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# Reduced Fertility in Schizophrenia. A Consequence of the Disorder, of Premorbid Personality or Other Factors?

Heinz Häfner*[1], Peter Propping[2], Wolfram an der Heiden[1], Daniel Ropeter[1]

[1]*Schizophrenia Research Group, Central Institute of Mental Health, Medical Faculty Mannheim / Heidelberg University, Germany*

[2]*Institute of Human Genetics, University of Bonn, Germany*

**Corresponding author:* *Prof. Dr. Hc. Mult. Heinz Häfner, Schizophrenia Research Group, Central Institute of Mental Health, J5, D-68159 Mannheim, Germany, Tel: +49 62117032952; E-mail: heinz.haefner@zi-mannheim.de*

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## Abstract

### Background

Since about 1965 fertility rates in the general population have kept decreasing in Germany. We studied whether fertility rates for patients with schizophrenia decreased in parallel with, more slowly or more rapidly than those for the general population. After finding differences, we explored the underlying reasons.

### Methods

We conducted three subsequent studies in the same semi-urban, semi-rural German population using the same unchanged diagnostic definitions. The overall period covered was about 50 years. Study 1 relied on retrospectively collected data for 1949-50 and follow-up data for 1962-1963, Study 2 on data for 1965-67 and a follow-up in 1978-80 and Study 3 on data for 1987-89 and a follow-up in 1999-2002. At each wave, patients were compared with age- and sex-matched population controls from the study area. In Study 3, based on a population-based sample of first illness episodes of schizophrenia, we also studied at which stage of illness patients' fertility changed and how their reproductive wishes developed compared with healthy controls.

### Results

Over the period covered, marriage rates fell drastically and the number of children born out of wedlock grew markedly in the former East Germany. In the former West Germany these trends were markedly less pronounced. Fertility in schizophrenia fell steadily and more markedly compared with the control population, and the decrease was more pronounced for male than female patients. Patients' fertility started to fall slightly in the prodromal period, but the largest reduction occurred after the onset of manifest psychosis. Before illness onset, patients' reproductive wishes resembled those of healthy controls, but became markedly reduced over time as a result of how they experienced the disorder and its consequences.

**Conclusions**

Reduced fertility in schizophrenia, observable not yet before psychosis onset, but in full-blown illness, indicates that underlying it is a changed reproductive motivation, a reduced wish of persons of reproductive age to have children after experiencing the disorder and its consequences. A direct biological effect is unlikely.

**Keywords:** Schizophrenia; Epidemiology of Schizophrenia; Fertility in Schizophrenia, Time Trends in Fertility; Causes of Reduced Fertility

## Introduction

### Factors Influencing Fertility in Schizophrenia

In the following we will discuss a few seminal studies on the topic.

According to Ornulf Odegård's [1] long-term study based on data from the Norwegian case register and covering a period from 1936 to 1975, female fertility fell from 3.2 to 2.4 children per woman. The decrease was less pronounced in the general population than for patients with schizophrenia. Like ours, Odegård's study, too, compared data in several waves over the total period covered.

In order to take account of the economic and political factors unique to Germany, we included in our analysis fertility rates from the former East Germany (German Democratic Republic – DDR) before and after its reunification with West Germany and compared them with those for West Germany (Federal Republic of Germany - BRD), the entire German population and for a socioeconomically particularly stable West-German state, namely Baden-Württemberg. We concluded from these comparisons that the nationwide data for Germany are based on fairly stable social trends.

Shearer et al [2] studied 8,728 women of reproductive age diagnosed with schizophrenia and treated at six mental hospitals in Michigan. The authors collected data for six different years over a period of 30 years (1935-1964). They found that in this period patients' fertility increased more markedly than that of the general population, from 17 births/1000 women and year to 61.2 births/1000 women of this age. That would have amounted to an increase of 360%, which seems unlikely in comparison with results from the majority of studies.

In analysis of long-term trends changes in the socioeconomic conditions and ethnic aspects of the populations studied should be considered as a rule. In the USA the period studied by Shearer et al. was characterized by considerable economic upheaval and World War II-related changes as well as by a profound shift in the diagnostic definition of schizophrenia. After a period of predominantly psychodynamic diagnostics Robins & Guze [3] paved the way for descriptive, precisely defined diagnoses especially in the diagnostics of schizophrenia, which ultimately produced the classification system DSM-III. So the results reported by Shearer et al. are probably attributable to the extremely imprecise diagnostic definition used before Robins & Guze's pioneering work and the introduction of DSM-III.

In contrast, data for former West Germany and after the 1990 German reunification for the Federal Republic of Germany permit one to study long-term trends in the fertility of persons with schizophrenia. West Germany enjoyed political stability after World War II and had a well-functioning welfare system and a classification system, the International Classification of Diseases - ICD (version 6 of 1948, version 9 of 1976) in place, which was based, as far as schizophrenia is concerned, on the Kraepelin-Schneiderean diagnostic categories: delusions, esp. delusional perceptions, hallucinations, esp. hearing voices conversing with each other, and negative symptoms, esp. cognitive deficits, with the exclusion of physical and affective disorders [4].

