

Seasonality of Birth in Schizophrenia in Taiwan

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Abstract

The phenomenon of seasonality of birth in schizophrenia is important to the study of the etiology of this mental disorder because it helps give directions for further research. Patients' hospital files from 1981 to 1991 at two of the largest hospitals with psychiatric wards in Taiwan were reviewed, and dates of birth were collected on 3,346 patients diagnosed with schizophrenia. After adjusting for the variations of the total monthly births in the population, an Auto-Regressive Integrated Moving Average model was applied. Results support a seasonality phenomenon and indicate a disproportional excess of births in schizophrenia in the cold months (November to February) compared with the hot months (May to August). These findings are compatible with many other studies in other countries and climates. Further investigations of season-related environmental factors in the etiology of schizophrenia are recommended.

Schizophrenia Bulletin, 21(1):
117-127, 1995.

The seasonality of birth in schizophrenia can be defined as "a tendency for individuals later diagnosed with schizophrenia to be born during certain months or seasons of the year in numbers disproportionate to those from the population at large" (Bradbury and Miller 1985, p. 569). The seasonality of birth in schizophrenia is very important in the etiology of this mental disorder because it helps give directions for further research.

Although the Chinese people

make up approximately a quarter of the world's population, there are only a few studies in Asia and none used appropriate statistical controls; therefore, this study investigated this phenomenon in Taiwan. It was facilitated by the fact that hospitals in Taiwan incorporate the *Diagnostic and Statistical Manual of Mental Disorders* system into the *International Classification of Diseases* system for diagnosis (Lu et al. 1985), as do most Western countries. Because the lifetime prevalence of schizophrenia in metropolitan Taipei in Taiwan was thus found to be 0.3 percent (Hwu et al. 1989), which is comparable to that of other countries, this study also offers an important cross-cultural comparison with previous studies.

Background

Previous Studies. The phenomenon of the seasonality of birth in schizophrenia was noticed by scientists more than 60 years ago. In 1929, a study done by Tramer (1929/1930) in Switzerland found that more persons with schizophrenia were born in winter than in summer. Since then, many studies on this phenomenon have been conducted in different countries or areas of the world. In 1985, Bradbury and Miller reviewed the results of 43 studies, and many more studies followed after that (e.g., Machón et al. 1983; Hsieh et al. 1986; Lo 1986; Kendell and Kemp 1987; Baron and Gruen 1988; Degreef et al. 1988; Newman and Bland 1988; Fananas et al.

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1989; Woodard and Feldman 1990; Kendell and Adams 1991; O'Callaghan et al. 1991). Their results can be generally summarized as follows:

1. There is evidence of a disproportional excess of schizophrenia births in the winter months in the Northern Hemisphere. However, most of the studies do not show any seasonality in schizophrenia births in the Southern Hemisphere (Dalén 1975; Jablensky 1989; also see Bradbury and Miller 1985).

2. There is evidence of a disproportional excess of schizophrenia births in the winter months for the low genetic risk group—that is, for persons born into families without a history of schizophrenia (O'Callaghan et al. 1991; also see Bradbury and Miller 1985).

3. Several other variables have been investigated in relation to the seasonality of birth, with mixed results. These variables include race, sex, birth order, birth year, birth-place, parents' ages at patient's birth, number of siblings, marital status, place of residence, socioeconomic status (SES), age at onset, length of hospitalization, and subtypes of schizophrenia. With many of these variables, there are conflicting results in different studies. Probably too few studies include these variables to be assured of reliable conclusions (Barry and Barry 1964; Parker and Neilson 1976; Machón et al. 1983; Pulver et al. 1983; Nasrallah and McCalley-Whitters 1984; Bradbury and Miller 1985, 1986; Hsieh et al. 1986; Kendell and Kemp 1987; Baron and Gruen 1988; Malama et al. 1988; Fananas et al. 1989).

4. Most of the studies are carried out with European or North American samples. There are only a few studies in Asia: two in

Japan, one in the Philippines, and one in Hong Kong (Lo 1986; also see Bradbury and Miller 1985).

