observed between subscore DAH (delusions and hallucinations), which showed a maximum in the medium-age group and a minimum in the youngest.

When the presence of 38 PSE syndromes was compared by age, the profiles of the three age groups were astonishingly similar (Fig. 4). Significant differences were found for 6 syndromes only. Whereas four unspecific syndromes had maximum values in the youngest age group, the two productive syndromes mainly appeared in the older groups, namely delusions of reference in the medium and delusions of persecution in the oldest group. The negative syndromes show almost no difference among the age groups.

Turning to the item level, i.e. comparing the items from the PSE, PIRS, SANS and DAS additionally to the 38 CATEGO syndromes by age, in total 272 comparisons resulted. Thirty-five (= 12.9%) showed differences reaching a significance level of at least 0.05. For α-correction we split the sample into two random halves and weighted the two subsamples by 2. Our criteria of validity were an age difference at a significance level of at least $P \leq 0.05$ in the total and in one subsample and an age difference of at least $P \leq 0.10$ in the other subsample. Twenty-two items fulfilled these criteria.

There were significant age differences in negative symptomatology in the item of poor concentration – a symptom of little specificity – showing its maximum value in the medium age group, and in the items for re-

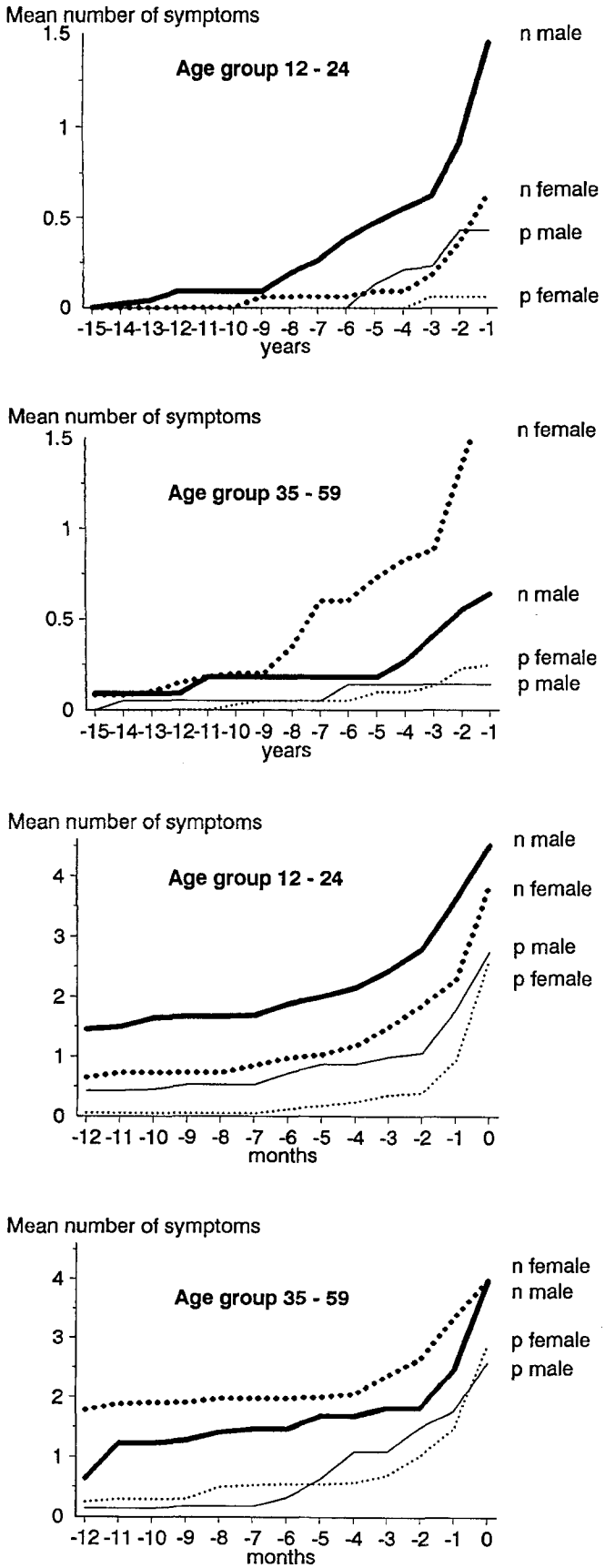

Fig. 3. Cumulative values of positive and negative symptoms until first hospital admission for schizophrenia: age groups 12–24 and 35–59 compared (n = negative, p = positive) (Source: Häfner et al. 1991b)

