Causes and Consequences of the Gender Difference in Age at Onset of Schizophrenia

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Abstract

The ABC (age, beginning, course) schizophrenia study was commenced in 1987 to generate and test hypotheses about pathogenic aspects of schizophrenia. One of the main branches of the study focused on how gender influences the age distribution of onset, symptomatology, illness behavior, and early course in schizophrenia. Proceeding from one of the rare, strikingly deviating, consistent findings—the gender difference in age at first admission—we launched a systematic search for explanations by generating and testing hypotheses in a series of substudies. We moved from the epidemiological to the neurobiological and finally to the clinical level. The present article is an attempt to provide a brief overview of the individual stages of the ABC study and the different levels of investigation involved in formulating and testing the estrogen hypothesis in animal experiments and in demonstrating its applicability to human schizophrenia. From these results, three hypotheses were formulated and tested on data from an ABC study sample of 232 first-episode cases of schizophrenia. The analyses described here represent the latest stages of the ABC study.

Key words: Gender differences, age at onset, early course.

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Research Strategy of the ABC (age, beginning, course) Schizophrenia Study

The first part of the comprehensive ABC schizophrenia study comprised nine consecutive substudies (table 1). A brief account of the early stages of the ABC study will show the basis of the hypotheses. Studies numbered 1 to 6 were carried out at the epidemiological level, 7 and 8 at the neurobiological, and 9 at the clinical level. The new substudies, 10 to 12, also shown in table 1, were modeled on the estrogen hypothesis (Mendelson et al. 1977; Seeman 1983; Loranger 1984; Lewine 1988; Seeman and Lang 1990), which was invoked to explain the delay of onset in women compared to men and the peculiar pattern of distribution of onset across the female life cycle.

The substudies involved five different sources of data: Studies 1 to 3 were based on the Danish and the Mannheim case registers (secondary data) and the World Health Organization (WHO) Determinants of Outcome study (Jablensky et al. 1992), and studies 4 to 6 and 10 to 12 on a representative sample of 232 first-episode cases of schizophrenia (ABC study sample; primary data). Animal experiments and postmortem brains were employed in studies 7 and 8. Study 9, a controlled clinical study, was conducted among women with acute schizophrenia and acute depressive symptoms (Riecher-Rössler et al. 1994*b*).

Gender Differences in Age at First Admission: Transnational Replication by Case Register and WHO Data (Studies 1 to 3). Women are several years older at first admission for schizophrenia than men. This result, reported by Emil Kraepelin as early as 1909 and replicated since then in a majority of more than 50 studies (for a review see Angermeyer and Kühn 1988), was the starting point of our project. The finding was tested for transnational validity on service-utilization data by comparing first admissions with a diagnosis of schizophrenia in the Danish and the Mannheim case registers (Häfner et al. 1989).

Cumulative psychiatric case registers are health information systems of geographically delimited areas. For a condition like schizophrenia, which has a high visibility in an area with well-developed services, "treated" incidence and prevalence may permit relatively reliable esti-

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Table 1. Research strategy of the ABC schizophrenia study for explaining the gender difference in age at first admission for schizophrenia

Substudy	Level of investigation	Source of data
1. Transnational replication	Epidemiological (secondary data)	Case registers
2. Exclude artifacts	Epidemiological (secondary data)	WHO Determinants of Outcome study data
3. Test alternative hypotheses	Epidemiological (secondary data)	WHO Determinants of Outcome study data
4. Direct test of hypothesis: Gender difference in age at onset explains difference in age at first admission	Epidemiological (primary data)	ABC first-episode sample
5. Test plausibility: Psychological vs. biological explanation	Epidemiological (primary data)	ABC first-episode sample
6. Generate causal hypotheses	Epidemiological (primary data)	ABC first-episode sample
7. Experimental testing of estrogen hypothesis	Neurobiological	Animal models
8. Detect underlying neurobiological mechanism	Neurobiological	Postmortem brains
9. Test applicability to human schizophrenia	Clinical	Controlled clinical study
10. Early age at onset in men impedes social development at an earlier stage[1]	Epidemiological (primary data)	ABC first-episode sample
11. Expected and observed social development in the prodromal phase[1]	Epidemiological (primary data)	Case-control study
12. Test hypotheses on consequences of a higher vulnerability threshold in women until menopause	Epidemiological (primary data)	ABC first-episode sample

Note.— ABC = age, beginning, course; WHO = World Health Organization. Studies 1–9 support the estrogen hypothesis; studies 10–12 seem to provide further support for the estrogen hypothesis.

[1]Test of estrogen hypotheses on consequences of the age difference at onset.

mates of true rates (Wing 1986; Hambrecht et al. 1994). From the two case registers we obtained data on all 12- to 59-year-old Danish citizens (527 men and 642 women) who were hospitalized for the first time with an International Classification of Diseases (ICD–8 World Health Organization 1967) diagnosis of schizophrenia (ICD–8: 295) or schizophrenialike disorder (ICD–8 297, 298.3, 301.83) in 1976, as well as on all Mannheim, Germany, inhabitants (160 men and 176 women) who were hospitalized for the first time with the same diagnosis between 1978 and 1980. The age-group related and population-based rates showed a highly significant 4- to 5-year difference in age at first admission between men and women in Denmark and in Germany (table 2) for both a broad diagnostic definition (schizophrenia and schizophrenialike disorders) and a narrow one (ICD–8 295 only).

Danish and German case-register samples were also used to test whether differences in the period of latency between onset and first admission might explain the sex difference—for example, more severe symptoms or an earlier perception by the patients themselves or others at onset of schizophrenia in men because of men's higher occupational status. But both employed and nonemployed patients displayed the same sex difference in age at onset. An analysis of variance showed a significant main effect for sex and not for occupational status (Häfner et al. 1993*a*).

