Excess Seasonality of Births Among Patients With Schizophrenia and Seasonal Ovopathy

by Esther G.M. Pallast, Piet H. Jongbloet, Huub M. Straatman, and Gerhard A. Zielhuis

Abstract

In this study we examined whether the well-known winter excess of schizophrenic births exists among Dutch schizophrenia patients when statistical artifacts such as the age-incidence and age-prevalence effects are avoided and, if so, whether the seasonal preovulatory release of overripe ovum (SPrOO) hypothesis, that is, seasonally bound ovopathy, might be an explanation for this excess. We analyzed the month-of-birth distribution of 1,037 Dutch schizophrenia patients born between 1962 and 1966 and first admitted to a psychiatric hospital between 1978 and 1990 by the so-called window analysis to avoid the artifacts mentioned. The results show a winter excess of births among Dutch schizophrenia patients, even when statistical artifacts are avoided, and that the SPrOO hypothesis might be an explanation for this excess. Further research is needed to support the hypothesis that ovopathy, either seasonally bound or not, could be involved in the etiology of schizophrenia.


Since 1929, studies have investigated the seasonality of schizophrenic births (Tramer 1929). Two reviews of about 40 studies in 14 countries have been published on this topic (Bradbury and Miller 1985; Boyd et al. 1986). The majority of these studies, which were conducted in the northern hemisphere and were free from major methodologic problems, revealed that an established excess (10%–15%) of schizophrenia individuals were born in the first quarter of the year. Some other studies also showed a significant excess in December, April, and May. Bradbury and Miller reviewed six studies performed in the southern hemisphere. However, the only one of this group that avoided major methodologic shortcomings revealed a significant winter and spring excess (May through October) of schizophrenic births for females only (Dalén 1975). Although many explanations have been proposed—viral infections, radiation, obstetric or perinatal complications, malnutrition, vitamin deficiency, temperature, seasonal variation of intercourse frequency of the parents of schizophrenia patients, selective survival of winter-born babies prone to schizophrenia (see Bradbury and Miller 1985)—the reason for the seasonality of births among individuals with schizophrenia is still unknown.

In 1981, Lewis and Griffin questioned whether the season-of-birth finding might be due to statistical artifacts, that is, the age-incidence effect (first described by Hare et al. 1974 and Dalén 1975) and the age-prevalence effect (first described by Lewis and Griffin 1981). The age-incidence effect stems from the fact that the incidence of new cases of schizophrenia increases from ages 15 to about 34. Therefore, individuals within that age range born in the first months of a given calendar year will be a few months older than those born in the last months of that same year.
year. As a result, those born in the first months of a given year will have a slightly higher risk of developing schizophrenia. The age-prevalence effect proceeds from the fact that the cumulative risk of schizophrenia increases with age. Therefore, again, those born in the first months of a given calendar year will display higher incidence rates per admission year than those born in the last months of that year simply because the former have had more exposure to the risk of acquiring schizophrenia. Both effects are based on the explicit use of calendar years in season-of-birth studies.

The objectives of the present study are twofold. The first is to examine whether there is also a seasonality of birth among schizophrenia patients born in The Netherlands and, if so, to examine whether this seasonality is still present when statistical artifacts are avoided. The second objective is to examine whether the release of a seasonal preovulatory overripe ovum (SPrOO) can explain this seasonality.

The SPrOO hypothesis was first put forward by Jongbloet (1975) and is based on three assumptions. (1) There is a seasonal variation in ovulation rates because some women ovulate seasonally, not every month. (This is thought to be the result of the seasonal changes in photoperiodicity, which affects the plasma level of melatonin, a hormone with antagonodotropic and thus ovulation-inhibiting activity in humans.) Seasons characterized by high ovulation rates are called ovulatory seasons, while seasons characterized by low ovulation rates are called anovulatory seasons. (2) Hormonal imbalance at the transitional stages of these seasons leads to delayed ovulation and thus to SPrOO. (3) The fertilization of such an over-ripe ovum can have teratogenic consequences such as chromosomal and developmental anomalies. Some observational studies in humans that give circumstantial evidence for the first two assumptions were reviewed by Jongbloet (1990). Several empirical studies in animals provide evidence for the last assumption (Mikamo 1968; Witschi 1970; Butcher 1981).

The SPrOO hypothesis as stated above might explain a seasonality in pathologic (schizophrenic) births; also, the first assumption of this hypothesis provides an explanation for the known seasonality in all births.