duced mimic and facial expression with maximum values in the youngest age group. Anxiety and depressive syndromes reach their maximum values in those age groups where the highest incidence rates are found in population studies as well. The maxima of positive symptoms across the three age groups reveal a tendency from simple, undifferentiated delusions in the youngest group, via structured delusions and hallucinations in the medium to systematized paranoid delusions in the oldest age group.

To assess whether the observed age differences were mediated by sex differences, the percentages of positively rated items showing significant age differences were compared between males and females. Surprisingly, only for 1 of the 22 reported age-specific items also significant gender differences appeared. This means that for nearly all age-specific items a mediating effect of gender on age clearly can be excluded. Otherwise, most of the age differences applied to both males and females. After controlling for reduced sample size for the male and female subgroups, age differences were present at least as a tendency ($P \leq 0.10$) for 18 of these items in males and for 20 items in females.

The Influence of Sex: Comparison of Diagnoses, Syndromes, and Symptoms at the Time of First Admission

The comparison of clinical and operationalized diagnoses and diagnostic scores between men and women at the time of first admission yielded no significant difference between the two sexes. When the ratings of the PSE items grouped in 38 CATEGO syndromes were compared, the profiles also showed little difference (Fig. 5).

Turning now to the item level, for the control of α-error split-half-technique was used again. For the determination of gender-specific symptoms, eighteen (= 6.6%) of the 272 comparisons fulfilled the criteria already defined ($P \leq 0.05$ in the total sample and in one subsample; $P \leq 0.10$ in the other subsample). Three groups of differences emerged (Table 3):

1. *Positive symptoms:* Delusions of sexual content and of pregnancy were slightly more frequent in women.

2. *Unspecific symptoms:* obsessional symptoms were more frequently observed in males with a relative risk around 1.6 and delusions of guilt more often in females with a relative risk of 0.4.

3. *Disease behaviour:* the largest group of differences refers to behavioural items: self-neglect, social withdrawal, social inattentiveness, low social adjustment and so forth were more frequent in males, social overadaptation in females.

The Influence of Gender on Early Course

In order to compare the patterns of early course of the disease between the sexes we used again the 13 negative and 17 positive items of the IRAOS as measures of the two symptom dimensions. The sex differences in the ac-