Additional evidence for the transnational validity of the sex difference in age at first admission was gained from the total first-contact sample (n = 1,292), aged 15 to 55 years, of the 12-center, 10-country WHO Determinants of Outcome study (Jablensky et al. 1992). In this transnational study, all patients were assessed for psychopathology with a semistructured interview, the Present State Examination (PSE; Wing et al. 1974), supplemented by a computer algorithm, known as CATEGO, which can be used for classification purposes. As part of this process, the patients are allocated to one of nine descriptive CATEGO

Table 2. Mean age (in years) at first admission for a broad or a restricted definition of schizophrenia in Denmark (DK), 1976 and Mannheim (MA), 1978 to 1980 on the basis of population-based rates per 5-year age groups

	Broad definition		Restricted definition	
	DK (n = 1,169)	MA (n = 336)	DK (n = 475)	MA (n = 297)
Women	40.2	37.9	37.7	36.4
Men	34.8	33.1	32.8	32.5
Age difference	5.4	4.8	4.9	3.9

Note.—$p \leq 0.001$. Adapted from Häfner et al. 1989.

classes, depending on the prevailing symptomatology: for example S, containing central schizophrenia conditions (e.g., thought intrusion, delusions of control), P (paranoid symptomatology), or O (other psychoses). In a further step, four subscores from the PSE can be derived for each individual: DAH, comprising delusional and hallucinatory syndromes; BSO, psychotic characteristics of behavior, speech, and similar syndromes; SNR, specific neurotic syndromes; and NSN, nonspecific neurotic syndromes. When only the cases assigned to the PSE-CATEGO classes S, P, or O, comprising psychotic symptoms, were included in the analysis, a mean difference of 3.4 years between men and women was obtained (Hambrecht et al. 1992).

Gender Differences in Age at Onset Explain Differences in Age at First Admission: Analysis of Primary Data (Study 4). At this juncture it was necessary to determine whether age at first admission, also influenced by other than disease-inherent factors, might be accounted for completely or partially by the illness variable "age at first ever onset." We needed reliable primary data for directly determining the time point when the prodromal signs and various initial symptoms of schizophrenia appear. For this purpose, it was necessary to study, by applying standardized procedures, a sufficiently large sample drawn from a representative population of almost all new cases of clearly defined schizophrenia in the main age-of-risk period. Prospective population studies, however, are inapt for collecting age-at-onset data because of the low annual incidence rate. Another reason is that a majority of individuals with schizophrenia start with negative or nonspecific symptoms several years before specific—that is, positive or psychotic—symptoms appear (Häfner et al. 1991*b*, 1991*c*; Klosterkötter 1992; Loebel et al. 1992). We therefore had to trace information on onset and early course retrospectively (Maurer and Häfner 1995).

Any retrospective assessment of illness data presents the problem of reduced reliability and validity due to difficulties in recalling past events. This is well known from life event research (Jenkins et al. 1979; Monroe 1982) as well as from diagnostic efforts in lifetime diagnosis (Endicott and Spitzer 1978; McGuffin et al. 1986; Wittchen et al. 1989). But it seems that especially in schizophrenia, important events such as the first psychotic breakdown are clearly recalled even years later (Cutting and Dunne 1989).

Therefore, we developed a structured interview—Instrument for the Retrospective Assessment of Schizophrenia (IRAOS; Häfner et al. 1992). The item collection was based on a survey of instruments that might provide indicators of the onset of schizophrenia at four different levels: specific and nonspecific symptomatology; psychological impairments, and cognitive and social deficits; changes in social life, such as dropping out of school or separating; and help-seeking behavior as a reaction to perceived changes in mental health. In addition, the IRAOS allows assessment of demographic and social characteristics. The instrument is used on three independent sources of information: the patient, a close relative, and case notes or other records. As for a valid assessment of time-related symptom information, the use of specific memory aids is suggested (Wittchen et al. 1989). The units of information are arranged into a time matrix with the help of generally known or personal anchor events. A detailed description of the instrument and the results on its reliability and validity have been published elsewhere (Häfner et al. 1992; Maurer and Häfner 1995).

The ABC study sample. The catchment area of the ABC schizophrenia study is in central Germany with a semirural, semiurban population of about 1.5 million. The sample comprised all patients aged 12 to 59 years who were admitted to any of the 10 hospitals and psychiatric units in and around the catchment area over a period of 2 years (1987–89) with a clinical diagnosis of schizophrenia or related disorder (ICD–9; World Health Organization 1978; 295, 297, 298.3, 298.4). For further details, see Häfner et al. (1993*a*).

PSE interviews were administered within a few days of first admission in 276 cases; 267 subjects also went

through complete IRAOS interviews about 6 weeks later, after remission from or improvement of the psychotic episode. The 232 cases (84%) of the ABC sample, on which the following analyses are based, were first episodes, that is, these patients had never had a delimited period of positive symptoms before the onset of the first psychotic episode followed by the first admission.