**Method**

**Subjects.** The study population consisted of a sample of individuals who were reported to a national register called the Patiëntenregister Intramuraale Geestelijke Gezondheidszorg (PIGG). This register was started in 1978 and contains information on all patients residing in a psychiatric hospital at that time and on all patients admitted since that year. From this register a study population was selected of 1,607 individuals who met the following criteria:

2. Included in the PIGG register for the first time with a diagnosis of schizophrenia according to the International Classification of Diseases (ICD–9; World Health Organization 1978) (ICD-code 295) between 1/1/78 and 12/31/90.
3. If discharged, discharge diagnosis was schizophrenia \( (n = 1,435) \).

Patients born after 1/1/62 were under age 16 in 1978 and the risk of schizophrenia at this age is very small. Thus, it is likely that the first inclusion of these patients in the PIGG register was also their first admission to a psychiatric hospital. Therefore, criterion 1 ensured that only incident cases were part of the study population. Criterion 2 was set because the register was completed up to and including 12/31/90. Criterion 3 was required to increase the probability that the study population consisted exclusively of schizophrenia subjects. Criterion 4 was set because expected values were based on all live births in The Netherlands.

Because most schizophrenia patients (93%) in the PIGG register had been admitted to a general psychiatric hospital and because almost all (95%–100%) general psychiatric hospitals in The Netherlands took part in this registration from the start, it can be assumed that the registration of admitted schizophrenia patients is nearly complete.

**Data Analysis.** We performed three different analyses to compare the observed month-of-birth distribution of the study population with the expected month-of-birth distribution. The first was a crude analysis \( (n = 1,607) \) without correction for the age-incidence and age-prevalence effect. The second was a correction analysis \( (n = 1,607) \), which corrected for the difference in person-months at risk (age-prevalence) by applying the correction test proposed by Lewis and Griffin (1981). The third analysis \( (n = 1,037) \), which avoids both the age-incidence and age-prevalence effect, was called the window analysis. For every month of birth
cohort between 1962 and 1966, it was calculated how many patients were included in the PIGG register with the diagnosis of schizophrenia between ages 16 and 24. (One might consider this age range a time window.) For example, we calculated how many of the people born in January 1962 became ill with schizophrenia (and were reported to the PIGG register) between January 1978 (age 16) and January 1986 (age 24). For individuals born in December 1966, we calculated how many became ill between December 1982 (age 16) and December 1990 (age 24). By restricting the study population to a specific age range, the effects of age incidence and age prevalence are avoided. Another result of this restriction in the study population is that this window analysis consists of only 1,037 patients of the original study population (ages 12–28) used in the crude and correction analyses.

The expected month-of-birth distribution was based on all live births in The Netherlands in the same period (1962–66) and was calculated in such a way as to control for the effects of year-to-year variations in the monthly pattern of all live births (see Lewis and Griffin 1981).

The chi-square test with 11 degrees of freedom (df) was used to test for a birth seasonality of schizophrenia patients. The chi-square (1 df) was used to test whether individuals that have schizophrenia are born more often in the SPrOO risk months than in the SPrOO nonrisk months. Because the SPrOO hypothesis predicts that pathologic conceptions will occur at the transitional stages of the anovulatory to ovulatory seasons and vice versa, the pathologic births would be expected at the transitional stages of seasons with a low birth rate to seasons with a high birth rate and vice versa, that is, at the slopes of the total birth curve. The dotted line in figure 1 represents the total birth curve in the period 1962–66. (The total number of live births per month are divided by the number of births expected, i.e., equal numbers of births in every month taking into consideration the small difference in length of months, to obtain monthly observed-to-expected rates that can be compared directly with the rates computed for the schizophrenic births.) This bimodal birth curve, consisting of a major peak in spring and a small peak in September, is typical for countries in northwestern Europe and might, at least in part (i.e., the major spring peak), be explained by the first assumption of the SPrOO hypothesis.

On the basis of this curve, SPrOO risk months are January, February, the first half of March, the second half of May, and the month of June—the “slope” months. SPrOO nonrisk months

![Figure 1. Monthly distribution of schizophrenic birth rates and all live birth rates in the period 1962-66, corrected for length of month](image)
are the second half of March, the month of April, the first half of May, and the months of July, November, and December—the “top and valley” months. It is not clear whether the small excess of births in September could also be due to a high rate of ovulation 9 months before and consequently whether more pathologic births could be expected at the slopes around the September peak. Therefore, we left August, September, and October out of the analyses.

**Results**

Tables 1, 2, and 3 show the observed and expected month-of-birth distribution of schizophrenic births as well as the rate of the observed and expected values for the three methods described above, respectively. The chi-square test (11 df) is not significant at the 0.05 level in tables 1 and 2 and barely misses significance in table 3. Without correction for the age-incidence and age-prevalence effect.