Although the phenomenon of excess schizophrenia births in the winter months is far from conclusively established, some explanations have been offered to account for it. One explanation is infectious agents. Some studies indicate that the seasonality of birth in schizophrenia correlates with the seasonal epidemics of certain infectious diseases such as diphtheria, rubella, pneumonia, influenza, measles, varicella-zoster, and poliomyelitis. Thus, it is inferred that schizophrenia might be related to infections of the above diseases or of some unknown antigen, either prenatally or neonatally (Torrey et al. 1977; Watson et al. 1984; Bradbury and Miller 1985; Hare 1986; Baron and Gruen 1988; Kendell and Adams 1991; O'Callaghan et al. 1991). Another potential explanation is perinatal brain damage. As seasonal distributions of stillbirths or premature deliveries are found in some studies, it is inferred that infants born in certain months of the year might be more likely to incur brain damage (Hare 1986; Degreef et al. 1988; Muller and Kleider 1990; also see Bradbury and Miller 1985; Boyd et al. 1986). Nutritional deficiencies have also been proposed as mediational variables. Infants born in winter might have nutritional deficiencies (e.g., in protein, calcium, or vitamins C, D, or K) that lead to the eventual onset of schizophrenia (Bradbury and Miller 1985). Finally, it has been proposed that some genetic factors might lead to increased vulnerability to environmental factors such as infections, perinatal brain damage, or nutritional deficiencies, as discussed

above (Bradbury and Miller 1985; Baron and Gruen 1988).

Methodological Problems. In studies on the seasonality of birth in schizophrenia, some methodological problems arise:

1. Control groups: Some studies either do not have control groups (e.g., Lo 1986; Woodard and Feldman 1990) or use control subjects whose birth years only partly overlap with those of the schizophrenia patients being studied (Norris and Chowning 1962; Bradbury and Miller 1985, 1986). For example, Parker and Neilson (1976) studied the seasonality of birth of schizophrenia subjects born between 1905 and 1959, but they used the number of births in the general population from 1962 to 1971 as the control variable. Therefore, the results of these studies are suspect. Since birth rates generally vary with time, the total number of births in the same months and years as the schizophrenia births should be used as control variables in the analyses.

2. Hospital data: Many studies rely on hospital chart diagnoses and patients' demographic information from record files ("hospital data"). Relying solely on these data might provide some reliability or validity problems (Hare 1975, 1986; Torrey et al. 1977; Kendell and Kemp 1987; Baron and Gruen 1988; Kendell and Adams 1991; O'Callaghan et al. 1991). Nevertheless, hospital data provide conveniently large numbers of cases for statistical analysis (Hare 1986) and are being used abundantly in many areas of research.

3. Statistical analysis: Although many studies use the chi-square test to analyze seasonality data, this method cannot detect cyclic

trends efficiently (Edwards 1961; Shensky and Shur 1982; Bradbury and Miller 1985). To detect the seasonality reflected by the data accurately, time-series strategies seem more appropriate (Makridakis and Wheelwright 1978; Catalano et al. 1983; Pankratz 1983; SPSS, Inc. 1990).

4. Age-incidence and age-prevalence effects: If the risk of onset of schizophrenia is assumed to be related to age, this can lead to two effects that generate artificial excesses of schizophrenia births at the beginning of each year (Lewis and Griffin 1981; Lewis 1989a, 1990). The first statistical confound is known as the "age-incidence effect." People born in January are at least 10 months older than those born in December of the same year. Thus, if the incidence of schizophrenia is considered in a particular year afterward, there will be more individuals diagnosed with schizophrenia born in January than in December of the initial year. This is because the period of time of risk for the former is longer than that of the latter. The second artifact, closely related to the age-incidence effect, can be called the "age-prevalence effect." People born across multiple years also have age-incidence effects when the prevalence of schizophrenia is considered at a later time. Thus, the age-incidence effects become additive in prevalence studies.

Although appropriate mathematical methods or July-to-June reporting periods can eliminate age-incidence and age-prevalence effects, the phenomenon of the seasonality of births in schizophrenia still seems to exist (Watson et al. 1982; Pulver et al. 1983, 1990; Shur and Hare 1983; O'Callaghan et al.

1991). In addition, several studies in the Northern Hemisphere indicate that there are birth excesses in December (Torrey et al. 1977; Bradbury and Miller 1985; Watson 1990). Thus, the age-incidence and age-prevalence effects cannot fully account for the apparent seasonality phenomenon (Shur and Hare 1983; Dalén 1990; Torrey and Bowler 1990; Watson 1990).

The Present Study. The remainder of this article describes a seasonality study conducted in Taiwan. The hypotheses of this study are as follows:

1. There is a seasonality phenomenon in the monthly birth rates of individuals with schizophrenia after the effects of the total number of births per month in the population are taken into account.
2. There is a disproportional excess of individuals with schizophrenia born in the cold months compared with the hot months.

