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A case-control study of the seasonality effects on schizophrenic births on a tropical island

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Abstract

A substantial body of evidence from dozens of studies in many different countries suggests an excess number of individuals with schizophrenia are born in winter months. The presence of a seasonality effect in regions with year-round warm climate, however, has rarely been examined. The major purpose of this project was to better understand if the seasonality effect on schizophrenic births that has been reported in other, mostly cold regions of the Northern Hemisphere, also can be detected in a warm, tropical climate. We set out to study birth months as risk factors, quantifying the risk for being born with schizophrenia for every month of the winter season in terms of incidence rate ratios (IRRs) in the central region of Puerto Rico. We also analyzed climatic data in order to determine if there was any correlation between the rate of schizophrenic births ($n = 710$) to births in the general population ($n = 101,248$) and average rainfall and temperature for every month of the year in our period of study (January 1932–December 1967). Our results suggest that the risk of developing schizophrenia is 36.5% higher for people born in February than for people born in the other months of the year (95% C.I. = 6.6–74.8%). We also found correlations between the rate of schizophrenic to control births for any given month, and rainfall 4 months earlier ($r = 0.66$, $p = 0.010$), and temperature 5 months earlier ($r = 0.64$, $p = 0.013$) that remained significant after correcting for multiple comparisons.

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1. Introduction

The seasonality effect on schizophrenic births has been under formal study since 1929, when Tramer

published his analyses on birth data of Swiss schizophrenic patients (Torrey et al., 1997). This seasonality effect refers to an excess of schizophrenic births during specific seasons of the year, beyond any fluctuations that may be explained by the seasonal variations in the birth rates of the general population. A recent review of 76 published studies (Torrey et al., 1997), the vast majority of which were conducted in temperate or cold climates, identified a small but significant winter–spring birth excess, most on the order of 5–8%.

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Torrey et al. (1997) identified eight methodological problems that have frequently been encountered in studies of birth seasonality in schizophrenia: inaccuracy of birth data, duplication of subject count, lack of standardization of diagnosis, use of inappropriate controls, immigration and emigration, inappropriate periods of analysis, inadequate sample size and use of inappropriate statistical tests. An additional problem is the reliability of diagnoses, as most large studies pull their data from case registers, without further diagnosis verification.

Few studies on seasonality effects have been conducted in warm climates. The 10 studies included in the 1997 review (Torrey et al.) that were conducted in milder Southern Hemisphere climates yielded mixed results: nine of them reported at least a nominal excess number of schizophrenic births during the winter, but only four of those were statistically significant ($p < 0.05$). A more recent meta-analysis of 12 Southern Hemisphere studies (McGrath and Welham, 1999) found a nonsignificant excess in winter schizophrenic births. In the Philippines, where temperature does not vary much throughout the year, Parker and Balza (1977) found a 15% excess of winter schizophrenic births. In Singapore, a “season-less” area just north of the Equator, there was no observed excess of schizophrenic births in any season among the study’s subjects (Parker et al., 2000). In a region of Brazil with distinctive “wet” and “dry” seasons, an excess of schizophrenic births (during the months of May and June) was found, as well as a significant, positive correlation between the number of schizophrenic births and the amount of rainfall 3 months earlier (de Messias et al., 2001). Our own group conducted a study with a group of multiplex families in Puerto Rico, and we found a significant excess of winter schizophrenic births when comparing the schizophrenic patients to their own relatives (Carrión-Baralt et al., in preparation).

The major purpose of this project was to examine more comprehensively a possible seasonality effect on schizophrenic births in a warm, tropical climate. Specifically, we wanted to determine if our previous findings (Carrión-Baralt et al., in preparation) would be replicated with a larger, nonoverlapping sample of patients not necessarily related to multiplex families, and also, if there was one or more specific months within the winter season that represented a signifi-

cantly larger risk for schizophrenia births. We set out to study winter birth months as risk factors in three towns in the central mountain region of Puerto Rico: Cayey, Aibonito and Cidra. We quantified the risk for developing schizophrenia for every winter month in terms of incidence rate ratios (IRRs).