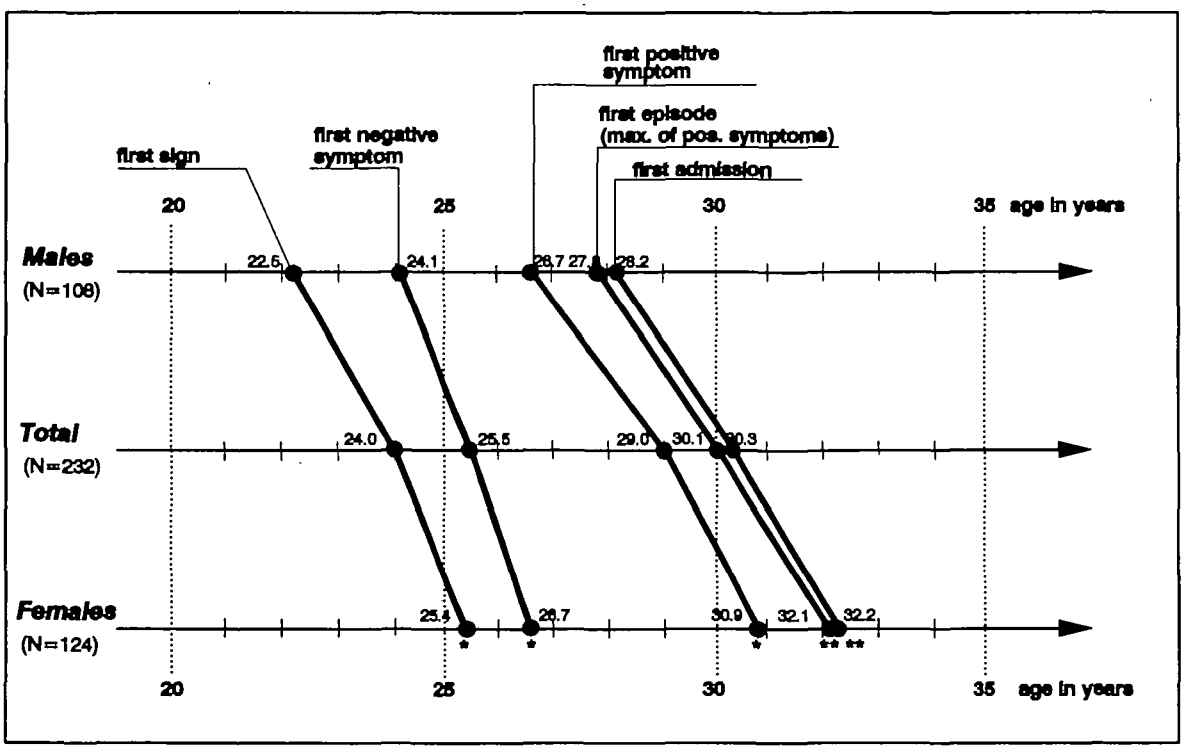
In addition to PSE and IRAOS, the following instruments, among others, were administered after first admission: Disability Assessment Schedule (DAS; World Health Organization 1988; German version: DAS–M; Jung et al. 1989), an instrument for rating overall behavior and functioning in different social role domains (e.g., general interests, household activities, marriage, occupation); the Psychological Impairment Rating Schedule (PIRS; Biehl et al. 1989), a supplement of the PSE that allows a detailed recording of the patient's observed behavior during the interview with emphasis on interaction skills considered essential for day-to-day social behavior; and Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1989).

While studies 1 through 3 were conducted to test the transnational stability of the gender difference in age at first admission, controlling for confounding influences due to demographic, diagnostic, and selection characteristics, the aim of the primary data analysis was to test the hypothesis that a real gender difference in age at onset and, thus, the disease process itself might account for the gender difference in age at first admission (study 4).

The age means for men and women were compared by five operational definitions of illness onset of major clinical relevance (figure 1): first (nonspecific) sign of a mental disturbance, first negative symptom, first positive symptom, moment of maximum accumulation of positive symptoms, and first hospital admission. Ranging approximately from 3 to 4 years, all the age differences observed between men and women attained significance and largely explained the gender difference in age at first admission. The consecutive definitions of onset from the first sign of the disorder to the climax of the first episode also represented milestones of the early development of the psychosis before first admission. The validity of the patients' statements about recent events were taken as a crude indicator of the reliability of more remote events.

Gender Differences in Age at Onset: Psychosocial Versus Biological Explanations (Studies 5 and 6). Having learned that gender explained the difference in age at onset directly, we set out to look for a plausible explanation of that effect. First we had to decide which of

Figure 1. Mean age values at five definitions of onset until first admission



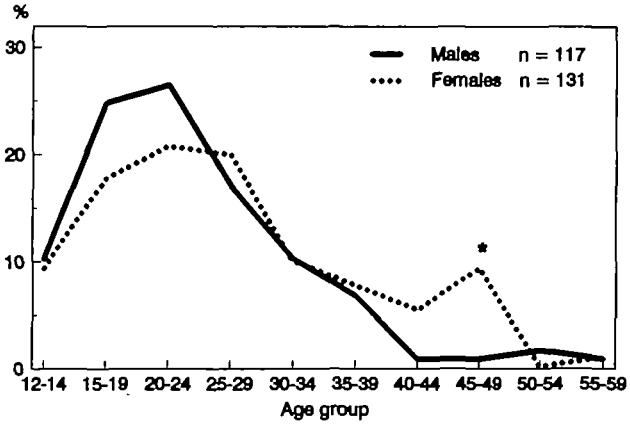
Difference between men and women: $^{*}p \leq 0.05$; $^{**}p \leq 0.01$. (First episode sample of broad definition schizophrenia, $n = 232$.)

the alternative explanations, biological or psychosocial, seemed more plausible. In view of the transcultural stability of the finding (Hambrecht et al. 1992), which rendered psychosocial variables less likely, and the fact that the psychosocial explanation had proved less likely, a biological hypothesis was considered.

Study 6 focused on the gender distribution of onset across the total age-of-risk range. Figure 2 gives the percentages of onset for successive age groups from 12 to 59 years of age. Of those 248 patients in the ABC sample who were able to state when their first sign of mental disorder appeared, men showed an early increase and a pronounced peak in adolescence and early adulthood followed by a monotonous fall. Women showed a slightly later increase, a lower peak followed first by a continuous fall, as among men, and then by a lower second peak in the age group 45 to 49 years. The importance of the finding of a second peak in age-at-onset rates for women is underlined by the fact that it has also emerged on case register data for the Danish population (Häfner et al., in press) and the Camberwell District in Southeast London, England (Castle and Murray 1993).

A cumulative depiction of the population-based incidence rates in successive 5-year age groups showed, as expected, that men consumed their lifetime risk clearly faster than women. But from about age 30 on, the rates for women became increasingly similar to those of men, reaching a final value of 13.1/100,000 versus 13.2/100,000 per year for men. These rates were based on a broad definition of schizophrenia (ICD–9 295, 297, 298.3–4). Limited to those patients allocated to the PSE-CATEGO classes S, P, and O, the rate was 11.5/100,000. When the most restricted definition, the PSE-CATEGO nuclear syndrome S+, comprising the Schneiderian first-rank symptoms only (Schneider 1950), was applied (see also Jablensky et al. 1992), the rate was 9.3/100,000. This rate was of the same magnitude as those (mean 10/100,000) for the restrictively defined S+ syndrome in the age range 15 to 55 years in the transnational WHO Determinants of Outcome study. But it is still unclear whether and under what circumstances paranoid syndromes of older age should be classified as schizophrenias and, thus, cases with onset beyond 60 years added to the lifetime risk.