Method

Subjects and Procedure. The computerized hospital data from 1981 to 1991 from the Taipei City Psychiatric Center and the Tri-Service General Hospital (also located in Taipei City) were reviewed, and the sex, date of birth, and diagnosis were collected on patients with schizophrenia. Diagnoses were made via nonstructured patient interviews conducted by staff psychiatrists upon admission and during treatment of patients over the course of the 11 study years. Records from the hospital contained discharge diagnoses only; thus, the data should reflect potential amendments of diagnoses during treatment. Records from the

psychiatric center had both an admittance and a discharge diagnosis for each subject; to encompass diagnostic revisions, only the latter was used for this study. The data set of the psychiatric center contained the dates of diagnosis while that of the hospital contained the dates of admission; therefore, these dates were collected in each hospital.

Table 1 shows the demographic characteristics for the subjects at both study sites. The numbers of schizophrenia subjects born in each month from 1955 to 1966 were tabulated, and the cases were checked carefully to avoid duplication. The ages of the patients ranged from adolescence through early adulthood—the usual onset period of schizophrenia (Department of Health, Taiwan Provincial Government, Republic of China 1981, 1982, 1983, 1984; American Psychiatric Association 1987; Rin 1987; Jablensky 1989; Lewis 1989b; Beiser and Iacono 1990; Folnegovic-Smalc et al. 1990); this is shown in table 2.

By using the age span for each birth year, as shown in the table, the age-incidence effect was eliminated. For example, people born in January 1955 were aged 26 years 0 months in January 1981 and 36 years 0 months in January 1991. If they were diagnosed as having schizophrenia or were admitted to hospitals after January 1991, they were not included in this study. Similarly, people born in December 1955 were aged 26 years 0 months in December 1981 and 36 years 0 months in December 1991. Thus, both groups had the same age span in the study, so there was no age-incidence effect. This was true for every birth year from 1955 to 1966. And because the age-incidence effect was eliminated,

Table 1. Demographic characteristics of subjects

	Hospital	
	Taipei City Psychiatric Center	Tri-Service General Hospital
Sex		
Male	1329	745
Female	1076	196
Marital status ¹		
Single ²	2072	NA
Married ³	309	NA
Diagnostic subtypes		
Paranoid	315	317
Nonparanoid	2090	624

Note.—NA = not available.

¹There are 24 unknown cases for the Taipei City Psychiatric Center.

²Includes divorced or widowed subjects.

³Includes separated subjects.

Table 2. Age span of subjects listed by birth year

Birth year	n	Age span	
		yr-mo	yr-mo
1955	239	26-0	36-0
1956	232	25-0	35-0
1957	264	24-0	34-0
1958	231	23-0	33-0
1959	324	22-0	32-0
1960	270	21-0	31-0
1961	302	20-0	30-0
1962	328	19-0	29-0
1963	326	18-0	28-0
1964	306	17-0	27-0
1965	290	16-0	26-0
1966	234	15-0	25-0

the age-prevalence effect was also minimized.

There were 2,405 and 941 cases from the Taipei City Psychiatric Center and the Tri-Service General Hospital, respectively. Of the 3,346 cases, 2,074 were in males and 1,272 were in females.

The nonredundant number of cases per month from 1955 to 1966

in both hospitals was then added together. The number of persons with schizophrenia born in each month and year was divided by the number of births of the population during those periods (Department of Health, Taiwan Provincial Government, Republic of China 1973) to obtain monthly birth rates for the schizophrenic

population. Thus, a time series of 144 terms (figure 1) was obtained.

Overview of Data Analysis. As mentioned above, many studies have used the chi-square test to analyze seasonality data. However, since the chi-square cannot detect cyclic trends efficiently (Edwards 1961; Shensky and Shur 1982; Bradbury and Miller 1985), time-series strategies have been suggested as more appropriate (Makridakis and Wheelwright 1978; Catalano et al. 1983; Pankratz 1983; SPSS, Inc. 1990). The Auto-Regressive Integrated Moving Average (ARIMA) model of time-series analysis was used to test for a seasonal component in the data. A summary of this model is given below.

In the simplest terms, the purpose of a univariate ARIMA model is to identify a mathematical equation that fits into a set of measurements of an independent variable x , which varies with time t . In its least extensive form, the ARIMA model is analogous to a cross-lag correlation analysis. In a cross-lag correlation design, one variable, A , is hypothesized to bear a temporal causative relation to a second variable, B . A and B are each measured on two different occasions. Thus, two different correlations can be calculated across the time lag, as shown in figure 2.