Torrey et al. (1997) have suggested, as the most plausible causes of the seasonality effect, seasonal parental procreational habits, genetic factors, pregnancy and birth complications, seasonal variation in external toxins, seasonal nutritional deficiencies and temperature and weather effects. There are many studies in the literature that link schizophrenic births to prenatal exposure to viral agents such as influenza (cf. Yolken and Torrey, 1995) especially during the second trimester of pregnancy. Furthermore, rainfall, humidity and temperature contribute positively to the transmission of pathogens such as dengue and influenza (National Research Council, 2001); dengue transmission in Puerto Rico has a seasonal peak during months with high rainfall and humidity (usually September–November) (Gubler et al., 2001). This would suggest that if there was viral transmission in schizophrenia, an increase in rainfall, humidity or temperature would likely increase the number of pathogens in the environment and that this, in turn, would increase the number of schizophrenic births born to women who were in their second trimester of pregnancy at the time of increased rainfall or temperature. For this reason, we analyzed climatic data in order to determine if there was any correlation between the rate of schizophrenic births to births in the general population and rainfall and temperature in the month of birth and from 1 to 8 months earlier, throughout our period of study (January 1932–December 1967).

Our study aimed to overcome the methodological problems found in previous studies and is one of the first large-scale published studies to feature individualized, careful review of the medical record for each putative case to ensure diagnostic accuracy.

2. Methods

2.1. Geographical setting

Puerto Rico is a tropical island between the Caribbean Sea and the North Atlantic Ocean (18.07°N,

66.09°W), east of the Dominican Republic. It is located about 1000 miles (1600 km) southeast of Miami, FL. Cayey (population, 47,370) is located in the island's central mountains, about 20 miles southwest of San Juan, the capital of Puerto Rico. It is surrounded by smaller towns and by the larger city of Caguas to the northeast. We selected the Cayey area to conduct our study because of its large, full-service psychiatric facility, the Cayey Mental Health Center (C-MHC), the relatively small migration movements to and from the area (Vázquez Calzada, 1981) and the availability of both demographic and climatologic data specific to this compact geographic area, by month, since 1931. The C-MHC mainly serves the towns of Cayey, Aibonito (population, 26,493) and Cidra (population, 42,753). The latter two towns are less than 15 miles away from Cayey.

Puerto Rico, in general, and the Cayey area specifically are warm, tropical areas where temperatures do not vary much throughout the year. Average monthly temperatures from 1932 until 1967 range from a low of 69 °F in January and February to a high of 77 °F in August and September (Fig. 1). To examine climatic differences that may have occurred over the years, we divided the time of study in two periods: from 1932 to 1950 and from 1953 to 1967. These two periods were chosen because there was

almost no climatic data available for this region in 1951 and 1952. Fig. 1 shows that the difference in mean monthly temperature during these two periods was minimal.

2.2. Samples

We studied all rigorously diagnosable schizophrenic births between January 1, 1932, and December 31, 1967, among patients who were ever served by the C-MHC. A total of 710 schizophrenic subjects (per DSM-IV diagnostic criteria) were included in the study. The controls were all registered births in the towns of Cayey, Aibonito and Cidra from January 1932 to December 1967 ($n=101,248$). Data for the schizophrenic population was obtained from the medical records of the C-MHC.

2.3. Procedure

The 18,234 records at the C-MHC at the beginning of the study were individually reviewed by one of two study diagnosticians (JCB or ZF), or one of three case managers who assisted the authors in this initial phase of the study. All records with a diagnosis of schizophrenia were selected for further review ($n=1113$). The study diagnosticians reviewed all cases blind to