Figure 2. Age distribution of onset of schizophrenia (first sign of mental disorder) for men and women



Schizophrenia diagnoses = International Classification of Diseases–9 295, 297, 298.3, 298.4 (World Health Organization 1978); subjects are from the ABC (age, beginning, course) sample—Mannheim, Heidelberg, Rhine-Neckar District, Upper Palatinate District; *$p < 0.05$. Adapted from Häfner et al. 1993*b*.

Gender Differences in Age at Onset: Testing the Estrogen Hypothesis in Animal Experiments (Studies 7 and 8). An identically accumulated risk over the total age range suggested that gender does not have any lifelong influence on the outbreak of the disorder and, hence, neither on the lifetime risk nor on the etiology of schizophrenia. What we had to look for in generating hypotheses were factors associated with being female and delaying the outbreak of schizophrenia.

The greater plausibility of a biological rather than a psychosocial explanation, the pattern of distribution of onset across the female life cycle, and the neurolepticlike effect of short-term estrogen applications in animal experiments (Fields and Gordon 1982; DiPaolo and Falardeau 1985; Hruska 1986) led us first to a hypothesis considered by Mendelson and coworkers (1977), Seeman (1983), Loranger (1984), Lewine (1988), and Seeman and Lang (1990): First, in women, estrogen starts to delay onset of schizophrenia at an early age—possibly as early as during brain maturation—by raising the vulnerability threshold for schizophrenia; second, considering the second peak of onset around menopause, we further presumed that fading estrogen secretion might cause women—predisposed to schizophrenia, but until then protected by estrogen—to fall ill with late-onset schizophrenia.

To test the two hypotheses, we had to move from the epidemiological to the neurobiological level. We employed the classic paradigm of dopamine-induced behavior by apomorphine stimulation in animal experiments. Having treated castrated female rats with 17-β-estradiol over a period of 4 weeks and comparing them with two groups of placebo-treated animals—one sham-operated and with physiological estrogen levels, the other castrated and, hence, almost estrogen-free—we observed a significant attenuation of dopaminergic behavior (oral stereotypes, sitting and grooming) in the experimental group. This result supported our hypothesis (Häfner et al. 1991*a*; Gattaz et al. 1992).

Our next step (study 8) was to clarify the underlying neurobiological mechanism. Determination of ^3H sulpiride binding—a D_2 ligand—in striatal tissue did not reveal any difference in the number of binding sites between the estradiol-treated group and the controls. But the dissociation constant kd was 2.8 times and thus significantly higher in the estrogen-treated group, pointing to a markedly reduced affinity of estradiol-treated D_2 receptors to the ligand. In adult animals all the effects were in the same direction, but slightly weaker. We concluded that estrogen treatment reduced the sensitivity of D_2 receptors (Häfner et al. 1991*a*).

The Estrogen Hypothesis: Testing Applicability to Human Schizophrenia (Study 9). Before we could show with a certain degree of probability that the mechanism plays a role in delaying the onset of schizophrenia in women, we had to establish its applicability to human schizophrenia. This was done in study 9, a controlled clinical study (Riecher-Rössler et al. 1994*a*, 1994*b*). We investigated 32 women with acute schizophrenia and 29 controls with acute depressive episodes, both with normal menstrual cycles. We examined the patients at six defined days of their cycle. Each time we analyzed their estradiol serum level and different other hormonal parameters, as well as their psychopathology, with the following instruments: Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962); Nurses' Observation Scale for Inpatient Evaluation (NOSIE; Honigfeld et al. 1976); Paranoid-Depressivitäts-Skala (PDS; von Zerssen and Koeller 1976); and Befindlichkeits-Skala (BfS; von Zerssen and Koeller 1976). To provide security for a diagnosis of acute depressive episode in the control group, we also introduced the Hamilton Depression Scale (HAM-D; Hamilton 1976).

To determine the association of estradiol blood levels with psychopathology scores throughout the menstrual cycle, cross-correlations (Jenkins and Watts 1968) were computed with correlations calculated intraindividually (estradiol × each psychopathology score), thus obtaining 10 association parameters for each schizophrenia patient and 11 association parameters for each control patient.

A significant negative correlation was found between estradiol serum levels or the corresponding menstrual phase on the one hand and schizophrenia and nonspecific symptomatology on the other hand (table 3). In contrast, no correlation between estrogen levels and measures of depressive symptomatology was observed either in the schizophrenia group or among the depressive controls. The only significant correlation in controls was connected with general behavior on the ward, as measured by the NOSIE, a measure of general behavior including schizophrenia and affective symptoms: the higher the estradiol level the more balanced the behavior was judged to be. In total, further assuming that more severe symptoms will result in an earlier outbreak of schizophrenia, the findings confirmed our assumption that the neuromodulatory effect of estrogen might play a decisive role in delaying onset in women. Recently, Sumner and Fink (1995) showed that estrogen treatment in castrated rats also leads to significant, agonistic effects on the serotonin transmitter system. The results of still another recent study (Woolley and McEwen 1994) suggest that estrogen might act on *N*-methyl-D-aspartate receptors, too, both in the menstrual cycle and over a longer period of time, and that these effects presumably contribute to the protective effect of estrogen in schizophrenia.

The neurohormonal mechanism involved in the estrogen effect, which possibly enhances the vulnerability threshold in schizophrenia, acts on the same neurotransmitter system as the most potent antipsychotic therapy currently known, that is, the blockade of D_2 receptors by neuroleptics. Like estrogen, classic neuroleptics reduce acute symptoms in schizophrenia and delay relapses, but do not reduce the lifetime risk. Very likely the mechanism has no etiological relevance. It seems to be part of a system whose functioning is a precondition for the production of one of the rare pathological response patterns of the brain known as schizophrenic psychosis, but also of some other psychotic or excitatory syndromes, such as exogenous psychoses, delusional disorders, mania, and delusional depression (Häfner et al. 1995*a*). The etiological factors that produce this particular pattern of response—for example, neurodevelopmental disorders, some toxic substances like amphetamine and phencyclidine (Javitt and Zukin 1991), and some brain diseases such as Huntington's disease, Wilson's disease, encephalomyelitis disseminata, porphyrinuria, and metachromatic leucodystrophy—are obviously not very specific.