If the correlation between A at time 1 and B at time 2 is appreciably greater than the correlation between B at time 1 and A at time 2, there is support for the hypothesis that A causes B . This can be determined by partialling the B_1-A_2 correlation from the A_1-B_2 correlation. If the partial correlation is significant, the hypothesis is supported. The ARIMA time

Figure 1. Monthly birth rates of schizophrenia subjects (1955–66)

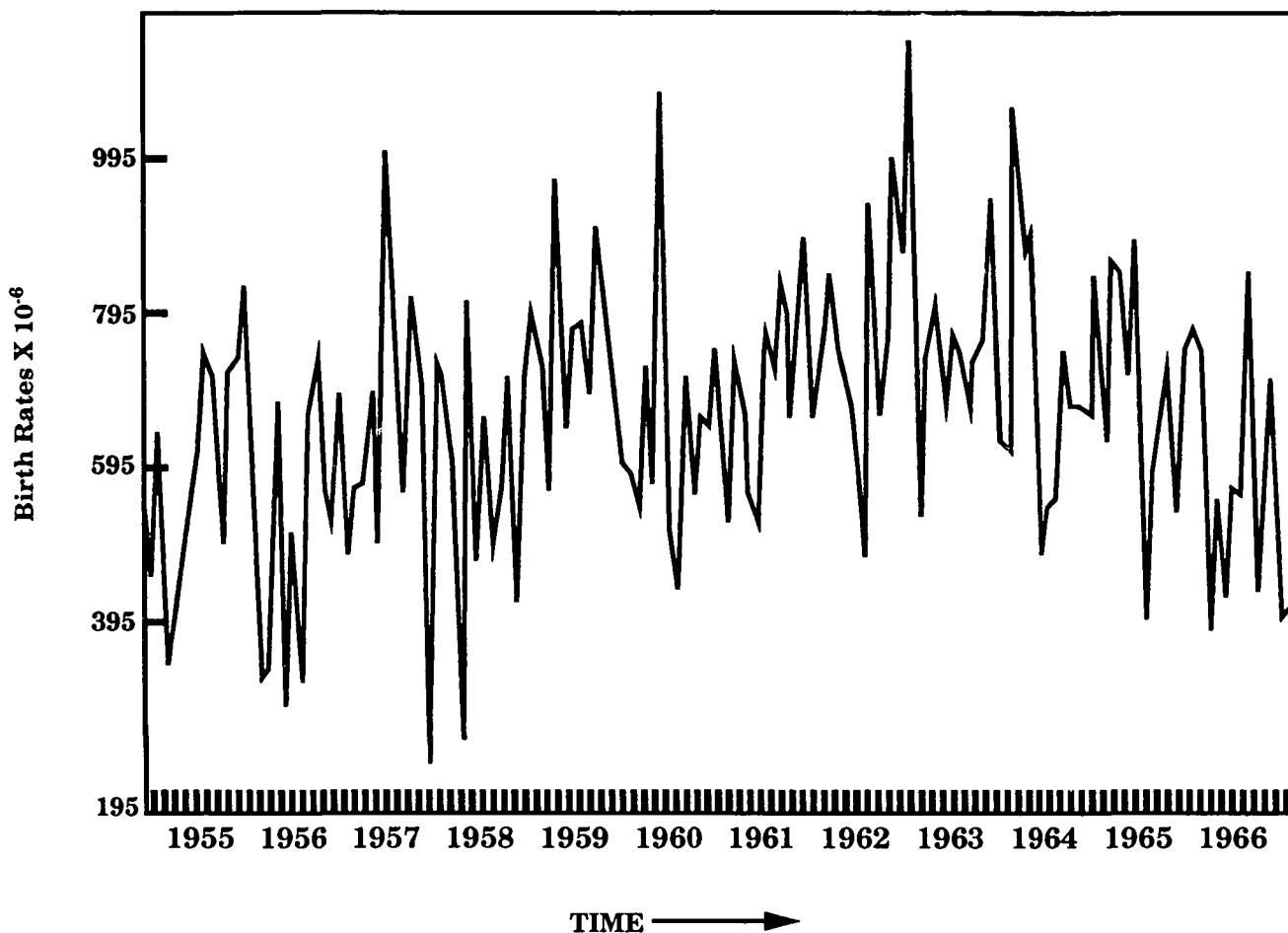
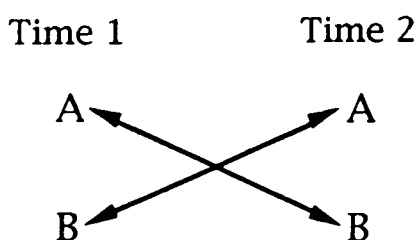


Figure 2. Relevant correlations in a cross-lag correlation design



series analysis essentially incorporates a running series of cross-lag correlations and determines, in this case, the extent to which there is repetitiveness in the birth rates by season. In other words, it can determine whether there is any support for considering the season of birth (or correlates thereof) as a potential causal factor of increased schizophrenia births.

