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ORIGINAL PAPER

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The ABC schizophrenia study: a preliminary overview of the results

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Abstract The ABC Schizophrenia Study, a large-scale epidemiological and neurobiological research project commenced in 1987, initially pursued two aims: (1) to elucidate the possible causes of the sex difference in age at first admission for schizophrenia and (2) to analyse the early course of the disorder from onset until first contact and its implications for further course and outcome. First, transnational case-register data (for Denmark and Germany) were compared, second, a population-based sample of first-episode cases of schizophrenia ($n = 232$) were selected and third, the results obtained were compared with data from the WHO Determinants of Outcome Study by using a systematic methodology. A consistent result was a 3–4 years higher age of onset for women by any definition of onset, which was not explainable by social variables, such as differences in the male-female societal roles. A sensitivity-reducing effect of oestrogen on central D2 receptors was identified as the underlying neurobiological mechanism in animal experiments. Applicability to humans with schizophrenia was established in a controlled clinical study. A comparison of familial and sporadic cases showed that in cases with a high genetic load, the sex difference in age of onset disappeared due to a clearly reduced age of onset in women, whereas in sporadic cases it increased. To analyse early course retrospectively, a semistructured interview, IRAOS, was developed. The early stages of the disorder were reconstructed in comparison with age- and sex-matched controls from the same population of origin. The initial signs consisted mainly of negative and affective symptoms, which accumulated exponentially until the first episode, as did the later emerging positive symptoms. Social disability appeared 2–4 years before first admission on average. In early-onset cases, social course and outcome, studied prospectively over 5 years, was determined by the level of social development at onset through social stagnation. In late-onset cases, decline from initially high social statuses occurred. Socially negative illness behaviour contributed to the poor social outcome of young men. Symptomatology and other proxy variables of the disorder showed stable courses and no sex differences. Further aspects tested were the sequence of onset and the influence of substance abuse on the course of schizophrenia, primary and secondary negative symptoms, structural models and symptom clusters from onset until 5 years after first admission.

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The objectives of the study

The ABC (Age, Beginning, Course) Schizophrenia Study was planned in 1985/1986 with the aim of conducting a 12-year research project on topics of the general and clinical epidemiology of schizophrenia. Its funding by the German Research Association (Deutsche Forschungsgemeinschaft) began on January 1 1987 and is planned to terminate on December 31 1998. The project was launched to pursue the following objectives:

1. To elucidate the possible causes of the sex difference in age at first admission for schizophrenia, known since Kraepelin (1909) and confirmed in 50 of the 53 studies reviewed by Angermeyer and Kühn (1988)
2. A controlled study of the hidden course of schizophrenia from first contact with the mental health services back to true onset, hardly researched at that time.

Based on the results of the initial substudies, further objectives were included; for example, to continue the controlled retrospective study of the course of schizophrenia from onset until first admission with a prospective design covering six cross-sections over 5 years after first admission. Meanwhile, the seventh cross-sectional assessment of the ABC first-episode sample 10 years after first admission is underway.

Gender differences in age at first admission (a comparative case-register study)

The research design of the project was based on a systematic methodology. Hypotheses were generated and tested step by step on the basis of the results achieved by taking artefacts into account and refuting alternative explanations (Häfner et al. 1989). The project was commenced in 1986 with the development of the instrument for the retrospective assessment of the onset of schizophrenia (IRAOS; Häfner et al. 1992) – a semi-structured interview based on internationally approved instruments and expert ratings. The IRAOS provides information on prodromal signs, symptoms, functional impairment, social disability and the patient's social development by means of a time matrix based on anchoring events from three sources: the patient, his/her closest relative and case records. A retrospective approach is necessary in studying the onset and early course of schizophrenia, because a prospective mode is impractical due to the low annual incidence rates of schizophrenia and the predominance of non-specific symptoms at onset.

The first step of our analyses consisted of a transnational replication of the sex difference in age of first admission on data from the Danish national and the Mannheim case register (Häfner et al. 1989). To avoid diagnostic artefacts the analysis of first-admission age was based on various diagnostic definitions. The definitions applied yielded, for both Denmark and Mannheim, significant differences of 4–5 years in age of first admission between men and women. Alternative explanations, such as different periods of latency between onset and first contact due to a delayed perception or greater tolerance of the disorder in women – as a result of milder symptoms or a different social role – were refuted by showing that the sex difference in age of first admission also existed between employed and nonemployed patients and by comparing the initial symptoms of the psychosis between men and women (Häfner et al. 1989).