Analyses of sufficiently large and methodologically sound population-based studies are consistent in showing geographic stability in the reduced reproductive probability of patients with schizophrenia [5] with a few differences in its size and with some sex differences attributable to women's higher age of onset of schizophrenia and a reduced number of children born to male patients because of their earlier age of illness onset.

### Explaining the Lower Fertility in Schizophrenia by a Hypothesized Biological Compensation

To resolve the discrepancy between reduced reproductive probability and the intergenerational stability of schizophrenia incidence Erlenmeyer-Kimling & Paradowksi [6] postulated in 1966 a compensatory effect of a greater biological fitness and higher reproductive rates of next of kin of people with schizophrenia. The authors reported slightly increased fertility rates for the healthy siblings of patients with schizophrenia. The hypothesis soon attracted a lot of interest, because genetic transmission was handily likened to the particular, recessive mode of inheritance of sickle cell anemia [5]. However, attempts to confirm the hypothesis have failed. Buck et al. [7] conducted a careful large-scale study based on data for 1195 siblings of persons diagnosed with schizophrenia and on census data for the general population and taking into account the influence of sex, age at marriage and duration of marriage. The authors found no evidence clearly supporting the hypothesis. Nor did a number of other studies [8-14].

On the basis of the results of a review of the literature on the topic Haverkamp et al. [5] estimated that the reproductive rate of patients diagnosed with schizophrenia amounted to 30% to

80% of the average reproductive rate of the general population.

In the last decade three large-scale epidemiological studies addressing the hypothesis of a compensation of the reduced fertility in schizophrenia were published. They compared fertility rates for the general population, for patients with schizophrenia, for their siblings and in part also for their children and grandchildren. Proceeding from the Finnish birth cohort of 1950 to 1959 comprising 870,093 individuals, Haukka et al. [15], using the national hospital discharge register, identified all persons treated for schizophrenia (1.3%, a figure well in line with the results of epidemiological studies on schizophrenia incidence reported from various countries [16, 17]). Women with schizophrenia had 0.83, men with schizophrenia 0.44 children and, hence, both significantly fewer than their general-population counterparts. The number of children the sisters of patients with schizophrenia had was slightly higher than that for women in general (1.89 versus 1.83), whereas the figure for the patients' brothers was slightly lower compared with men in general (1.57 versus 1.65). The authors concluded that „*..the persistence of schizophrenia in the general population is not explained by this simple evolutionary mechanism*".

In the second study, Svensson et al**.** [18] studied three Swedish birth cohorts of older generations of individuals with schizophrenia: 1918-1927 (n=274,464), 1932-1941 (n=108,502) and 1951-1960 (n=103,105). On average, the fertility of men with schizophrenia was 70% lower, that of their female counterparts 48% lower than that of the age-matched general population. The fertility of male and female siblings of patients with schizophrenia did not differ from that of the general population. In contrast, the fertility of the patients' sons was 12% [fertility ratio FR = mean number of offspring (subjects/population): 0.88] lower, that of their daughters 6% (FR: 0.94) lower. For lack of further data these results are difficult to interpret. This study, too, failed to produce conclusive evidence for the hypothesis that the lower fertility of people with schizophrenia is offset by a higher fertility of their close relatives.

In the third study MacCabe et al. [19] examined a Swedish birth cohort comprising 12,168 individuals born in 1915 to 1929 and followed them up to 2002. The study design permitted the authors to compare two generations of patients with schizophrenia (n=58) and affective psychosis (n=153) with their siblings over the entire life-span by taking sociodemographic variables into account. Fertility among persons with schizophrenia (FR: 0.42) and even among their grandchildren (FR: 0.51) was lower than in the general population. The patients' low fertility was partly accounted for by their lower rate of marriage. But, showing that the patients' siblings had normal fertility ratios, this study, too, failed to provide any evidence for the hypothesis that the diminished fertility in schizophrenia is compensated for by a greater reproductive fitness of the patients' non-affected relatives.

Consequently, it can be regarded as fairly well established that the continuously low fertility of persons with schizophrenia, which does not have any greater effect on incidence, is not offset by an elevated reproductive output of their next of kin.