For readers interested in the mechanics of the ARIMA model, the remainder of this section should

provide a useful overview. For readers not so inclined, the results and discussion sections follow.

The ARIMA model applies to a stationary time series only, which means that the series has a mean and variance that are essentially constant through time. If a time series is not stationary, one of the mathematical methods to transform it into a stationary series is called "differencing." For example, a first-order differencing series is given by $x'_t = x_{t+1} - x_t$, a second-

order differencing series is given by $x''_t = x'_{t+1} - x'_t$, and so on. If y_t denotes an element in a stationary time series of order d , the general equation of the ARIMA(p, d, q) model is

$$y_t = c + \phi_1 y_{t-1} + \phi_2 y_{t-2} + \dots + \phi_p y_{t-p} + e_t - \theta_1 e_{t-1} - \dots - \theta_q e_{t-q} \quad (1)$$

where c , ϕ_i , and θ_i are constants, and e_i denotes the random component of the value y_i . If $d \geq 1$, c is equal to zero.

To estimate the values of p and q , the autocorrelation function and partial autocorrelation function are calculated, and their patterns are compared with theoretical standards. The autocorrelation function r_k is given by the following formula:

$$r_k = (\sum_{t=1}^{n-k} (y_t - \bar{y})(y_{t+k} - \bar{y})) / (\sum_{t=1}^n (y_t - \bar{y})^2) \quad (2)$$

where n denotes the total number of terms y_t in the series, and $\bar{y}$ denotes the mean of y_t .

The partial autocorrelation function ϕ_k is given by the following equation:

$$y_{t+k} = b_1 y_{t+k-1} + b_2 y_{t+k-2} + \dots + \phi_k y_t + u_k \quad (3)$$

where b_i and u_k are constants.

Once the values of p and q are estimated, the constants c , ϕ_i , and θ_i in equation 1 can also be estimated. For the ARIMA(p, d, q) model to be valid, the estimated constants must satisfy the conditions of stationarity and invertibility. Moreover, the values of the component e_i must be random (cf. Catalano et al. 1983 for a discussion of the stationarity and invertibility conditions).

Different valid ARIMA models

for a time series can be compared with each other by means of their predictability and goodness of fit.

The above time-series analysis techniques can also be applied to a time series z_t having both seasonal and nonseasonal components. For this case, the mathematical model is $z = \text{ARIMA}(p, d, q)$ model of nonseasonal components multiplied by ARIMA(p', d', q') model of seasonal components, or more simply:

$$z = \text{ARIMA}(p, d, q)(p', d', q')_s \quad (4)$$

where s denotes the cyclical period.

Results

When the time series given in figure 1 was differenced once with a period of 12 months, a fairly stationary series (figure 3) was obtained. The first 120 terms of the series were used to estimate the model, and the last 24 terms were used to check its predictability. The autocorrelation function and partial autocorrelation function are shown in figures 4 and 5, respectively. In these figures, the correlations are plotted against the lag numbers (i.e., the various time intervals used in the analysis). As explained earlier, these correlations are analogous to those from a cross-lag correlation; but in this model, there are multiple observations along a repetitive (yearly) time course. These functions were then compared with a set of standards (Makridakis and Wheelwright 1978; Pankratz 1983) to determine the appropriate statistical model. The best model found to fit this time series was ARIMA(0,0,0)(0,1,1)₁₂. This indicated that