Does the Earlier Onset of Schizophrenia in Men Produce Gender Differences in Early Course (Studies 10 and 11)? From the results discussed, we generated several new hypotheses about the consequences of the gender difference in age at onset. There is an old controversy about whether the negative social class gradient of the cumulative prevalence of schizophrenia is attributable to disease-related selection mechanisms in open societies (social drift), or whether it represents a consequence of unfavorable social conditions that patients with schizophrenia have been exposed to in their childhood and adolescence (social causation). Conducting a large-scale population study in Israel, Dohrenwend et al. (1992) concluded that the social class gradient of the morbid risk

Table 3. Correlations between psychopathology scores and estradiol serum levels throughout hospital stay of women schizophrenia patients and nonschizophrenia controls

	Schizophrenia patients (n = 32)				Nonschizophrenia controls (n = 29)			
Parameters	n[1]	**Mean**	**(SD)**	p	n[1]	**Mean**	**(SD)**	p
BPRS total score	31	–0.25	(0.41)	<0.01	29	0.03	(0.55)	NS
BPRS subscores								
Anxiety/depression	31	–0.10	(0.52)	NS	29	0.00	(0.52)	NS
Anergia	31	–0.15	(0.42)	<0.10	28	–0.04	(0.53)	NS
Thought disturbance	31	–0.28	(0.44)	<0.01	15	–0.13	(0.55)	NS
Activation	31	–0.27	(0.41)	<0.01	29	–0.06	(0.49)	NS
Hostile-suspiciousness	31	–0.19	(0.47)	<0.10	22	–0.13	(0.45)	NS
NOSIE total score[2]	32	0.25	(0.49)	<0.01	29	0.22	(0.43)	<0.01
BfS total score	32	–0.20	(0.43)	<0.05	29	–0.02	(0.56)	NS
PDS paranoid subscore	32	–0.17	(0.42)	<0.05	27	0.06	(0.51)	NS
PDS depression subscore	32	–0.10	(0.52)	NS	29	0.01	(0.56)	NS
HAM–D total score	Not evaluated				29	0.03	(0.53)	NS

Note.—Shown as means of individual correlation coefficients. NS = not significant. BPRS = Brief Psychiatric Rating Scale (Overall and Gorham 1962); NOSIE = Nurses' Observation Scale for Inpatient Evaluation (Honigfeld et al. 1976); BfS = Befindlichkeits-Skala (von Zerssen and Koeller 1976); PDS = Paranoid-Depressivitäts-Skala (von Zerssen and Koeller 1976); HAM–D = Hamilton Depression Scale (Hamilton 1976). Adapted from Riecher-Rössler et al. 1994*a*.

[1]The slightly varying numbers are partly due to missing data, partly due to exclusions: patients who never showed symptoms of a certain score or never showed variability in a certain score were excluded from analysis concerning the response score (14 controls concerning "thought disturbance," 6 controls concerning "hostile-suspiciousness," and 2 controls concerning "PDS—paranoid subscore").

[2]Contrary to the other scores, in the total NOSIE score a higher value means *less* psychopathology.

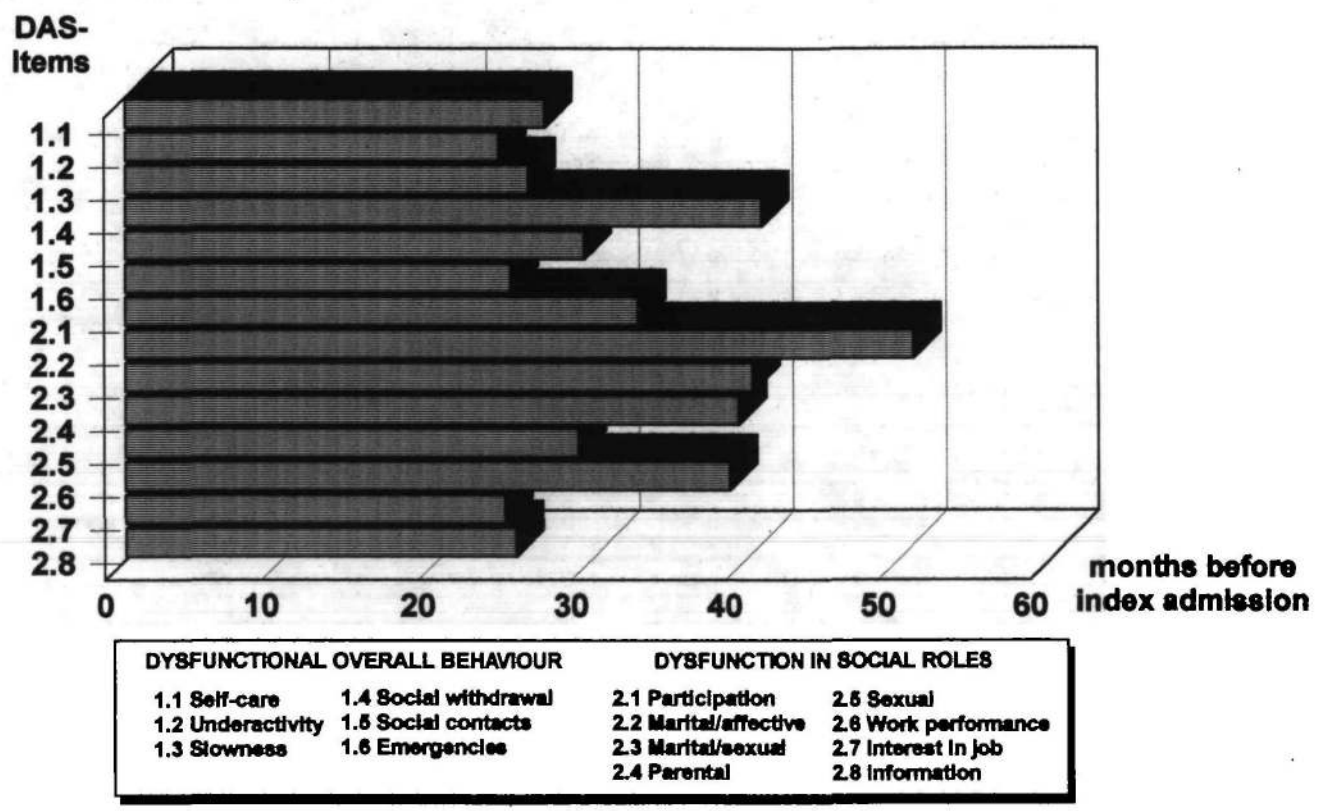
of schizophrenia can be explained by social selection rather than social causation. This finding prompted us to ask when and how social disadvantage emerges in schizophrenia.