Heritability in schizophrenia, i.e. the percentage of phenotypic variation explained by genetic variation in a population, is estimated at about 80% [20-22], quite a high figure. There is no explanation yet for the fact that the frequency of the disorder remains unchanged despite the lower fertility of the persons affected. A complete genetic model of schizophrenia is still lacking, but recent findings offer important clues to partial explanations. Genetically, schizophrenia is a highly heterogeneous disorder. Genome-wide association studies focusing on single nucleotide polymorphisms (SNPs) in very large patient collectives and controls indicate that a large number of genotypes must exist in the general population, each genotype contributing only a tiny fraction to the schizophrenia risk [23]. However, these genotypes are not specific for schizophrenia. They also contribute to the etiology of other disorders of the central nervous system, such as bipolar disorder, major depressive disorder and autism spectrum disorder [24, 25]. While a majority of the SNPs provide indirect indication - via linkage disequilibrium - of the existence of risk-enhancing gene variants, a few gene variants have also been shown to be likely to play a functional role [26]. In addition, a series of microdeletions have been identified which increase the risk for various CNS disorders, among others for schizophrenia [27, 28]. Each one of these microdeletions is rare in the general population and frequently the result of a de novo mutation. A series of rare protein-altering mutations in various genes have been identified by exome sequencing. Some of them, consequences of new mutations, increase the risk for schizophrenia [29]. It is a future challenge to quantify the individual share of the various gene variants and new mutations in the etiology of schizophrenia and to integrate them in a model that explains the stability of schizophrenia incidence in the progeny despite differences in the fertility of the risk carriers in the parental generation.

## Materials and Methods

### Questions studied

Focusing on the association between illness and fertility, we explored long-term time trends of reduced fertility among patients of reproductive age (16 to 55 years) diagnosed with schizophrenia on the basis of the rate (and number) of children born to them in and out of wedlock in comparison with the general population and age- and sex-matched controls drawn from the German population of the study area. Our aim was to show whether those time trends really exist and, if so, what are the factors governing them. A further aim was to clarify at which stage of illness fertility becomes reduced, for example before illness onset as a genuine anomaly or at the prodromal stage or after illness onset as a result of all the con-

sequences that event has for the patients' lives. We also tested the hypothesis positing that schizophrenia has a direct biological effect on fertility or, as an alternative, that this effect is mediated through how patients experience the disorder and/or its consequences.

**Samples**

Our analyses are based on six controlled assessments of three representative cohorts of – first ever admitted – patients with schizophrenia of the same diagnostic definition. The cohorts were drawn from the German population of one and the same semi-rural, semi-urban catchment area (Mannheim/Heidelberg/Rhine Neckar District).

**Study 1** [30]: first assessment of 62 German men and 121 German women aged 16 to 55 years with a diagnosis of schizophrenia (consecutive first admissions) in 1949-50 (two years); follow-up assessment an average of 13 years later in 1962-63. Time prior to each assessment was chosen as exposure period.

**Study 2** [30]: first assessment of 82 men and 146 women with schizophrenia (consecutive first admissions) aged 16 to 55 years in 1965-67 (two years) with follow-up an average of 13 years later in 1978-80

**Study 3**: first assessment of the A(ge) B(eginning) C(ourse) schizophrenia sample [31, 32] in 1987-89 (two years); final follow-up an average of 12.3 years later in 1999-2002. The analyses are based on a representative cohort of 232 first episodes of schizophrenia (= 84% of the first admissions included, 108 German men, 124 German women; age range: 12-59 years) drawn from the same population of origin. In this sample we determined the time of first-ever onset of symptoms, i.e. the beginning of the prodromal stage of the disorder on data collected retrospectively using the Interview for the Retrospective Assessment of the Onset of Schizophrenia - IRAOS [33].

Study 3 was conducted as part of our larger A(age), B(beginning) C(course) Study covering 25 years [34, 35]. The main objective of that research project was and still is to elucidate the causes underlying the sex difference in age at schizophrenia onset and to address a few other unresolved issues in order to demonstrate how age and sex influence the long-term course of schizophrenia and how genetic and environmental risk factors, including the purely biological risk, act.

For each of these three patient samples a sample of "healthy" controls, matched for age and sex - in Studies 1 and 2 also for birth year, denomination and size of the municipality - was drawn from the population of the catchment area and assessed using the same instruments as the patients.

In Study 3 the patients of the first-episode sample were individually assessed at first admission, and their history was traced back to illness onset using the IRAOS [33]. The controls were assessed in the same way and at the same age as the patients. The mean duration of the prepsychotic prodromal stage extending from the first sign of illness to the onset of the first psychotic symptom was 4.8 years (median: 2.3). When the psychotic prephase leading to first admission was included, it was 6 years (median 2.8) [36][1].

At follow-up, an average of 12.3 years later, we re-examined all the patients from the original Study 3 sample we could reach and who consented (N=107). We also interviewed on the phone an age- and sex-matched control sample, drawn from the population of the same area (N=107), using an adapted version of the IRAOS. The follow-up sample was tested for its representativity of the original sample, but no significant differences were found in demographic or selected illness variables [37].