**Table 1. Observed (O) and expected (E) number of schizophrenic births per month, crude analysis (n = 1,607)**

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<td>Observed</td>
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<td>Rate of O/E</td>
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<td>1.13</td>
<td>1.08</td>
<td>0.93</td>
<td>1.01</td>
<td>1.07</td>
<td>0.94</td>
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<td>0.91</td>
<td>0.77</td>
<td>0.95</td>
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Note.—Seasonality of schizophrenic births: \( \chi^2(11) = 16.35, p = 0.13 \). Observed/Expected schizophrenic births: Jan–Mar.: \( \chi^2(1) = 4.13, p = 0.04 \); Dec.–Mar.: \( \chi^2(1) = 8.33, p = 0.004 \).

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Note.—Seasonality of schizophrenic births: \( \chi^2(11) = 16.35, p = 0.13 \). Observed/Expected schizophrenic births: Jan–Mar.: \( \chi^2(1) = 4.13, p = 0.04 \); Dec.–Mar.: \( \chi^2(1) = 8.33, p = 0.004 \).

**Table 2. Observed (O) and expected (E) number of schizophrenic births per month, correction analysis (n = 1,607)**

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<td>1.03</td>
<td>0.95</td>
<td>0.82</td>
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Note.—Seasonality of schizophrenic births: \( \chi^2(11) = 15.32, p = 0.17 \). Observed/Expected schizophrenic births: Jan–Mar.: \( \chi^2(1) = 0.23, p = 0.63 \); Dec.–Mar.: \( \chi^2(1) = 4.05, p = 0.04 \).

1 Lewis correction test for the age-prevalence effect.

**Table 3. Observed (O) and expected (E) number of schizophrenic births per month, window analysis (n = 1,037)**

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<td>1.00</td>
<td>0.99</td>
<td>0.79</td>
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Note.—Seasonality of schizophrenic births: \( \chi^2(11) = 18.44, p = 0.07 \). Observed/Expected schizophrenic births: Jan–Mar.: \( \chi^2(1) = 2.04, p = 0.15 \); Dec.–Mar.: \( \chi^2(1) = 8.11, p = 0.004 \).

1 Correction for the age-incidence and the age-prevalence effect.
effects (table 1, n = 1,607), the observed number of individuals with schizophrenia born in the winter is, respectively, 8.8 percent (winter: January–March) and 10.3 percent (winter: December–March) more than expected. This excess is statistically significant in both cases (p = 0.04 and p = 0.004, respectively). After correction for the difference in person-months at risk (correction test of Lewis, table 2, n = 1,607), the excess of schizophrenic births in the first quarter of the year disappears (p = 0.63) as predicted by Lewis and Griffin (1981). The birth rate in the December–March period is still significantly higher than in the rest of the year because of the high birth rate in December (p = 0.04). When the effects of age incidence and age prevalence are eliminated by the window analysis (table 3, n = 1,037), the excess of individuals with schizophrenia born in the first quarter of the year diminishes only slightly and becomes statistically insignificant (p = 0.15). The excess in the December–March period again remains highly significant (p = 0.004).

The results of the window analysis are also presented in figure 1. As expected, the birth rate of schizophrenia subjects is high in January and February (slope months) and low around April (top month). However, the high schizophrenic birth rates in July and December are not in line with the SPrOO hypothesis. Testing whether significantly more schizophrenic patients are born in the SPrOO risk months than in the SPrOO nonrisk months resulted in a chi-square value of 2.8 (df = 1, n = 795, p = 0.09). For individuals born in the SPrOO risk months, the risk ratio for schizophrenia is 1.12 (95% confidence interval = 0.97–1.29) compared to the SPrOO nonrisk months.

Discussion

In accordance with other investigators (Watson et al. 1982; Pulver et al. 1983; Shur and Hare 1983) we have shown with Dutch data that the significant winter-birth excess of schizophrenia patients remains intact even when the distorting effects of age incidence and age prevalence are avoided and after correction for year-to-year variations in the monthly pattern of all live births. The rate of observed-to-expected schizophrenic births is especially high in December. This December excess has also been reported by other researchers (Templer et al. 1978; Watson et al. 1982, 1984), and it contradicts the explanation of an artifact as suggested by Lewis and Griffin (1981). (The latter explanation predicts an excess of schizophrenic births in the first quarter of the year and a deficit in the last quarter of the year.)

Another argument against Lewis and Griffins’ explanation is the similarity of the results from the crude analysis and those from the cohort analysis, that is, when there is no distortion due to the age-incidence or age-prevalence effect. Theoretically the age-incidence and age-prevalence effects are strongest in a population of young schizophrenia patients. However, our study population consisted of young schizophrenia subjects (12–28 years in the crude and correction analysis, 16–24 in the window analysis), and these effects were small. In addition, assuming that the window analysis is a gold standard, we conclude that the method of Lewis and Griffin, which corrects only for the age-prevalence effect, leads to overcorrection. This correction method is based on the assumption that the risk of developing schizophrenia in a given year is proportional to the number of months in which a person is at risk. Apparently this assumption is incorrect.