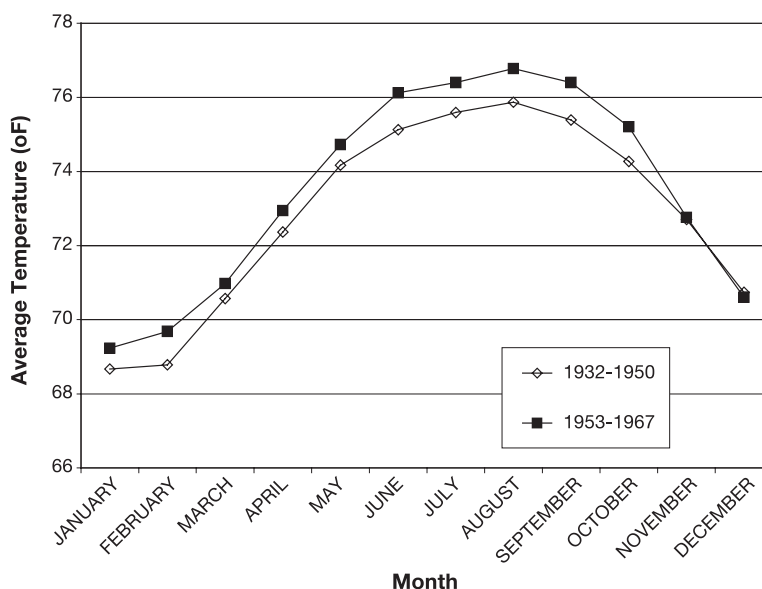


Fig. 1. Monthly average temperature in Cayey area, 1932–1967.

birth information. Maintaining the “blind” was easy to achieve since this information was routinely (and in the most cases exclusively) entered on a demographics page in a separate section of the record that was temporarily excised prior to the review. Of the 1113 records with a schizophrenia diagnosis, 31 were missing their birth dates, 144 had birth dates before January 1, 1932, or after December 31, 1967, and 228 did not unequivocally meet DSM-IV criteria for schizophrenia. These 228 records were excluded for one or more of the following reasons: (a) presence of substance or alcohol abuse or dependence disorders prior to the appearance of psychotic symptoms; (b) possible malingering, as suggested by the request of disability benefits by the subjects or their relatives during their first or second visit to the MHC; (c) history of severe head trauma, including loss of consciousness prior to the appearance of psychotic symptoms; (d) history of neurological brain damage prior to the appearance of psychotic symptoms; (e) course of illness that suggested a mood disorder with psychotic symptoms, mental retardation, Posttraumatic Stress Disorder, presenility or epilepsy rather than schizophrenia; (f) not enough information to make a clear diagnosis of schizophrenia. Whenever diagnostic questions arose, JCB and ZF discussed the cases jointly and, if still no clear diagnosis could be agreed upon, the case was discarded. Following these exclusions, there were 710 records of patients with unambiguous DSM-IV schizophrenia included in the study.

Birth data for the control group was obtained from the Puerto Rico Demographic Registry Office in the form of number of births, per month and per town, for the period of study in Cayey, Aibonito and Cidra, the three towns served by the Cayey MHC. Climatic data was obtained from the United States National Climatic Data Center in the form of mean rainfall and mean temperature for Cayey, per month, for the period of study.

2.4. Statistical analyses

A standard Pearson chi-square statistic was used to test whether the distribution of births across all 12 months was significantly different for the schizophrenic group than for the general population. Because such an analysis might wash out an effect found in only one or a small number of months, we also

calculated the adjusted standardized residuals (ASRs) to determine if there were significant excess schizophrenic births in any of the winter months. The adjusted standardized residuals are calculated by dividing the difference between the observed count for a cell and its expected count by an estimate of the residual's standard error and are distributed approximately as *Z* scores (SPSS, 1999). Therefore, an adjusted standardized residual of 1.96 or greater is significant at $\alpha=0.05$. Next, we used Poisson regression analyses to investigate differences in relative risk in the form of incidence rate ratios (IRRs) for schizophrenic births for every month of the year, comparing each month with the other 11 months of the year. We used as the dependent variable the number of schizophrenic births for each month of every year in our period of study. For every analysis, we used as the exposure factor the month of birth and the offset variable was the natural logarithm of the number of control births for that month. Poisson regression analyses have been used quite successfully in medical applications to model the occurrence of rare events such as skin cancer (Kleinbaum et al., 1998) and also in the study of risk factors for schizophrenia (Suvisaari et al., 1999). Based on prior research both elsewhere and in our own earlier study, we hypothesized that one or more of the three winter months (January, February or March) would present a significantly higher IRR than the other months of the year. Since we were conducting three independent analyses, we evaluated the significance of our results by the Bonferroni inequality. That is, the obtained levels of significance (*p*) for the winter months would be considered significant only if *p* was smaller than 0.05 divided by the number of tests of significance (in this case $0.05/3=0.0167$).