There are age differences between the three study cohorts to take into account. In Study 1 (1949-50) patients' mean age at first admission was 34.2 years (men 30.0, women 36.4), in Study 2 it was 34.8 years (men 30.3, women 37.4). In Study 3 the patients were a few years younger, on average 26.5 years old (men 23.6, women 29.2). Consequently, the preceding reproductive period in Study 3 was correspondingly shorter. The reason is that in Study 3 the age threshold for inclusion was lower, 12 years, and that first admissions of patients who had previously experienced one or more episodes without receiving inpatient treatment were excluded. In Studies 1 and 2 the age threshold was 15 years and first admissions were analysed. In all three studies women were several years older, a fact well known from epidemiological research [38].

Follow-ups (1962-63, 1978-80, and 1999-2002) were done after an additional exposure period of 12 to 13 years on average. Fertility was ascertained for time before and time following first admission [30, 37, 39]. Only in Study 3 could fairly exact comparisons also be done between premorbid and prodromal fertility [37].

**Fertility Rates in the General Population (Germany as a Whole, Former West Germany, New States, State of Baden-Württemberg)**

For purposes of comparison we first studied fertility trends in the populations of former West and East Germany (after 1990 unified Germany) and the state of Baden-Württemberg, the home state of our study samples (Figure 1). In all these German populations the annual fertility rates (children per woman) fell markedly starting in 1965 presumably in conjunction with the spread of hormonal contraceptives. After 1990 the rates stabilised on a low level, showing only slight differences between these populations. The only outliers were the fertility rates of the former German Democratic Republic (East Germany) some 10 years before the reunification and those of the



1 Because the decision to reproduce or the actual conception is followed by a time-span of nine months or longer, included in the fertility rates at the prodromal stage are a few premorbidly conceived births. Similarly, some births conceived late at the prodromal stage fall in the subsequent stage of full-blown illness. These aspects had to be neglected in the analyses.

eastern states of Germany some 10 years after the reunification. They reflect the fundamental change in the political system and the population's living conditions.

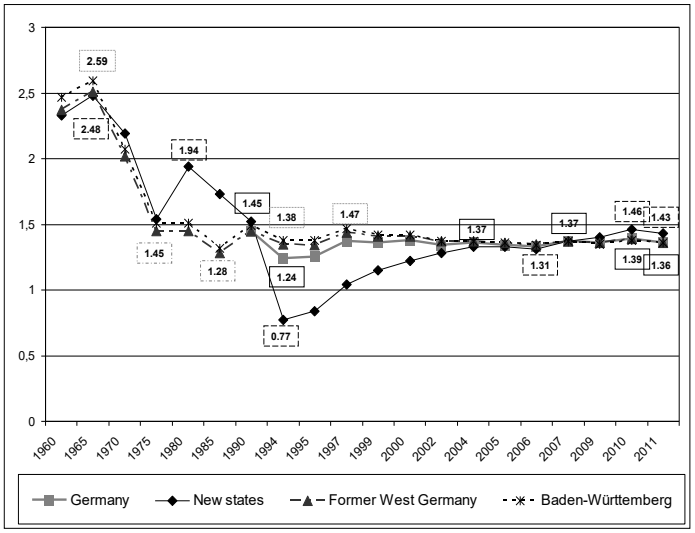


**Figure 1.** Birth rates in Germany – Germany as a whole, former West Germany, new states, state of Baden-Württemberg – in 1960 to 2011 (based on data from the Federal Statistical Office and the Statistical Office of the state of Baden-Württemberg).

## Frequency of Marriage, Marital and Non-Marital Births

Because changes in the conditions under which persons of reproductive age are willing to conceive, give birth to and raise offspring probably influence their reproductive motivations, we compared reproductive rates between married and unmarried individuals among patients and controls.

We will first look at the frequencies of marriage and marital and non-marital births. Interpreting these trends we must consider the gradually changing age composition of the German population, including a falling number of women of reproductive age, and a declining frequency of marriage (by 23% from 1980 to 2010; by 26% from 1990 to 2010) with a simultaneous increase in the proportion of out-of-wedlock births in Germany. In all three populations (new states, former West Germany, state of Baden-Württemberg) the number of marriages fell continuously. This is the reason why both the number and share of children born out of wedlock increased, albeit to a very different extent in the populations studied (Figure 2). The state of Baden-Württemberg, socio-politically the most stable state, where our study was conducted, showed the lowest increase, the new states the largest. This raises the question whether these developments also influenced fertility in schizophrenia.

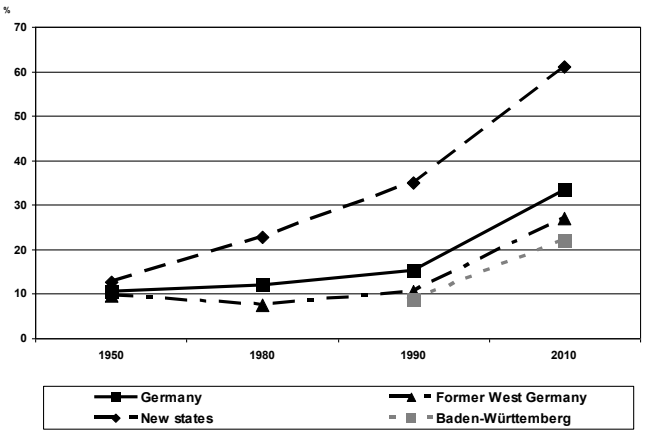


**Figure 2.** Percetages of children born out of wedlock among live births in 1950 to 2010 in Germany as a whole, new states, former West Germany, state of Baden-Württemberg (no data available for Baden-Württemberg before 1990; based on data from the Federal Statistical Office and the Statistical Office of the state of Baden-Württemberg).