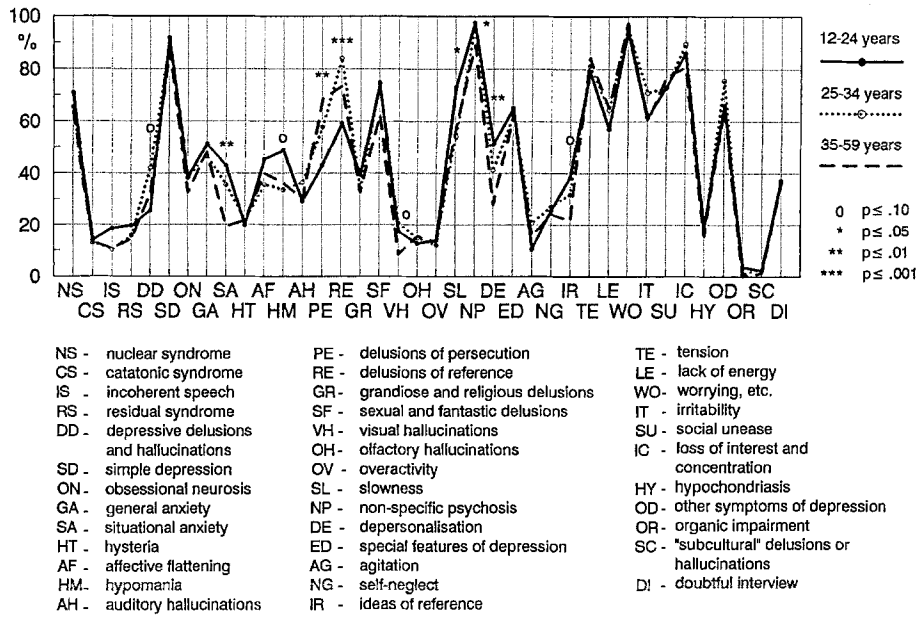

Fig. 4. Age specific CATEGO-syndrome profiles (n = 276) (Source: Häfner et al. 1991c)

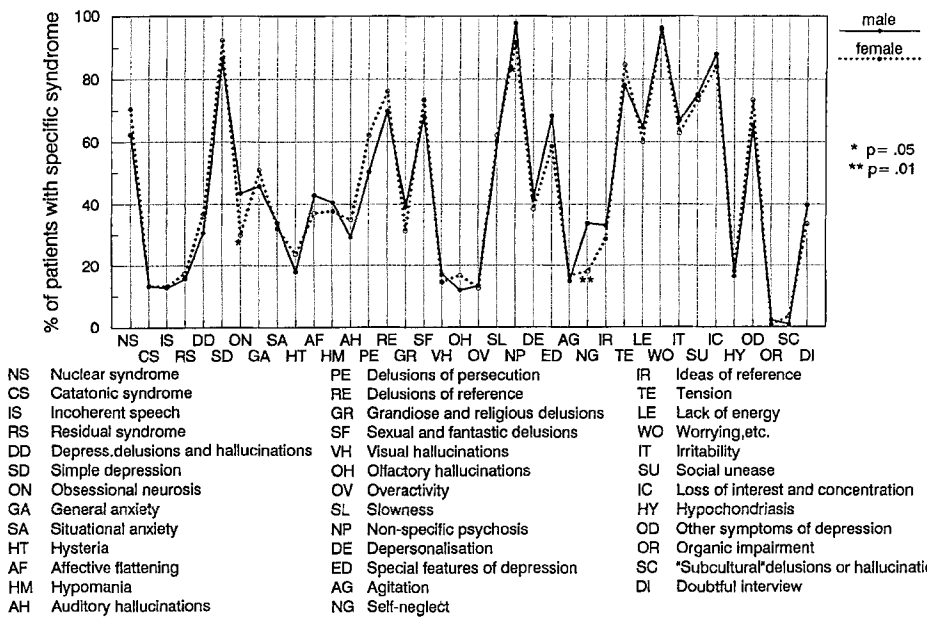

Fig. 5. Male and female profiles of 38 CATEGO syndromes at first admission for schizophrenia broad definition (ICD-9 295, 297, 298.3, 298.4) (male: n = 133; female: n = 143) (Source: Häfner et al. 1991d)

cumulation of symptoms from onset until first admission were minimal and disappeared at the onset of acute psychosis.

Onset of the Disease and Social Biography

In order to test the old hypothesis "social causation versus social drift" by individual biographies we focused on three life events with negative social consequences: loss of partner, of job, and of income and set them in a temporal relation to the three definitions of onset (Fig. 6). The first sign of mental disorder precedes the first socially negative life event by approximately 1 year on average. Apart from the difference in age of onset between males and females we did not observe any significant sex differences. But the discontinuation of a social role means that it has actually been performed or adopted. Social role adoption usually takes place in the period of age characterized by a maximum of schizophrenic onsets. A comparison between males and females regarding the average number of social roles (e.g. professional qualification, employment, income and partnership) actually performed prior to first admission revealed significant differences ($P \leq 0.05$) (Fätkenheuer et al. 1992). Despite a lower number of roles performed, males had significantly more breaks in the performance of these roles prior to first admission. The size of the male-female differences in the various areas of social functioning is depicted in Fig. 7.