We used Pearson correlations to determine which climatic variables were more closely associated with the number of schizophrenic births in that month and also births in subsequent months. For the reasons mentioned in the Introduction, we hypothesized that the correlation between the rate of schizophrenic to control births and rainfall and temperature 3, 4 or 5 months earlier would be significant. Since we were again conducting three analyses simultaneously, we applied the Bonferroni criterion described earlier. Therefore, in order for a correlation to be significant, *p* would have to be less than 0.0167.

We considered doing time series analyses, but our sample was too small. In the last year included in the study (1967), there were several months with just one subject in the schizophrenia group. A time series analyses would have reflected a diminishing trend in the incidence of schizophrenia; this would have been inaccurate since this decrease is most likely due to the fact that many subjects born in the later years of our study (late 1960s) may not have sought treatment in the CMHC until after we concluded our study (2000).

3. Results

Table 1 shows the monthly distribution of births for the two groups studied, from 1932 to 1967. Across the 12 months of the year, the difference between the distribution of births in the schizophrenic population and the distribution in the general population was not significant ($p=0.640$). However, the ASR for the month of February was 2.15, which suggests that the number of observed schizophrenic births for that month was significantly higher than what would be expected, if the distribution of births for both groups were similar throughout the year. In order to be able to compare the relative distribution of births between the two groups, we constructed the following chart (Fig. 2), which plots the monthly percentages of births for the two groups.

Several things are evident in Fig. 2. First, the percentages of control births are very close throughout the year to the percentage of expected births for every month. All monthly control birth percentages are within 0.3% of the expected birth percentage for that month. The percentage of expected births was calculated dividing the number of days in every month (28.5 for February to account for leap years) by 365.

Second, the distribution of birth percentages among the schizophrenic population is much less evenly spread out throughout the year. There are marked peaks and troughs going from a minimum 7.04% of births in July and March to 9.86% in February. Only January (8.45%), April (8.03%), October (8.873%) and November (8.45%) have birth percentages less than 0.5% over or under the expected birth percentage for that month. Third, even though the changes in monthly percentages are more pronounced in the schizophrenic population than in the control population, the overall trends in increase or decrease of birth percentages are similar for the two populations, likely following the common seasonality mating and birthing patterns of both groups. Fourth, the exceptions to the overall similarity occur in February, March and July. For these months, there are marked opposite trends between the two populations.

Table 2 shows the differences in relative risk (IRR) for schizophrenic births. As hypothesized, February presents the highest IRR (1.3648, $p=0.014$) of all months. No other month presents an IRR that even approaches significance, when compared to the other 11 months of the year. This means that the risk of developing schizophrenia is 36.48% higher for people born in February than for people born during the other months of the year (95% C.I. 6.58–74.76%). This result remains significant after applying the Bonferroni criterion ($p<0.0167$). The ratio of deviance/degrees of freedom is 1.2095, which suggests a good fit of the model to the data (Kleinbaum et al., 1998).