Since the annual first-admission rates obtained on the Danish data were about 50% lower than the Mannheim rates, we conducted a validation study together with our Danish colleagues by studying a representative case-register sample of 116 first admissions for a diagnosis of schizophrenia or related disorder (Löffler et al. 1994). On the basis of the patients' case notes provided by the Danish mental hospitals, symptomatology was assessed with the IRAOS and the clinical case-register diagnoses compared with operational diagnoses computed with the CATEGO programme (Wing et al. 1994). First, the results confirmed that we were studying the same syndrome in both Denmark and Mannheim. They also showed that Danish psychiatrists were more cautious in giving a diagnosis of schizophrenia at first admission, especially to women. Only 32% of the women and 51% of the men qualifying for an operational diagnosis of CATEGO 295 had also been assigned a clinical diagnosis of schizophrenia documented in the case register. When the operational diagnosis of schizophrenia was compared between Denmark and Mannheim, the annual first-admission rates for schizophrenia turned out to be the same.

The ABC study sample and subsamples

Having thus confirmed the transnational validity of the sex difference in age of first admission, we tested to what extent it was determined by an illness-related sex difference in age of first onset. To accomplish this we had to move from secondary data to studying age at first onset directly. For this purpose we studied a population-based sample of 276 consecutive first admissions in the years 1987–1989 to the ten mental hospitals serving a semi-urban, semi-rural German population of about 1.5 million in the cities of Mannheim and Heidelberg and surrounding regions. The patients had to be 12–59 years old and qualify for a broad diagnosis of schizophrenia (ICD-9: 295, 297, 298.3/4) to be included in the sample. To assess symptoms in the psychotic episode the patients were rated on a number of scales, including the PSE (Wing et al. 1974), DAS-M (WHO 1988, Jung et al. 1989), PIRS (Biehl et al. 1989), SANS (Andreasen 1983), the prognostic scale proposed by Strauss and Carpenter (1974) and IRAOS (Häfner et al. 1992) immediately upon hospital admission. The sample has been described in detail elsewhere (Häfner et al. 1993).

To avoid psychotic distortions of memory, the IRAOS interview was administered only after psychotic symptoms had remitted, that is, within 3–5 weeks of first admission. The interview was also performed with the closest relative and applied to all available documents (case notes etc.). In this way the onset and early course of the disorder were reconstructed. A total of 232 patients (108 men, 124 women; 84% of the sample) were in their first episodes at the time of the interview, that is, had not had any previous psychotic episode. For purposes of comparison (Hambrecht et al. 1992a, b) the World Health Organization provided us with data of the WHO transnational Determinants of Outcome Study (Sartorius et al. 1986; Jablensky et al. 1992) and of the Disability Study (Jablensky et al. 1980).

To study the course of schizophrenia we singled out a representative cohort of 133 cases from the 276 first admissions. Of these 133 cases 115 were first episodes. As part of the entire first-episode sample, the cohort was assessed retrospectively from first admission to onset by

the IRAOS interview and, additionally, followed up prospectively at five cross-sections, $\frac{1}{2}$, 1, 2, 3 and 5 years after first admission, by various instruments [PSE, FU-HSD (WHO 1980), WHO-DAS, WHO-PIRS etc.]. Meanwhile, a 10-year follow-up of the total first-episode sample is underway.

Sex difference in age of onset and how we explained it

The significant sex difference in first-admission age (Table 1) turned out to be attributable to a significant mean age difference of 3–4 years by any definition of onset, ranging from the first sign of the disorder to the climax of the first psychotic episode (operationalized by a maximum of positive symptoms). These milestones of the incipient disorder were parallel in men and women, which we interpreted as indicating that the early course of schizophrenia is similar in men and women. Studying the distribution of onsets across the life cycle until age 55–59 we found, as based on the first sign of the disorder, an early and steep increase in incidence with a peak between ages 15 and 25 years for men and a slightly smaller increase with a somewhat lower and broader peak between ages 15 and 30 years for women. After that, male incidence decreased monotonously, whereas female incidence showed a second peak significantly different from the male incidence in the age group 45–49 years (Häfner et al. 1998a).