Our finding of a modest excess of schizophrenic births in July was also remarkable. A review of the literature showed that no one else has reported a summer excess except Shur and Hare (1983), who found a clear June excess among 11,728 schizophrenia subjects born between 1921 and 1955 in England and Wales and first admitted to a hospital between 1970 and 1974. Shur and Hare attributed this anomaly to random variation. At this moment we do not have a better explanation.

Our hypothesis—that more schizophrenia individuals than expected are born in SPrOO risk months—still holds true, although our data were not statistically significant. There are several explanations for the lack of any genuine SPrOO effect in birth rates in real data. First, it should be noted that the recent birth distribution results from both nature (seasonally ovulating women) and, especially in modern societies, from nurture (e.g., family planning). However, our study population was born in the sixties, and it can be assumed that modern contraceptives for family planning did not yet play an important role. Second, this “distortion” of the natural birth curve by nurture makes it difficult to define the exact SPrOO risk months because, for example, it is not clear whether the small birth peak in September can be considered the result of seasonally ovulating women, like the major
spring birth peak. To avoid this problem we have ignored the minor September birth peak and the adjacent slope months of August and October (the shaded area in figure 1). Third, it is assumed that only a still unknown fraction of all women are seasonal ovulators (Jongbloet 1990), and only a proportion of these women conceive at the transitional stage of the anovulatory to ovulatory season or vice versa. Fourth, some authors assume that the gestational age at birth of schizophrenia patients is low (Müller and Kleider 1990). Therefore, the birth dates of these patients do not reflect the conception dates by subtracting 9 months. This fact might also explain the high excess of schizophrenic births in December, which is certainly not a SPrOO risk month: Because of preterm birth, people conceived in April, a month between the nonovulatory and ovulatory season and thus at high risk of schizophrenia according to the SPrOO hypothesis, would not be born in the SPrOO risk month of January but in December. All of these methodologic flaws of the study will lead to dilution of SPrOO effects. We nevertheless found a risk ratio for schizophrenia of 1.12 \((p = 0.09)\) for people born in the SPrOO risk months compared to people born in the SPrOO nonrisk months. It can therefore be concluded that the SPrOO hypothesis might form an explanation for the seasonality of birth, at least in young schizophrenic subjects.

Although the SPrOO hypothesis cannot explain the difference in birth distribution in the United States (major birth peak in September) and that in most of northwestern Europe (major birth peak in the spring), this hypothesis can explain some of the other epidemiologic findings about schizophrenia. For example, the often-mentioned connection between obstetric complications and schizophrenia (McNeil and Kaij 1978; Jacobsen and Kinney 1980; Machón et al. 1987) could have ovopathy as a common cause. The higher risk of schizophrenia with advanced maternal age (Dalén 1977) might also be explained by ovopathy because women have hormonal imbalances at the end of their reproductive life. Pulver et al. (1992a) found that the relatives of schizophrenia patients born during the winter and spring were more likely to have schizophrenia than the relatives of schizophrenia patients not born in the winter. In our view, schizophrenia individuals born in the winter and spring are children born to seasonally ovulating women. These women, however, are not only more likely to suffer hormonal imbalance at the transitional stages of the seasons but are also generally more susceptible to ovopathy. The greater spacing between the births of the mothers of schizophrenia patients born during the winter and spring months than of the mothers of unaffected controls born in the winter and spring months reported by Pulver et al. (1992b) can also be understood if it is assumed that the former mothers are seasonal ovulators and thus women who have more difficulty becoming pregnant. Finally, support for the SPrOO hypothesis is also found in birth excesses on the slopes of the total birth curve for other conditions, such as diabetes mellitus (Jongbloet et al. 1988) and Down’s syndrome, type maternal meiosis I (Jongbloet and Vrieze 1985).

Further research is needed to support the theory that ovopathy is involved in the etiology of a subgroup of schizophrenia. At the transitional stages of the anovulatory to ovulatory seasons and vice versa, delayed ovulation due to hormonal imbalance can also be expected to occur more frequently during any transitional stage of reproductive life, that is, just after the menarche and parturition, just before the menopause, and probably also in women with an irregular menstrual cycle (Jongbloet 1986).

More epidemiologic studies investigating whether more schizophrenic patients are conceived in such high-risk situations than in a reference population could further test the credibility of this hypothesis.

References


Acknowledgments

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