Table 3 shows the Pearson correlations between the rate of schizophrenic births to control births and temperature and the amount of rainfall for that month and for each of the previous 8 months throughout the period from January 1932 to December 1967. The relationship between the rate of schizophrenic to

Table 1
Total number of monthly schizophrenic births vs. control births in Cayey area (1932–1967) with adjusted standardized residuals for schizophrenic births

	January	February	March	April	May	June	July	August	September	October	November	December
Schizophrenia	60	70	50	57	55	52	50	66	63	63	60	64
Control	8822	7794	8328	8408	8602	8190	8345	8601	8560	8721	8190	8687

Pearson chi-square = 8.8033, d.f. = 11, p = 0.640
 ASR for SZ Group -0.25 2.15 -1.14 -0.27 -0.71 -0.75 -1.16 0.76 0.40 0.25 0.35 0.41

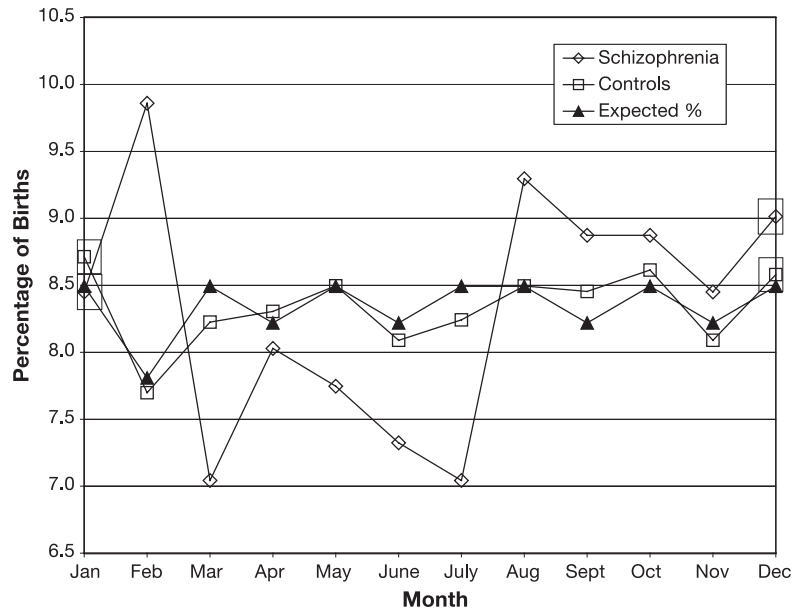


Fig. 2. Percentage of monthly schizophrenic births vs. control births and expected births in Cayey area, 1932–1967.

control births and rainfall 3 and 4 months prior to birth and temperature 4 and 5 months prior to birth showed strong associations. After applying the Bonferroni criterion, the relationships with rainfall 4 months prior to birth ($p=0.010$) and temperature 5 months prior to birth ($p=0.013$) remain significant ($p<0.0167$).

It is also worth noting that the correlations of both temperature and rainfall with the rate of schizophrenic

to control births exhibit a systematic pattern across the 9-month period of gestation, starting with a low value at month of birth, increasing until reaching the maximum values mentioned (during the second trimester of pregnancy), and then descending again until another low value is reached at the month of conception.

Fig. 3 shows graphically the association between the ratio of schizophrenic to control births and the climatic variables mentioned earlier. When their val-

Table 2

Relative risk ratios for schizophrenic births for every month (when compared to the other 11 months of the year)

Month	IRR	Standard error	Z	$P> Z $	[95% confidence interval]	
January	0.9691	0.1330	-0.23	0.819	0.7406	1.2683
February	1.3648	0.1722	2.47	0.014	1.0658	1.7476
March	0.8596	0.1274	-1.02	0.308	0.6429	1.1495
April	0.9831	0.1371	-0.12	0.902	0.7480	1.2921
May	0.8481	0.1246	-1.12	0.262	0.6359	1.1310
June	0.8947	0.1314	-0.76	0.449	0.6709	1.1931
July	0.8766	0.1288	-0.90	0.370	0.6573	1.1690
August	1.0720	0.1428	0.52	0.602	0.8257	1.3917
September	1.0967	0.1450	0.70	0.485	0.8464	1.4212
October	1.0000	0.1362	0.00	1.000	0.7657	1.3059
November	1.0511	0.1443	0.36	0.717	0.8032	1.3755
December	1.0229	0.1382	0.17	0.867	0.7848	1.3331

Table 3

Correlation between ratio of schizophrenic to control births and temperature and rainfall during the months previous to birth from 1932 to 1967

Months before birth	Temperature		Rainfall	
	Pearson <i>r</i>	Significance (<i>p</i>)	Pearson <i>r</i>	Significance (<i>p</i>)
0	−0.442	0.075	0.041	0.450
1	−0.228	0.238	0.177	0.291
2	0.022	0.473	0.314	0.160
3	0.364	0.123	0.599	0.020*
4	0.562	0.028*	0.658	0.010**
5	0.635	0.013**	0.306	0.166
6	0.480	0.057	−0.056	0.431
7	0.207	0.260	−0.228	0.238
8	−0.159	0.311	−0.454	0.069

d.f. = 8.