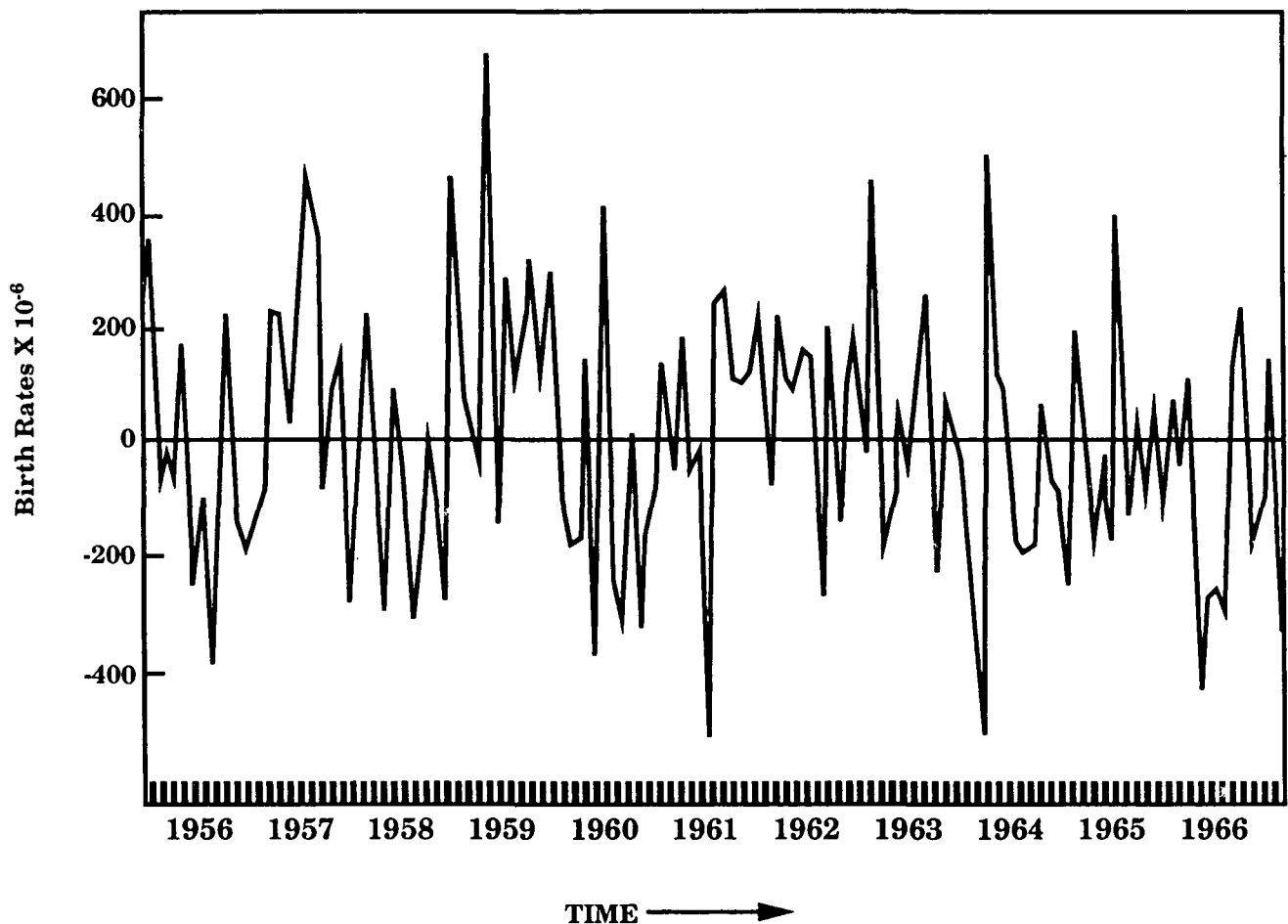
the time series had a seasonal component with a period of 12 months and no nonseasonal component. In other words, as can be seen by the large correlation at lag 12, there was a seasonal pattern that repeated itself at a 12-month interval. The mean absolute percentage error of this model was 22.6 percent, which means that, on average, the model accounted for 77.4 percent of each value of the birth-rate series.

In consideration of the monthly temperature variations in Taiwan (Central Weather Bureau, Republic of China 1991), the numbers of individuals with schizophrenia born in November through February and in May through August from 1955 to 1966 were summed together, and a chi-square test was calculated (table 3). The result was $\chi^2(1, n = 2,211) = 3.91, p < 0.05$. This confirms that significantly more persons with schizophrenia were born in the cold months than in the hot months.

In addition, the ratios of male to female subjects for the entire sample, the winter birth group, and the summer birth group were 1.63, 1.63, and 1.58, respectively. This supports the assumption that the seasonality phenomenon holds for both males and females.

It should be noted that a more sensitive test of these data might have been possible had the actual temperature variations in the specific months and years of the study been analyzed (such as in Kendell and Adams 1991). However, such data were not available from the Republic of China's Central Weather Bureau (1991). Therefore, average monthly temperatures across years of recording were used and grouped into extremes (i.e., warmest 4 months vs. coldest 4 months).