## Mental Health Care Reform (Dehospitalisation)

In Germany dehospitalisation began 15 to 20 years later than in the Anglo-American countries. In 1971 the federal government set up a commission of inquiry on mental health care to assess the state of psychiatric care and to produce recommendations for reforming the system. In that same year transition to outpatient and complementary care began, promoted by the availability of neuroleptic medications, and increasingly gained momentum after the publication of the commission's recommendations in 1975 [40] (Figure 3).

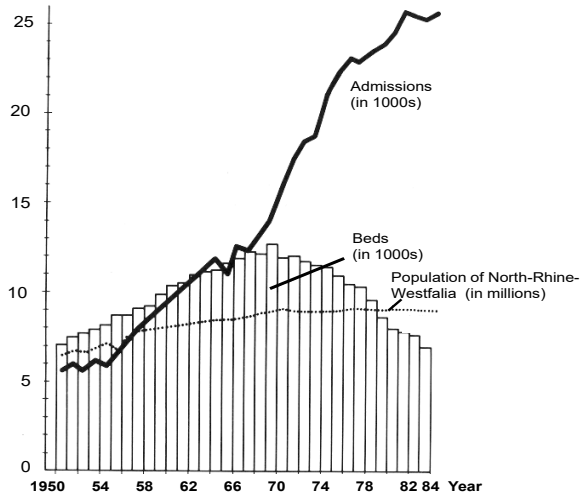


**Figure 3.** Admissions to and occupied beds at Rhineland state mental hospitals (Rheinische Landeskliniken für Psychiatrie) in 1950 to 1984 (Based on statistics of the Rhineland Regional Council for the Rhineland state mental hospitals) (Source: [41]).

In the "old" - formerly West-German - states the number of mental-hospital beds fell by 64.4% (from 115,857 to 41,219) between 1975 and 2011. In reunified Germany it decreased by 36.7 % between 1991 and 2011. If dehospitalisation had led to an increase in the fertility of people with schizophrenia, the patients' fertility figures should have been on the rise since about 1975.

## Results

In the years after 1975 when dehospitalisation was gaining momentum and thereafter the rates of births per woman for patients with schizophrenia did not rise as expected. Especially in the later exposure periods – at follow-up in Study 2 and 3 in particular – patients showed considerably lower rates than their healthy peers.

In Studies 1 and 2 we counted the total number of days patients spent in inpatient hospital care as an indicator of social isolation versus better opportunities in the community for finding a partner (Table 1). It can be assumed that until the early 1970s inpatient hospital care was almost invariably closed (intramural) in type, but since then has continuously been replaced by growing proportions of outpatient and other forms of care.

| | Men | | Women | |
|---|---|---|---|---|
| | Study 1: 1949-50 | Study 2: 1965-67 | Study 1: 1949-50 | Study 2: 1965-67 |
| | Mean number of days in inpatient care | | | |
| Single | 169.5 | 266.3 | 186.7 | 120.5 |
| Ever married | 148.0 | 65.7 | 88.0 | 66.6 |

**Table 1.** Mean number of days spent in inpatient care by marital status and sex (based on data from [30])

The number of inpatient days fell in the pre-reform period from 1949 (FU 1962-63) to 1965-67(FU 1978-80) with the exception of the figures for single men, which included a few extremely long stays. Figure 3 already demonstrated an increase in the number of inpatient admissions as a corollary of the dehospitalisation programmes implemented.

Table 2 illustrates the comparison of fertility (mean number of children per person) between patients and controls by sex in the period from 1949-50 to 1999-2002 in the three studies. The considerably lower figures for both patients and controls at first admission in Study 3 are probably accounted for by the lower age of the men in particular in this cohort (mean age: total 26.5, men 23.6, women 29.2 years) as compared with the corresponding figures in Study 1 (mean age: total 34.2, men 30.0, women 36.4 years) and Study 2 (mean age: total 34.8, men 20.3, women 37.4 years) [37]. The reason for the higher figures at follow-up is that they are lifetime data, i.e. include the rates ascertained at first admission.