On the basis of the distribution of the incidence of schizophrenia across the female life cycle and in view of previous speculation about a protective effect of oestrogen (Lewine 1988; Seeman and Lang 1990), and animal experiments actually showing dopamin-antagonistic neuroleptic-like effects of oestrogen, we hypothesized that either testosterone via agonistic effects on the dopaminergic neurotransmission accelerates or oestrogen via antagonistic effects delays the onset of schizophrenia. Analogous effects have in the meantime also been demonstrated on serotoninergic and glutamatergic neurotransmission (Woolley and McEwen 1994; Sumner and Fink 1995).

These neuroendocrine hypotheses were tested in animal experiments. A 4-week oestrogen treatment of newborn and adult sterilized rats led to a significant attenuation of apomorphine-induced dopaminergic behaviour, whereas an analogous testosterone treatment had no significant effects. We were able to show by post mortem studies that the underlying neurobiological mechanism consisted in attenuation of the sensitivity of central D2 receptors by oestrogen (Häfner et al. 1991).

The applicability of these results from animal experiments to human schizophrenia was tested in a controlled clinical study of 32 schizophrenic and 29 depressive women with normal menstrual cycles (Riecher-Rössler et al. 1994). We found a significant negative correlation between plasma oestrogen levels and all measures of schizophrenic and related symptoms, but no such correlation for depressive symptoms either in the index or the control patients. Meanwhile, the results of an 8-week open pilot study on the substitution of neuroleptic therapy in acute schizophrenic psychosis by oestrogen have appeared (Kulkarni et al. 1996). They indicate a more rapid and better response of psychotic symptoms, but the effect lasts only for a few weeks. Our hypothesis is being tested systematically in ongoing intervention studies, for example, in a long-term double-blind study taking relapse risk into account (Mundt in Heidelberg/Germany, Kulkarni in Melbourne/Australia).

The oestrogen effect led us to the following hypotheses: given the protective effect of oestrogen, lasting until premenopause, there should be a greater incidence and severity of schizophrenia in women after waning of the protective effect. Men, in contrast, due to the missing protective effect of oestrogen, should develop the most severe illnesses at an early age, and increasingly fewer cases and milder forms of the disorder with increasing age. We were able to confirm both hypotheses: late-onset schizophrenias turned out to be, as has long been recognised (Harris and Jeste 1988), significantly more frequent in women than men. They were also more severe in women in terms of negative symptoms. Late-onset schizophrenias in men were significantly milder on almost all symptom dimensions than the most severe early-onset schizophrenias.

Early course of schizophrenia

The IRAOS data of the first-episode sample enabled us to reconstruct the early course of schizophrenia until the climax of the first episode or first admission. In 73% of the cases the disorder, based on a broad diagnostic definition, began with a prodromal phase, which lasted on average 5 years. The psychotic prephase, from the appearance of the first psychotic symptom until the cli-

Table 1 Mean age (years) at five milestones of early course for men and women, in the ABC first-episode sample ($N = 232$) of broadly defined schizophrenia

Definition of onset	Men	Women	Male-female difference	*P*-value
First sign of the disorder	22.5	25.4	2.9	*
First negative symptom	24.1	26.7	2.6	*
First positive symptom	26.7	30.9	4.2	*
First episode (max. of pos. symptoms)	27.8	32.1	4.3	**
First admission	28.2	32.2	4.0	**

$^{*}P \leq 0.05$; $^{**}P \leq 0.01$

max of the episode, operationalized by the first maximum of the sum score for positive symptoms, lasted 1.1 years. The sum score for negative and non-specific symptoms showed a slow, exponential increase. The sum score for positive symptoms, which appeared several years later, also increased exponentially and steeply, exceeding negative and non-specific symptoms at the height of the episode. The remission of symptoms after the climax of the first episode led to decreases in both symptom scores: the score for positive symptoms approached zero, and negative symptoms fell to a slightly higher level with no significant increases, but a steady state emerging at the following five follow-up assessments until 5 years after first admission.

Data on the accumulation of symptoms and their sequence of appearance also allowed us to empirically test phase models of the onset of schizophrenia. Testing Conrad's phase model (1958), we obtained evidence for the sequence of trema and apopheny, but none for the sequence of the other phases.