Figure 3. Monthly birth rates of schizophrenia subjects after one 12-month period differencing, 1955–66



Discussion

The results of this study support the above hypotheses that there is a seasonality phenomenon in the monthly birth rates of people with schizophrenia and a disproportional excess of such people born in the cold months compared with the hot months. These findings are compatible with those of many former studies (cf. review papers by Bradbury and Miller 1985; Boyd et al. 1986). Although the

etiology of schizophrenia is complex (Mirsky and Duncan 1986), these studies reveal that there are some season-related environmental factors that seem to be independent of race and geographic location. However, it is too early at present to identify exactly what the factors are, and further research is needed.

The seasonality phenomenon in this study was detected by using the ARIMA models of the time-series analysis techniques. How-

ever, if the data had been analyzed by using the chi-square test, as most former studies do, no significant results would have been obtained ($\chi^2[11, n = 3,346] = 10.57, p = 0.5$). This is because the chi-square test can be applied only to data collapsed across years for each month, making it more highly influenced by outliers. Time-series analysis deals with the measurements separately and is thus able to take outliers into account in detecting seasonality.

Figure 4. Autocorrelation function of monthly birth rates of schizophrenia subjects

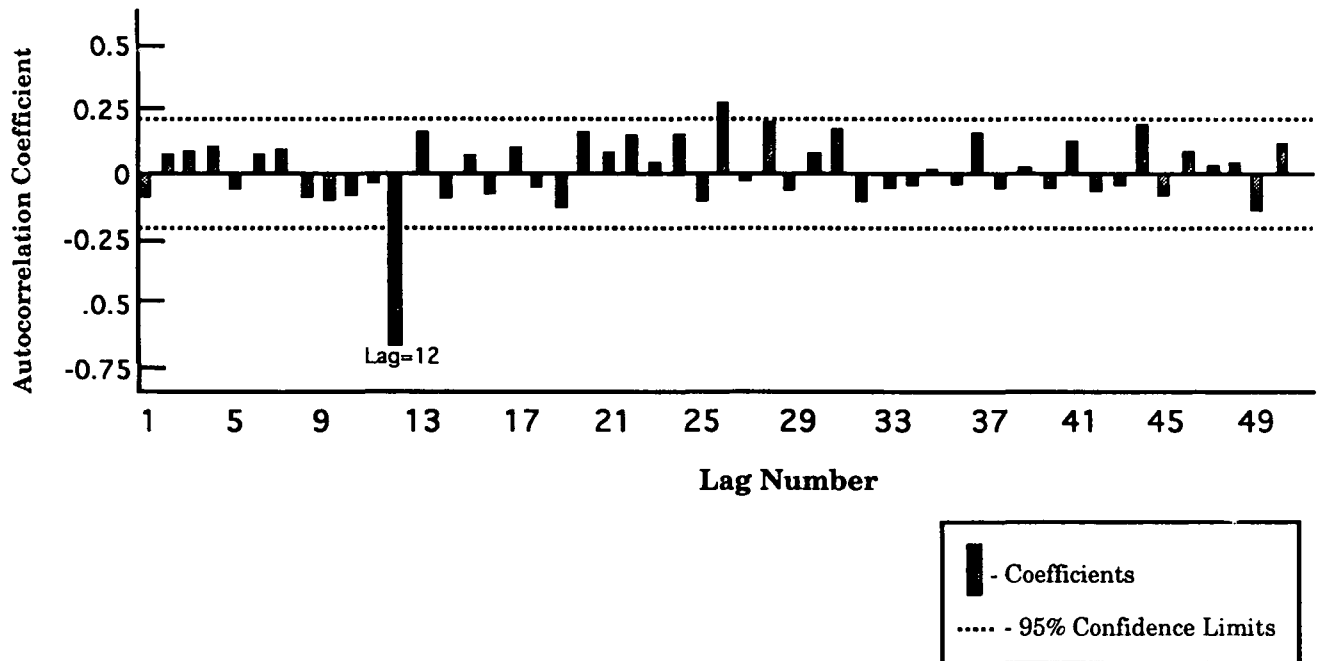


Figure 5. Partial autocorrelation function of monthly birth rates of schizophrenia subjects