| | Study 1 | | Study 2 | | Study 3 | |
|---|---|---|---|---|---|---|
| | 1st admission 1949-1950 | Follow-up 1962-1963 | 1st admission 1965-1967 | Follow-up 1978-1980 | 1st admission 1987-1989 | Follow-up 1999-2002 |
| Men | *Patients/controls N=62 respectively* | | *Patients/controls N=82 resp.* | | *Patients/controls N=48 resp.* | |
| Patients | 0.70 (40) | 1.34 (83) | 0.35 (29) | 0.62 (51) | 0.23 (11) | 0.42 (20) |
| | * | | ** | ** | | ** |
| Controls | 0.35 (22) | 1.48 (92) | 0.78 (64) | 1.44 (113) | 0.23 (11) | 0.92 (44) |
| Women | *Patients/controls N=121 resp.* | | *Patients/controls N=146 resp.* | | *Patients/controls N=59 resp.* | |
| Patients | 1.04 (126) | 1.27 (154) | 1.00 (146) | 1.14 (166) | 0.69 (41) | 0.94 (56) |
| | | | | | | ** |
| Controls | 0.89 (108) | 1.30 (158) | 1.10 (161) | 1.37 (200) | 0.78 (46) | 1.70 (100) |

**Table 2.** Comparison of male and female fertility - mean number of children per person and total number of children (in brackets) - between patients with schizophrenia and healthy controls in the three studies (based on data from [37]).

A parallel trend of more markedly falling fertility for patients than controls also emerges from the rates for both sexes at follow-up across the three studies: 1.29 (for controls 1.37) in Study 1, 0.95 (for controls 1.39) in Study 2 and 0.71 (for controls 1.34) in Study 3 [30, 37, 39].

If „parenthood rates" (percentages of patients and controls with at least one child ever born) at follow-up are compared across the three studies, patients' decreasing fertility and growing gap to controls over the four decades becomes evident. In Study 1 the proportion of patients with at least one child was 54.6% (controls 64.5%). In Study 2 it fell to 46.9% (controls 65.8%), in Study 3 further to 40.2% (controls 71%), while the corresponding figures for the controls rose slightly [30, 37, 39].

With the decrease in the proportion of patients with children (Table 2) the percentage of childless patients rose: in the 1949-50 first-admission cohort the figure for men was 48% (n=30), in the corresponding 1965-67 cohort 71% (n=58), compared with 26% (n=16) and 32% (n=26) for control men respectively. In contrast, the proportion of childless female patients did not change much, being 44% (n=53) in Study 1 and 43% (n=63) in Study 2 as against 41% (n=49) and 36% (n=52) for control women respectively.

In Study 3 the figures for both childless patients and controls, as ascertained at first admission, were considerably higher [for male patients 85.4% (n=41), male controls 85.4% (n=41), for female patients 66.1% (n=39), female controls 52.5% (n=31)]. These figures can be explained by the age-related shorter exposure period.

**How to Explain these Findings?**

Looking for factors that might explain the decrease in the fertility of patients with schizophrenia it is worth starting by taking a look at long-term fertility trends in the general population. Corresponding to the pronounced fall in the overall number of births in the population from 1965 to 1980 there is an almost parallel trend of decline in births for patients with schizophrenia starting in that same period of risk (1965-67). A key factor is presumably an easier access to contraceptives. It is likely to have influenced the reproductive behaviour of people with schizophrenia, too.

Another factor is the decline in marriage. Reproductive probability is considerably higher for the married than singles both among patients with schizophrenia and in the general population. The proportion of married individuals in the West-German population decreased considerably more than in our control samples: by 43% between 1950 and 2011 and by 57.4% in Germany as a whole over the same period (data from the Federal Statistical Office).

Several epidemiological studies have reported lower rates of marriage for patients with schizophrenia – both male and female [15, 18, 19]. Our data, too, confirmed this finding, revealing lower rates for male than female patients and even showing a further marked decline, which, too, was more pronounced for male patients (Table 3).

| Percentages of patients and controls ever married (temporal effects) | | | | | | |
|---|---|---|---|---|---|---|
| | Study 1 1949-50 | | Study 2 1965-67 | | Study 3 1987-89 | |
| | 1st admission | Follow-up 1962-63 | 1st admission | Follow-up 1978-80 | 1st admission | Follow-up 1999-2002 |
| MEN | *Patients/Controls N=62 respectively* | | *Patients/Controls N=82 resp.* | | *Patients/Controls N=48 resp.* | |
| Patients | 38.7% (n=24) | 66.1% (n=41) | 29.3% (n=24) | 39.0% (n=32) | 16.7% (n=8) | 27.1% (n=13) |
| Controls | No data | 93.5% (n=58) | No data | 82.9% (n=68) | 22.9% (n=11) | 66.7% (n=32) |
| WOMEN | *Patients/Controls N=121 resp.* | | *Patients/Controls N=146 resp.* | | *Patients/Controls N=59 resp.* | |
| Patients | 62.8% (n=76) | 65.3% (n=79) | 61.0% (n=89) | 68.5% (n=100) | 44.1% (n=26) | 67.8% (n=40) |
| Controls | No data | 81.8% (n=99) | No data | 81.5% (n=119) | 53.4% (n=31) | 88.1% (n=52) |