Since the main age of risk for schizophrenia (about 75% of schizophrenia patients fall ill between 15 and 30 years of age) coincides with the period of the steepest social ascent in human life, we hypothesized that an early intrusion of the disorder into the social biography might represent a greater impediment to further social development than would onset at a later age. Consequently, men, who fall ill with schizophrenia earlier then women, might be at a greater disadvantage in terms of early social course (study 10). In 82 percent of the men and 73 percent of the women in the ABC sample, the first sign of mental disorder appeared before age 30. About 73 percent of the schizophrenia patients went through a prodromal phase, which lasted 5 years on average from the first sign of the disorder until the first positive symptom, whereas the psychotic prephase, extending until the climax of positive symptoms, had a mean length of 1.1 years. First admission took place about 1.5 months later.

Figure 3 shows when, on average, social disabilities—as measured by subscales of the Disability Assessment Schedule (DAS; Jung et al. 1989)—appeared before first admission. Almost all the items studied emerged more than 2 years before first admission, on average, thus illustrating that schizophrenia frequently involves social and cognitive disability as early as the prodromal phase and, hence, long before the first contact with mental health services takes place.

The few epidemiological followup studies focusing on gender differences in the course of the illness have reported a poorer 5-year social outcome for men, but a similar symptom-related course for both men and women (Biehl et al. 1986; Salokangas et al. 1987; Tsuang and Fleming 1987; Shepherd et al. 1989). According to our leading hypothesis we presumed that, compared with women, men's younger age at onset, associated with the impediment of individual social development at an earlier stage, might contribute to their poorer social course. A comparison of individuals' fulfillment of social roles indicative of social ascent in the relevant age period confirmed the first part of the hypothesis: significantly more women were employed, had left their parental home for independent accommodation, and were married or living in a stable partnership when the first signs of mental disorder appeared. There were no gender differences with

Figure 3. Onset of social disabilities (months before index admission)



DAS = Disability Assessment Schedule.

respect to completed education and occupational training, obviously because only a small proportion develop schizophrenia at an early age (table 4). Nevertheless a considerable proportion of women, too, were affected by the disorder before all social roles were taken up.

The unfavorable social conditions at the onset of the psychosis among men, despite a similar symptom-related course, resulted in a poorer social course, at least in the first years after first admission, compared with women, who, because of their later onset, enjoyed more favorable conditions. In the long run, the social and possibly the symptom-related course may become obscured by the severity and the social consequences of recurrent or chronic illness, as well as by environmental and personality factors, such as coping resources.

The second part of the hypothesis—that schizophrenia might lead to considerable social disadvantage even before first admission—was further tested in a case-control design by comparing observed with reliably expected social development (study 11; Häfner et al. 1995*a*, 1995*b*). We compared a subsample of 57 schizophrenia patients from our ABC sample—first-admission patients living in Mannheim, Germany, a city with a population of about 320,000—with 57 controls drawn from the city's population register and matched for age and sex. In both groups, level of social development was assessed by IRAOS at exactly the same age, determined by age at onset of the prodromal phase, onset of the psychotic prephase, and first admission in the index group. Only one indicator of social development, marriage, will be discussed here.

Due to their 2.5-year older average age of marrying in the general population (communication of the Federal Bureau of Statistics 1990) men, both schizophrenia patients and controls, showed significantly lower percentages of being married at the age marked by onset of schizophrenia, compared with women (figure 4). But in the following 6 years, male controls reduced that difference by half. In contrast, among both male and female schizophrenia patients, the downward trend persisted throughout the prephase. At the age of first admission 17 percent of the men with schizophrenia compared with 60 percent of the "healthy" men and 33 percent of the women with schizophrenia compared with 78 percent of the "healthy" women were married or had a stable partnership.

These results and the analyses of other indicators, such as a regular job or independent living, supported the hypothesis that a considerable amount of the social disadvantage involved in schizophrenia emerges after onset and before first admission. Social disadvantage seems to come about by the impeding effects that the prodromal and the psychotic prephases frequently have on social ascent and consequently is mediated by the level of social development at onset.

Consequences of the Protective Effect of Estrogen on the Frequency and Severity of Late-Onset Schizophrenia in Women (Study 12). Assuming that a higher degree of severity is associated with an earlier outbreak of the disease, the effect of estrogen can be understood as a variable elevation of the vulnerability threshold. Men, since they lack the protective effects of estrogen, would therefore be expected to develop more severe forms of the disorder fairly early, but with increasing age, after nearly all the severe forms have become manifest, they only fall ill with clearly milder forms (figure 5). If women, on the other hand, are protected by an elevated vulnerability threshold until menopause, the risk of the onset of schizophrenia will be reduced. A certain proportion of severe schizophrenia will not become manifest as long as the protective effect of estrogen is present. But from premenopause on, when estrogen secretion ebbs and the protection is lost, women will have higher incidence rates. This result has been reported by several authors (e.g., Harris and Jeste 1988; Castle et al. 1995).