Age Distribution at First Onset of Males and Females

If the population-related incidence rates for both sexes are depicted in 5-year age groups over the entire age

Table 3. Significant gender differences established in 18 out of 272 items, validated according to split-half test, at time of first admission

$n = 276$		Positive ratings		Significance test			Relative risk $m_T : f_T$
		Males (%)	Females (%)	P_T	P_I	P_{II}	
Positive symptomatology							
PSE 86	Sexual delusions	3.8	14.8	**	*	***	0.26
PSE 85	Delusion of pregnancy	0.0	7.7	*	*	**	0
CATEGO 22	Non-specific psychosis	97.7	91.6	*	*	*	1.07
Unspecific symptoms							
CATEGO 7	Obsessional neurosis	43.6	30.1	*	*	*	1.45
PSE 44	Obsessional checking, repeating	25.2	14.9	*	○	*	1.69
PSE 88	Delusions of guilt	7.0	16.1	*	**	*	0.43
Behavioural items							
CATEGO 26	Self-neglect	33.8	18.2	**	***	*	1.86
PIRS 72	Self-neglect	34.9	18.4	**	***	*	1.90
DAS 44	Global evaluation of social adjustment	84.9	66.7	**	***	○	1.27
DAS 13	Social withdrawal	77.9	56.5	**	**	**	1.38
SANS 22	Anhedonia/asociality	76.6	62.6	*	**	○	1.22
SANS 23	Social inattentiveness	47.6	32.6	*	**	*	1.46
PIRS 85	Overadaptation	4.8	15.2	**	○	***	1.80
PSE 98	Drugs taken in past month	14.8	4.2	**	○	***	3.52
PIRS 31	Reclined or closed posture	13.3	3.6	**	*	***	3.69
DAS 40	Lack of interest in job	69.4	34.3	**	**	***	2.02
DAS 06	Underactivity during past month	83.7	59.3	***	***	**	1.41
SANS 12	Increased latency of response	24.6	13.7	*	*	*	1.80

P_T = total sample, P_I = first split-half sample, P_{II} = second split-half sample
Significance by chi^2-tests
P values: ○ = $P \leq 0.10$; * = $P \leq 0.05$; ** = $P \leq 0.01$; *** = $P \leq 0.001$

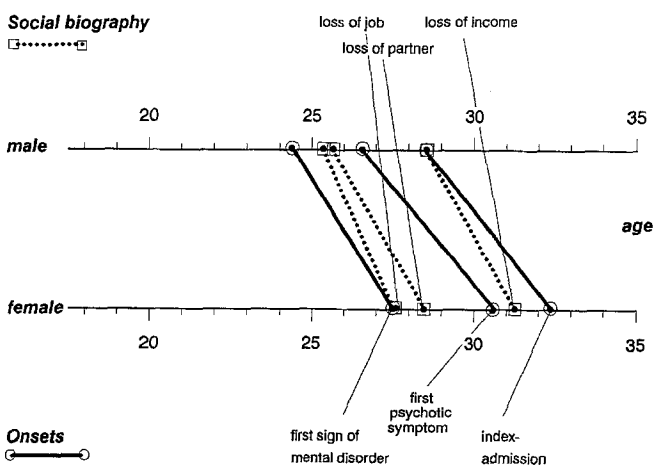

Fig. 6. Social biography and onset of schizophrenia

range of 12 to 59 years for a restricted diagnosis (ICD 295) on the basis of our ABC sample, then a result is confirmed, which we had already found on the first admission data on the Danish and the Mannheim case registers: The cumulative incidence for schizophrenia by the age of 60, a reliable indicator of the lifetime morbidity risk, is equal for both sexes with 13.1 and 13.2 respectively (calculated on the basis of the high-risk population aged 12 to 59, it is 16.4 for males and 16.6 for females). However, the figure also demonstrates that males consume the risk faster than females until the age of 30. After that the trend is reversed: By the age of 60 women have caught up reaching the same final value.