**P< 0.01; * P< 0.0

**Table 3.** Proportions of patients and controls ever married in the three studies (temporal effects) (based on data from [30, 39] for Study 1 and 2, from [37] for Study 3)

It is remarkable that decreasing fertility over time was clearly more pronounced for people with schizophrenia than for the general population. This contradicts the hypothesis that outpatient treatment with the benefit of freer life in the community might have favourably influenced patients' fertility. We tested this hypothesis on an individual basis in Studies 1 and 2. We counted the number and overall length of inpatient treatments as an indicator of the social isolation experienced at mental hospital versus better opportunities for finding a partner in the community. Length of hospital stays actually fell slightly over this period, which covered the preparatory stage and early days of mental-health care reform in Germany (1949-1963 and 1965-1980) (cf. Table 1). But patients' fertility did not increase in this period (cf. Table 2).

**Fertility at Different Stages of Illness (Study 3)**

This raises the question whether it is the disorder or its precursors, such as personality factors, that reduce patients' chances of marriage. We explored when fertility becomes reduced over the illness course. In Study 3 we retrospectively assessed illness onset, defined by the first-ever onset and subsequent accumulation of symptoms, using the IRAOS [42]. This approach allowed us to analyse fertility separately in the premorbid period and at the prodromal stage. At follow-up, about 12 years after first admission, the course of full-blown illness was assessed.

Before first admission - i.e. in the premorbid and prodromal period - the patients showed no deficits in total fertility (mean number of children per person), compared to their controls, yet. An indicator slightly more sensitive than the number of children (total fertility) for measuring fertility in the early illness course is the parenthood rate (at least one child) (Figure 4).

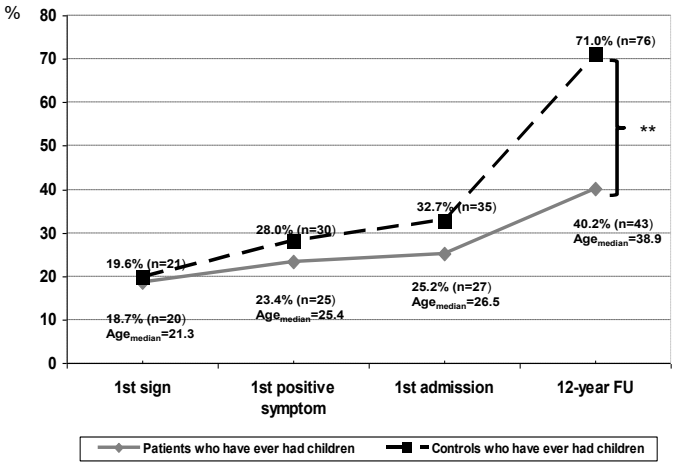


**Figure 4.** Percentage of patients and controls (Study 3) with at least one child ever (N=107) at four stages of illness (Source: [37]).

Obviously, there was no difference in the fertility of patients with schizophrenia and their controls before illness onset.

Hence, it is not premorbidly that fertility becomes reduced.

At the prodromal stage (mean 6, median 2.8 years) the fertility rates of patients and controls diverged only slightly. In the long term, however, the difference grew significant: 40.2% of the patients ever had a child compared with 71% of the controls.

The first thing that comes to mind by way of an explanation for the considerably lower fertility of male than female patients is a difference in their rates of marriage. In Study 3 we explored how the percentage of married patients changed over the four stages of illness between the premorbid period and the final follow-up. Clear-cut sex differences emerged. Before first admission only slightly fewer male patients than controls were ever married (6.3% before first sign of illness, 16.7% at the prodromal stage before first admission, compared with 10.4% and 22.9% of the controls respectively). After a history of 12 to 13 years of full-blown illness the rate for married male patients was a mere 27.1% and, thus, significantly lower than the rate for married male controls (66.7%).

From the very start, in the premorbid period, a larger proportion of female than male patients were married, reaching 44.1 % after the prodromal stage at first admission. At the final follow-up 67.8% of women with schizophrenia, compared with 88.1% of control women, were married [37], a difference of 20.3%.

As mentioned, one reason for the considerable sex difference persisting over the illness course lies in the reproductive period before illness onset. It is several years longer for women than men because of women's higher age at illness onset and men's higher mean age of marrying - by almost two years - in the general population. In full-blown illness (after first admission) the larger increase in the proportion of female than male patients ever married probably stems from the fact that women's severity of illness is milder before menopause [43]. Another factor is that unlike men women retain their attractiveness for relationships even after illness onset [44].

Patients' elevated rate of divorce at final follow-up is probably caused by the illness: the figure for women with schizophrenia was 18.6% as against 13.6% for controls, for men 38.5% as against 12.5% for controls.