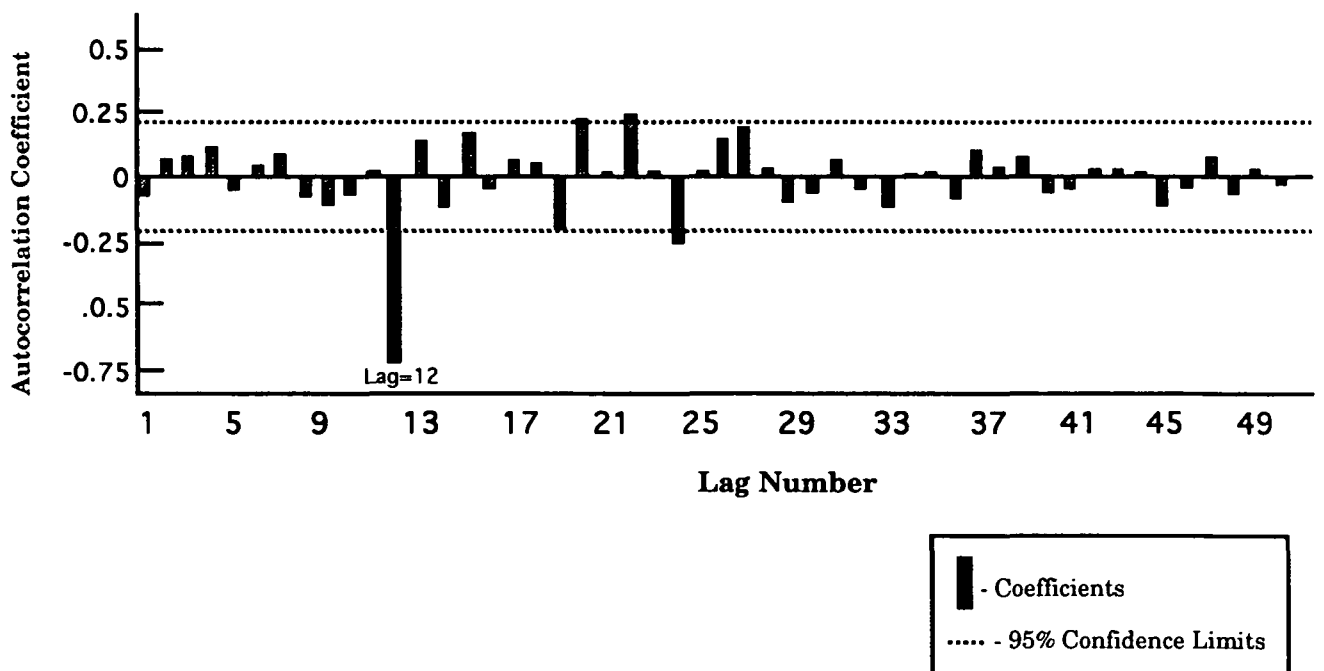


Table 3. Births of schizophrenia subjects from November through February and from May through August, 1955–66

	November to February	May to August
Observed numbers (Male/female)	1252.0 (776/476)	959.0 (588/371)
Expected numbers	1205.7	1005.3
$\chi^2(1, n = 2,211) = 3.91, p < 0.05.$		

Therefore, time-series techniques should be used in future studies.

Since this study is based on hospital data, generalization to the population of Taiwan depends on the representativeness of the selected hospitals. Although two of the largest hospitals with psychiatric wards were selected, there is no clear way to assess the representativeness of the sample. In addition, the hospital data, such as diagnosis, date of birth, and date of admission or diagnosis, might contain substantial errors. It is assumed, however, that in this study these errors are randomly distributed and therefore do not seriously affect the results obtained.

At present, the effects of certain mediating variables on the seasonality of birth in schizophrenia are not clear. These variables include race, sex, birth order, birth year, parents' ages at patient's birth, number of siblings, marital status, place of birth, place of residence, SES, age at onset, length of hospitalization, and subtypes of schizophrenia. For example, Torrey et al. (1977) divided their sample of schizophrenia subjects into paranoid and "process" (includes simple, hebephrenic, catatonic, and chronic undifferentiated schizophrenia) subgroups and found no significant differences with regard to seasonality of birth. On the other hand, a study by Hsieh et al.

(1986) revealed that male paranoid schizophrenia patients showed a significantly larger proportion of births during the first quarter of the year than did control subjects. Thus, it seems clear that further investigation is needed to elucidate the parameters of this phenomenon.

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Acknowledgments

The authors thank Drs. Wen-Yau Hsu of National Chengchi University, Ru-Band Lu and Hsiu-Ping Wang of Tri-Service General Hospital, and Hwei-Chuang Deng of Taipei City Psychiatric Center in Taiwan for their generous help with data collection; as well as Mr. Les Glover of the University of North Texas for assistance with data analysis.

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