Finally we grouped the age distributions for the three definitions of onset, first sign of a mental disorder, first psychotic symptom and first admission, into five-year age groups (Fig. 8). Based on the earliest indicator of onset, i.e. the first sign of a mental disorder the 248 patients were able to report, the curve of onset for males depicts an early beginning and steep increase with a peak already between 15 and 24 years followed by a fairly steady decrease. Females show a less steep increase and a lower peak between 20 and 29 years of age. After a first decrease a second lower, but still significant peak ($P \leq 0.05$, compared with males and the projected trend) appears in the age group 45 to 54 where the female number of onsets is approximately three times higher than that of males. In 62% of males but only 47% of females the outbreak of the disease is situated before the age of 25 years. In 10.3% of males and in 9.2% of females the first signs of a mental disorder occurred before the age of 15. Beyond 50 years of age however, the rate of onset is below 2%.

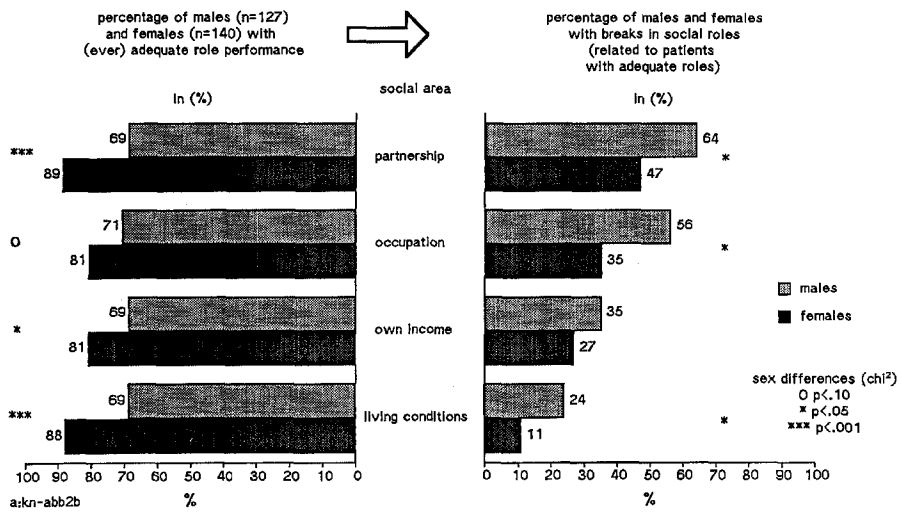

Fig. 7. Sex differences in social roles (Source: Fätkenheuer et al. 1992)