Symptom structure and its stability over time

To identify subtypes of schizophrenia and to test the stability of symptom patterns over time we put some of the models described in the literature to an empirical test. The models tested retrospectively on the early course of schizophrenia and prospectively over 5 years after first admission (Häfner and Maurer 1991; Maurer and Häfner 1991) were those proposed by Crow (1985) and Andreasen and Olsen (1982).

According to Crow's "dual process model" there are two independent types of schizophrenia (type I and type II). Andreasen and Olsen (1982) view the positive and the negative syndromes as two poles of a dimension and presume the two syndromes to be negatively correlated. We were able to show that in Crow's model the sum scores of positive and negative symptoms in the early course and over 5 years after first admission were positively correlated at a medium level. Furthermore, not all patients with pronounced negative symptoms also presented negative symptoms in the further course, as postulated by Crow.

Andreasen and Olsen (1982) presumed a negative association between the positive and the negative syndrome. We, however, found positive correlations of medium or small size between the two symptom scores in both the early and the 5-year course. Most patients presented symptoms of both categories simultaneously.

Unable to confirm the basic asumptions of Crow's and Andreasen and Olsen's models, we continued our analysis of the symptom structure by testing six different models in a sample homogeneous in their stages of illness. The result showed a slight superiority of the three-factor model proposed by Liddle and Barnes (1990) which proved stable from the beginning of the psychotic episode until the follow-up assessment (Löffler and Häfner 1998).

Our dimensional analyses of the course of schizophrenia at the initial stages and over 5 years supported the repeated finding of stability for negative symptoms and of poor stability for positive symptoms.

Besides these dimensional approaches we examined the psychotic prephase by way of cluster analysis among the 232 first-episode cases and identified six subgroups of symptoms on our retrospectively gathered data. These categories, only partly identical with the classic ICD-10 subgroups of schizophrenia, play an important role in predicting the course and outcome of the disorder. These subgroups showed no stability in their core characteristics over time either.

Within the frame of the multiple components model of negative symptoms we tested the Carpenter-Kirkpatric model of the deficit syndrome over time (Maurer and Häfner 1996). Carpenter et al. (1985) divided negative symptoms into primary components, "deficit symptoms" (disease inherent and irreversible), and secondary components, "non-deficit symptoms" (unstable, amenable to exogenous factors). Unlike Carpenter et al., we found that secondary factors had no influence on the group with "non-deficit symptoms". In the group with "deficit symptoms", however, these factors correlated with negative symptoms and, when the groups were compared with each other, were more pronounced in this group than in the one with "non-deficit symptoms". The findings indicated that patients with stable negative symptoms constitute a more severely ill group with a greater vulnerability, which is reinforced by the secondary factors.

Predictor analysis showed that negative symptoms correlated highly with social disability and social status at the 5-year follow-up, whereas disorganization and positive symptoms proved to be dimensions without any prognostic implications.

Symptomatology, illness behaviour and social disability: association with age and sex

Symptom structure (dimensions), symptomatology at follow-up, as well as course and outcome, e.g. accumulation of symptoms, acute, subacute and chronic type of onset, were compared by age and sex. No significant sex differences were found in the core symptoms or the other proxy variables of the disorder.

An exception was significant sex differences in behavioural items (e.g. self-neglect, lack of interest in a job, social withdrawal) in the first episode. The cumulative prevalence of alcohol and substance abuse was significantly higher for men than women in the early course of the disorder. Proceeding from this finding we tested the hypothesis that this sex-specific, age-dependent (the sex difference in socially negative behaviour decreases linearly with age) illness behaviour might contribute to the frequently reported finding of a poorer social outcome of schizophrenic men than women (Salokangas 1983; Shepherd et al. 1989).

Among the ten most frequent initial symptoms of schizophrenia, there were four indicators of functional impairment. Studying at which point in incipient schizophrenia social disabilities appear, we found that the patients scored 2 or more on any of the DAS-M items as early as 2–4 years before first admission. This finding made it clear that (1) the onset of schizophrenia is primarily characterized by a long prephase of persisting negative and non-specific symptoms, and that (2) disease-related social disabilities appear long before first contact with the mental health services (Häfner 1996).