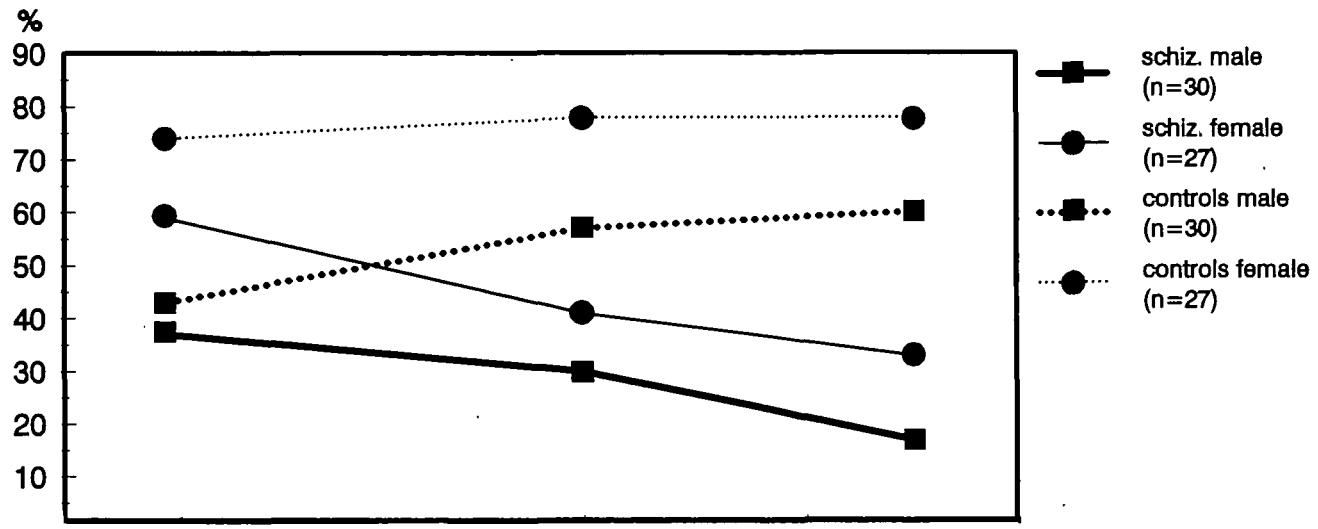
In older age, women should also present more severe forms of the disorder than men of the same age who developed the severe forms of schizophrenia earlier due to the lack of estrogen, whereas in women the onset of severe episodes is delayed by the effect of estrogen.

Table 4. Social role performance at the time of first sign of mental disorder

Age (in years)	Men (n = 108)	Women (n = 124)	Total (n = 232)	p
School education completed	70	69	70	NS
Occupational training	41	38	39	NS
Employment	37	52	45	≤ 0.05
Own accommodation	39	54	47	≤ 0.05
Marriage or stable partnership	28	52	41	≤ 0.01

Note.—Data are percentages except where indicated. NS = not significant.

Figure 4. Marriage or stable partnership in schizophrenia patients



Comparison groups	First sign	First psychotic symptom	Index admission
Schizophrenia patients vs. controls	—	$p \leq 0.01$	$p \leq 0.01$
Men schizophrenia patients vs. women schizophrenia patients	$p \leq 0.10$	—	$p \leq 0.10$
Control men vs. control women	$p \leq 0.05$	$p \leq 0.10$	$p \leq 0.10$
Men schizophrenia patients vs. control men	—	$p \leq 0.10$	$p \leq 0.01$
Women schizophrenia patients vs. control women	—	$p \leq 0.01$	$p \leq 0.01$

Schiz. = schizophrenia.

In keeping with these tentative conclusions, we derived two hypotheses from the estrogen effect (study 12): (1) If women are protected by an elevated vulnerability threshold until premenopause, they should, from that age on, show higher incidence rates of schizophrenia than men; and (2) in older age women should also present more severe forms of the disorder than men of the same age.

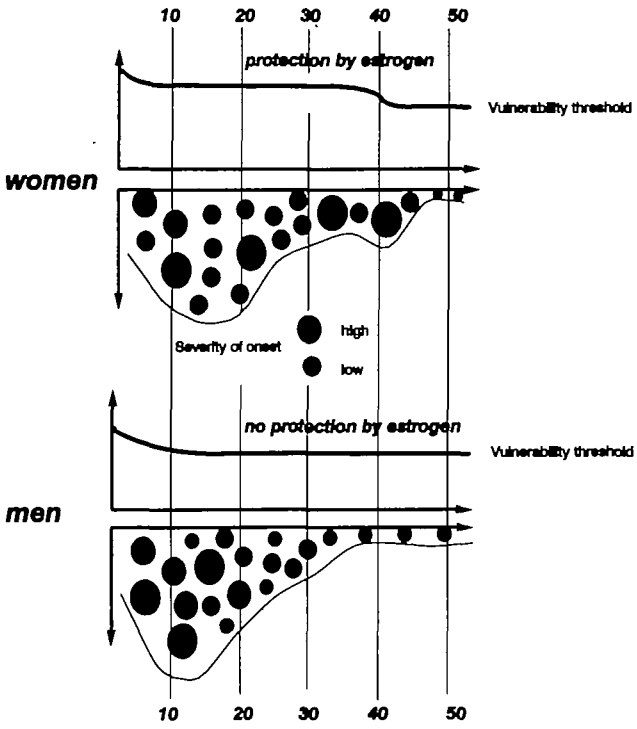
To test these two hypotheses we divided our first-episode sample into three groups by age at the first positive symptom (table 5): 49 children and adolescents younger than age 21; 136 young adults between ages 21 and 35; and 47 adults between ages 36 and 60.

Women predominated significantly in the oldest group, in line with the first of our two hypotheses: the higher incidence of late-onset schizophrenia in women compared with men. In contrast, the incidence rates in the youngest, the early-onset group, differed only slightly and not significantly between the sexes, possibly because of a certain number of estrogen-resistant women.

When looking at the accumulation of positive, negative, and nonspecific symptomatology—mean sum scores of IRAOS items per year until first admission as an indicator of severity of illness—as a whole, no significant differences emerged among the three age groups (Häfner and Nowotny 1995). The only exception was an earlier increase of nonspecific symptoms to a comparatively higher level in the youngest group.

Symptomatology in the first psychotic episode, assessed with the PSE immediately after first admission, showed a low but steady decrease of the CATEGO total score from 46 in the youngest group to 38 in the oldest group. This finding was well in agreement with the negative linear correlation of age and measures of symptomatology recently reported by Galdos and van Os (1995) on case-register data. It was not the schizophrenia-specific syndromes DAH (delusions and hallucinations) and BSO (behavior, speech, and other syndromes) that accounted for much of the age effect in the first place, but predominantly the nonschizophrenic syndromes SNR (specific neurotic syndrome) and NSN (nonspecific neurotic syndrome). Like fever in many infectious diseases, elevated scores of symptoms not specific to the illness in an acute phase may well be taken as indicative of a greater severity of illness in early-onset schizophrenia. This finding, well in line with the results of numerous clinical studies—for a review see, for example, Asarnow and Asarnow (1995)—

Figure 5. A theoretical model of age-dependent effects of different vulnerability thresholds in women and men



showed that early-onset schizophrenia is not only more severe, but also more frequently associated with neuromotor, behavioral, and emotional antecedents.