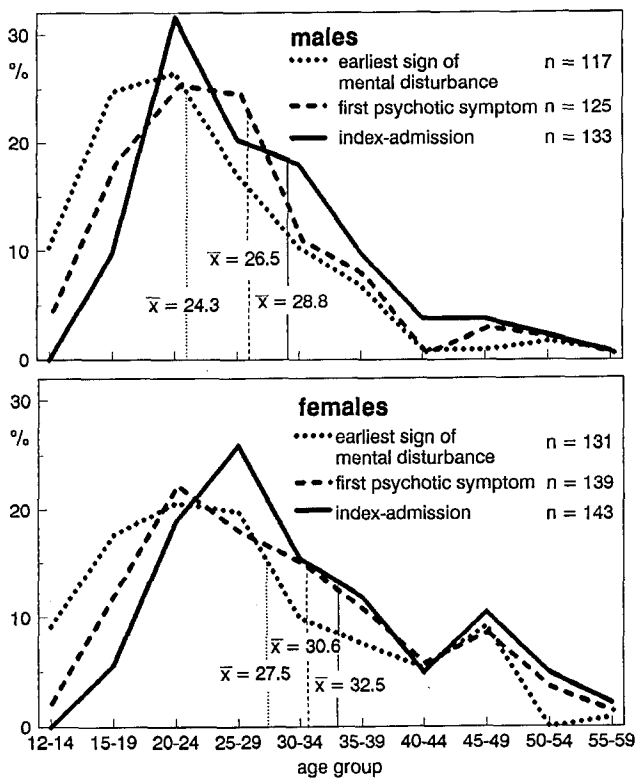

Fig. 8. Sex-specific age distribution at different points in time in the early course of schizophrenia broad definition (ICD 9-295, 297, 298.3, 298.4). Mannheim, Heidelberg, Rhine-Neckar District, Eastern Palatinate (Source: Häfner et al. 1991a)

Discussion

Our findings suggest that in the early symptomatology and course schizophrenia represents a rather uniform and fairly robust clinical picture. Except for some minor differences in a few non-specific symptoms (e.g. two compulsive symptoms in males, which may be the expression of different reaction patterns of the two sexes to the basic symptomatology of the disease, and delusions of guilt in females) and almost trivial differences in some delusional contents schizophrenic males and females differ mainly in their disease behaviour. The more frequent pathoplastic phenomenon (Birnbaum 1923) of delusions of sexual content in women is presumably due to psychological and in the case of delusions of pregnancy to trivial differences between the two sexes.

The higher frequency of socially negative behaviour in schizophrenic men compared with women also reported in many other studies (e.g. The WHO Determinants of Outcome Study, Hambrecht et al., 1992) is presumably a result of gender differences in disease behaviour rather than an effect of the disease itself. As in normal life, males show negative social attitudes and behaviour far more often than females. Together with the earlier irruption of the disease in the social career of males the differences in disease behaviour probably influence the social outcome of the disease in males and females.

The influence of age seems to be largely restricted not to disease-specific but to age-specific developmental factors producing for example a maximum of anxiety and depression at the time of first admission mainly in the age groups of maximum risk for the first occurrence of these symptoms in the general population. Age-specific factors of the cognitive development seem to influence the formation or differentiation of the positive symptoms, delusional symptoms in particular. This age trend is likely not to be due to the psychosis itself, but to the influence of cognitive maturity on the formation or differentiation of delusional symptoms. Moreover, the growing tendency with age of externalisation or a more projective coping style can provide an explanation for the steeply increasing frequency of paranoid delusions in old age independent of their cause.

In all age groups and in both sexes the onset of schizophrenia is characterized mainly by negative symptoms followed by positive symptoms with a considerable time lag. At the time of first admission we found no age and sex differences in the negative symptomatology. We assume that the negative symptomatology is more closely connected with the disease process itself than the positive symptomatology. The tendency towards uniformity of the early course of the disease, however, does not

infer a homogeneous etiology as can be shown by the example of the reaction pattern of "mental retardation", which is also fairly uniform despite the manifold causes. The attempts of isolating differential diseases in the core of schizophrenic symptomatology – such as T. Crow's Type I – Type II schizophrenia, Murray and Castle's male Kraepelinian and female affective or Leonhard's 12 types schizophrenia – are not supported by these results.

The early stage of schizophrenia prior to first admission is an essential part of the entire course of the disease. It has some consequences for predictor studies of schizophrenia. If in these studies first admission is defined as onset, insufficient premorbid social adjustment and work performance, which are consistently found to be powerful predictors of an unfavourable course, may often be caused by the early course of the disease.

A major social corollary of the earlier onset of male schizophrenia thus consists in a "non-starter" effect, i.e. the outbreak of the psychosis prior to a significant upward movement in the social career, as suggested by Dunham (1965) back in the 1960's.