**Reproductive Wish and Schizophrenia**

The reduced rate of marriage has a merely quantitative share in explaining the patients' lower fertility. It is an open question whether fertility is also influenced by illness-related biological factors or psychological consequences of the disorder. Lacking a promising access to biological factors, we examined patients' reproductive motives [37].

In Study 3 56.8% of the patients and 70.4% of the controls stated at first admission that they wished to have at least one or more children. At follow-up still 50.6% of the patients, compared with 74.1% of the controls, did so. 25.9% of the patients and 11.1% of the controls stated never to have had that wish. As mentioned, the proportion of patients who had wished to have children was considerably smaller compared with controls at first admission, and after a history of more than 12 years of illness their proportion had grown even smaller, while there was no such change over time in the controls' reproductive wishes [37].

In sum, a majority of the patients had wished to have children at illness onset, but only a certain proportion of them had been able to make this wish come true. When asked why this had been the case, the reaons most frequently stated at first admission were financial constraints and problems of partnership (30%). In contrast, 40% of the controls stated reasons related to work. At follow-up the patients mostly referred to health reasons (42%) and reasons pertaining to partnership (26%). Only minor sex differences were observed. The main reason given by the controls 12 years after their initial interview had to do with partnership (29%), followed by work-related problems (18%).

The decrease in the number of patients wishing to have children, the reduced number of children born after illness onset and the marked increase in the proportion of patients having given up their reproductive wishes for "health reasons" indicate that it is the way patients experience the disorder and its consequences that causes growing concerns, thus reducing their fertility. Another factor, the more pronounced decline in marriage rates and marital births among patients than controls, is probably also attributable to how the disorder and its consequences are experienced, in part perhaps also to the social stigma attached to schizophrenia [45, 46].

Considering the fact that patients' fertility before illness onset does not differ from healthy individuals' fertility, considering further the fact that fertility gradually becomes reduced in the course of the disorder and the fact that fertility in schizophrenia seems to be associated with how the full-blown disorder and its consequences are experienced by the patients it seems unlikely indeed that latent biological factors underlying the risk of developing the disorder account for the reduced reproductive outcome.

It seems reasonable to assume that the reduced fertility of patients with schizophrenia, especially since that phenomenon is observable after illness onset, could also be caused by sexual dysfunction, a frequent side-effect of therapeutically efficacious dosages of antipsychotic medications. In our Study 1 the period covered fell in the pre-neuroleptic era, so it can be ruled out with certainty that the reduced fertility observed resulted exclusively from a direct effect of antipsychotic drugs. In the subsequent Study 2, conducted in the early days when the use of antipsychotic medications was spreading, knowledge on

this question was still scarce, and we decided not to include the intake of medications in the information gathered. It was finally in the prospective Study 3 that we collected data on patients' intake of medications, including type, dosage, duration and combination with other substances, and on their doctors' prescriptions. However, the data we obtained were extremely heterogeneous and the picture that emerged was utterly confusing: the plethora of medications and dosages prescribed did not tally with the wealth of substances patients reported to have taken, and the same was true of the information obtained on dosage and duration of intake. This considerable variation in the data was not promising of yielding any replicable results, particularly since their reliability was not ascertained by blood-level monitoring. Comparisons with drug-free patients did not yield any significant differences either.

In sum, the results of our study do not permit a conclusive answer to the question of whether there is a direct effect of sexual dysfunction caused by antipsychotic medications contributing to reduced fertility in schizophrenia. What can at best be concluded reliably is that that effect is definitely not the only factor accounting for the reduced fertility, but in conjunction with other factors might exert a modest effect.

## Conclusion

Like numerous sound international long-term studies before, the present study with its results from three waves covering a total period of around 50 years strongly suggests that the fertility of persons diagnosed with schizophrenia is significantly reduced compared with that of age- and sex-matched controls drawn from the population of the same area. Over time, this difference tends to grow larger. Patients' lower fertility is probably in part explained by their declined marriage rates compared with the general population. Male patients' markedly lower rate of marriage also considerably contributes to their lower reproductive rate. The hypothesized convergence in the fertility rates after the abolishment of the hospital-centred care of patients with schizophrenia has not happened. A look at the fertility rates over the different stages of illness shows that patients' fertility does not differ from that of their healthy peers in the period before the onset of first symptoms. Differences start to appear at the prodromal stage, grow increasingly pronounced at the subsequent stages and reach a maximum in full-blown illness. The assumption that fertility in schizophrenia might become reduced due to sexual dysfunction patients suffer as a side-effect of antipsychotic medications could not be confirmed. But it can be ruled out with certainty that the reduction is attributable to direct drug effects alone. Testing the alternative hypotheses that the association between illness and reduced fertility is accounted for by (a) a direct biological effect or (b) a psychological effect of the disorder and its consequences for the patients' lives confirmed the latter. It is the experience of the disorder and the deficits involved that reduce patients' reproductive motivation.

### Declaration of Conflict of Interest

The authors declare that they have no conflict of interest.

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