Testing the implications of the level of social development at onset for the further social course we obtained differential results: the social development of young and medium-aged patients stagnated after onset, whereas late-onset patients with high social status at onset experienced social decline. Despite the decline, older patients showed better 5-year outcomes than the younger patients.

To compare the patients' social development with a norm and to test whether the main predictor of social outcome – poor premorbid social adjustment – was truly premorbid or a consequence of incipient illness, we conducted a case-control study among randomly selected, age- and sex-matched controls drawn from the Mannheim population register. First results achieved on a subsample showed no significant differences in any of the major social roles at onset between schizophrenics and controls. The social disadvantage of schizophrenics presumably appears in the prodromal phase, while young healthy controls continue to move upwards (Häfner 1996).

The influence of obstetric complications and genetic load on the sex difference in age of onset

For Kirov and co-workers' (1996) hypothesis that the sex difference in age of onset might entirely be accounted for by young schizophrenic men with versus without obstetric complications at birth we found no more evidence than for the schizophrenia model proposed by the authors (Murray et al. 1992). According to Kirov et al., schizophrenia in young males is characterized by a low degree of familiarity, an excess of obstetric complications and negative symptoms, as opposed to a high degree of familiarity and an excess of positive and emotional symptoms in older schizophrenic women.

DeLisi and co-workers' (1994) and Albus and Maier's (1995) finding that the sex difference in age of onset disappears in familial and increases in sporadic cases was corroborated on our population-based ABC sample.

We are currently testing whether the duration of positive symptoms or prodromal signs before treatment might be a negative prognostic indicator of course and outcome (Bilder et al. 1985; Crow et al. 1986). The two studies cited did not control confounding with type of onset.

Schizophrenia and substance abuse

The availability of exact data on the time of illness onset and the early course of schizophrenia was an opportunity to address further important issues of schizophrenia research, for example, the sequence of comorbidity with alcohol and substance abuse. We demonstrated that most patients developed alcohol and substance abuse only after the onset of schizophrenia, but frequently before first contact with the mental health services. We therefore presume that schizophrenias precipitated by substance abuse are of secondary importance. A more important factor is improper self-medication, especially since we found that negative symptoms were slightly reduced and positive symptoms increased over time (Hambrecht and Häfner 1996).

Age and sex

All the proxy variables of the disorder, initial symptoms, pattern of symptom accumulation, type of onset and core symptoms of the first episode showed no significant sex differences. Since even methodologically sound comparisons of neuropsychological test results between men and women have failed to yield any differences (Goldberg et al. 1995), we are confident that the disease process is the same in both men and women. Significant differences exist in age of onset and variables less closely linked with the disorder – illness behaviour in particular. Young age of onset as a result of a greater vulnerability, lack of the protective effect of oestrogen and socially negative behaviour as sex- and age-specific behavioural patterns all have adverse effects on the social course of schizophrenia in men. We have already discussed the interaction of age and sex, in part explainable by oestrogen effects in the life cycle and producing more severe illness in young men and milder illness in older men and more frequent and more severe late-onset schizophrenias in women (Häfner 1997).

The interaction between these determinants has prompted us in our ongoing studies to focus increasingly on generating and testing models of interaction between specific biological factors (vulnerability to schizophrenia), non-specific biological factors (elevation of the vulnerability threshold by oestrogen), developmental factors (e.g. level of development at onset, influence of cognitive maturity on symptom formation) and environmental factors (not yet sufficiently operationalized and studied). An unexpected recent finding of a comparison of symptomatology in the psychotic episode in 5-year age groups across the total age range, from under 15 to over 75 years, is encouraging us to pursue these issues further. A sample of 1109 first-admission cases with a diagnosis of schizophrenia and paranoid disorders from successive first admissions to the Central Institute of Mental Health (not a fully representative sample!) predominantly yielded no significant differences

in the symptom profiles. An exception was systematized and paranoid delusions, with a linear increase from very low values over the age range, whereas disorders of the self and thought disorders showed an opposite development, from high values at early onset to values close to zero in the highest age groups. The linearity attained significance. This finding very likely reflects the influence of developmental factors on symptom formation (Häfner et al. 1998b). The project is planned to continue with a controlled analysis of the course of schizophrenia from onset until first admission and a 10-year follow up.

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