The steps of social decline as demonstrated seem to be more often a consequence of the beginning disease rather than a precipitating factor for the first schizophrenic episode, which is in accordance with what B. Dohrenwend (1990) showed in a study of life events preceding the first episode. The irruption of the disease into the social biography, which occurs 3 to 4 years earlier in males, obviously leads to an earlier disruption of the latters' social career. Together with the more frequent socially negative disease behaviour in males this fact is bound to lead to a less favourable social course in comparison with females independently of the symptom-related course. This sex difference was demonstrated in the methodologically sophisticated follow-up studies conducted by Shepherd et al. (1989) and Salokangas et al. (1987).

The most important age difference is that of age at first onset: in females the onset of schizophrenia is 3–4 years later on average than in males, and a second peak of onsets in observed in the age group 45 to 54. The reason probably is a stronger structural and weaker functional effect of estrogen fading out around menopause. It probably results in an elevation of the vulnerability threshold for schizophrenia and in a weak antipsychotic effect in the acute psychosis by reducing the D_2 receptor sensitivity. This pathophysiological mechanism has no etiological importance, but it may open up interesting perspectives for preventive and therapeutic strategies.

The parallel shift of the age values for successive milestones in the early history of the psychosis is a first indicator of a fairly equal early course of schizophrenia in males and females. Together with the transnational stability of the gender differences in age at onset this suggests a biological rather than psychosocial explanation for the difference in age at onset.

Also the finding of an equal cumulative risk for males and females seems to be transnationally replicable not only between Denmark and Germany but also on the pooled data of the WHO Determinants of Outcome Study (Jablensky 1987, Hambrecht et al. 1992). *An identical lifetime risk suggests that sex has no influence on the etiology of schizophrenia. Rather, factors associated with the female sex seem to delay the outbreak of the disease, and factors associated with the male sex seem to accelerate the outbreak of the disease.*

On the basis of these epidemiological findings – the distribution of onsets over the female life cycle, the transnational stability of this finding and the animal experiments (Labrie et al. 1978; Raymond et al. 1978, Fields and Gordon 1982, DiPaolo and Falardeau 1985, Hruska 1986), which proved a neuroleptic-like effect of 17-β-estradiol, we generated three causal hypotheses related with the hypotheses put forward earlier by Seeman (1982), Lewine (1988) and Seeman and Lang (1990):

1. An early effect of estrogen acting already during brain maturation enhances the vulnerability threshold for schizophrenia and thus causes a delay of first manifestation in females.

2. From puberty on this structural effect is reinforced by a functional effect.

3. Both effects seem to fade out with subsiding estrogen secretion around menopause leading to the late onset of those genetically predisposed women who had until then not fallen ill because of the protective effect of estrogens.

Together with Gattaz and Behrens (Häfner et al. 1991a) we tested these hypotheses on the classical paradigms of dopamine-induced behaviour in animal experiments and found that chronic application of 17-β-E2 reduced both effects clearly and significantly with the effect being stronger in newborn than in adult animals. Post mortem conducted striatal binding experiments with (^{3}H) sulpiride confirmed that the underlying neurohormonal mechanism consists in the reduction of the D_2 receptor sensitivity in the brain through estradiol.

We suppose that this neuromodulatory effect of estrogen on D_2 receptors in the brain accounts for the delayed onset of schizophrenia in women by enhancing the vulnerability threshold.

In order to test the applicability of this model gained from animal experiments to human schizophrenia, A. Riecher-Rössler and our research group examined the temporal associations between phases of the menstrual cycle and plasma estrogen levels on the one hand, measures of schizophrenic and unspecific symptomatology on the other hand, in 32 women with normal menstrual cycle diagnosed as acute schizophrenics (Riecher-Rössler et al. 1992). There was a significant excess of acute hospitalization during the low estrogen phase as compared with other phases of the cycle ($P \leq 0.01$). Negative correlations were found between plasma estrogen level on the one hand and measures of schizophrenic and unspecific symptoms on the other hand.

This confirms our assumption that the neuromodulatory effect of estrogen on D_2 receptors in the brain traced in animal experiments is also effective in human schizophrenics.

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