When the three age groups were compared at first admission by single characteristics, no differences emerged in the positive and negative core symptoms apart from indistinct, poorly elaborated delusions in the youngest group and a significant increase of paranoid, particularly secondary, delusions in the oldest. This difference reflected above all the level of cognitive development in coping with the disorder. Galdos and van Os (1995) rightly pointed out that children with schizophrenia must have at least some knowledge of electromagnetic rays or interception devices before these can be included in an explanatory delusion.

For testing our second hypothesis—that late-onset schizophrenia in women might be associated with a greater severity of illness—a univariate analysis of variance was computed. A comparison of the extreme groups—first psychotic symptom before age 21 versus at age 40 or later—revealed that the lower syndrome scores in the late-onset group were accounted for solely by men, who showed considerably milder forms of illness in half of the measures compared with the early-onset men (table 6). There was no single main effect of gender, but four of eight indicators of severity showed a significant interaction between gender and onset. For women, not a single indicator was significantly more favorable (Wilcoxon test), and only one indicator, the SANS global score as a measure of negative symptomatology, was more unfavorable in the oldest group; this finding showed a trend at the 0.10 level. Overall, the table shows that early-onset schizophrenia in men is associated with a greater severity of illness. But female late-onset schizophrenia, which is clearly more severe compared with male late-onset schizophrenia, is not milder than female early-onset schizophrenia.

Conclusions

Men fall ill with schizophrenia at an earlier age than women. Although more recent studies have produced evidence that gender differences in age at onset cannot be observed in familial schizophrenia (DeLisi et al. 1994; Albus and Maier 1995), this holds true for the vast majority of isolated cases.

In our study, comprising 12 consecutive systematic substudies, after testing hypotheses on an epidemiological level, we showed that an elevated vulnerability threshold for women until menopause may explain the gender difference in the age at onset of schizophrenia. The underlying pathophysiological mechanism may be the sensitivity-reducing effect of estrogen on D_2 receptors in the central nervous system. This effect is possibly compounded by

Table 5. Gender distribution in three age groups (n = 232)

Age at onset (years)	Total		Men		Women		Ratio of men to women
	n	%	*n*	%	*n*	%	
< 21	49	21	28	57	21	43	1.3
21–35	136	59	65	48	71	52	0.9
36 < 60	47	20	15	32	32	68	0.5
Total	232	100	108	47	124	53	0.9

Note.—Onset is defined as first psychotic symptom. Adapted from Häfner and Nowotny 1995.

Table 6. Gender differences in symptom scores at time of first psychotic episode—Early versus late onset (age at first psychotic symptom < 21 vs. ≥ 40 years)

	Men		Women		Analysis of variance		
Symptomatology	Early ($n = 28$)	Late ($n = 9$)	Early ($n = 21$)	Late ($n = 24$)	Main effect: gender	Main effect: onset	Interaction: gender × onset
DAH	12.1	5.7[1]	10.0	10.5	NS	$p \leq 0.1$	$p \leq 0.05$
BSO	8.6	7.3	8.9	7.9	NS	NS	NS
SNR	10.7	7.3	8.2	7.1	NS	NS	NS
NSN	18.9	11.4[1]	13.0	13.8	NS	$p \leq 0.1$	$p \leq 0.05$
PSE total score	50.3	31.8[1]	40.0	39.2	NS	$p \leq 0.05$	$p \leq 0.05$
SANS	9.3	6.6	6.7	9.5[2]	NS	NS	$p \leq 0.05$
PIRS	10.7	8.4	9.8	10.5	NS	NS	NS
DAS-M	3.0	1.8[3]	1.9	1.8	NS	NS	NS

Note.—BSO = behavior, speech, and other symptoms; DAH = delusions and hallucinations; DAS-M = Disability Assessment Schedule–German version (Jung et al. 1989); NSN = nonspecific neurotic syndrome; PIRS = Psychological Impairment Rating; PSE = Present State Examination (Wing et al. 1974); SANS = Scale for the Assessment of Negative Symptoms (Andreasen 1989); SNR = specific neurotic syndrome; NS = not significant.

[1]Significant difference between early and late onset ($p \leq 0.05$; Wilcoxon test), downward trend.
[2]Significant difference between early and late onset ($p \leq 0.10$; Wilcoxon test), upward trend.
[3]Significant difference between early and late onset ($p \leq 0.10$; Wilcoxon test), downward trend.

agonistic effects of estrogen, acting as a neuromodulator, on other transmitter systems—serotonin and glutamate—as well. On the basis of these findings we formulated secondary hypotheses about the consequences the difference in age at onset has on the early social course of the disorder in men and women and about the consequences the difference in the male and female (until menopause) vulnerability thresholds has on the frequency and severity of schizophrenia at various ages.

From the results discussed, we concluded that, gender not considered, early-onset schizophrenia, defined by the appearance of the first psychotic symptom before age 21, is characterized by a more severe, but predominantly nonspecific symptomatology compared with late-onset schizophrenia, and is associated with a more unfavorable early social course. In contrast, initial symptoms, type of onset, and early symptom-related course do not show any substantial age differences, apart from the effects the level of cognitive development has on symptom formation and secondary symptomatology such as explanatory delusions. Late-onset schizophrenia is more frequent, with a relative risk of 2 to 3, and comparatively more severe in women than in men, whereas in men late-onset schizophrenia is less frequent and milder on average than early-onset schizophrenia. Our hypothesis of the missing protective effect of estrogen explains why almost all men develop severe schizophrenia at an earlier age, whereas some women with a severe disposition are unaffected until menopause thanks to the protective effect of estrogen, but then fall more gravely ill.

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