*Significant at *p* < 0.05 level.

**Significant after Bonferroni correction.

ues are standardized, these variables follow a very clear common pattern across the year and form a smooth band that descends from January to June and then climbs again from June to December. Therefore, there are no real “wet” and “dry” seasons in Puerto Rico, but rather months with more or less rain.

4. Discussion

Our analyses suggest that being born in February in our tropical region of study is a significant risk factor for schizophrenia. The risk of developing schizophrenia is 36.48% higher for people born in February than for people born in the other months of the year. These results are similar to those recently observed among schizophrenic family members from multiplex families from the same region of Puerto Rico (Carrión-Baralt et al., in preparation). A specific month effect was also observed in Brazil, another warm region with little seasonal temperature variation (de Messias et al., 2001). The Brazilian study was conducted in Rio Grande do Norte, which is located at 5.11°S, 37.21°W. In that study, however, May and June showed excess rates of schizophrenic births. Actually, temperatures vary little throughout the year in either location (northeast Brazil or Puerto Rico). This suggests that a seasonality/month effect in warm, tropical climates is unlikely explained by drastic changes in temperature and hence leads to a consideration of other biological or environmental factors.

Our climatic analyses reveal a significant correlation (after Bonferroni correction) between the rate of

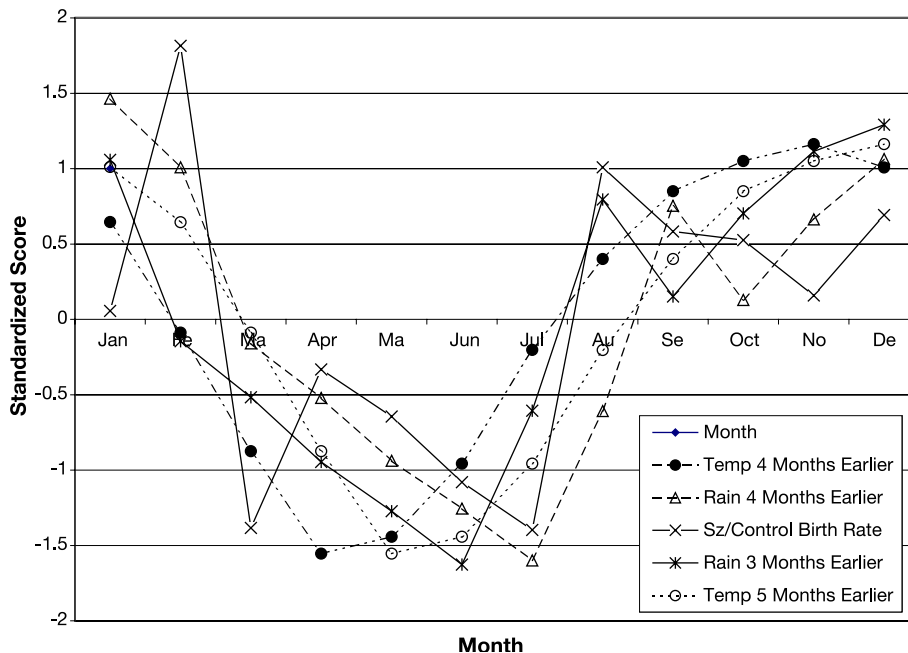


Fig. 3. Seasonal pattern of schizophrenia/control birth ratio, temperature 4 and 5 months earlier and rainfall 3 and 4 months earlier.

schizophrenic births to births in the general population and rainfall 4 months earlier. We note that this result is similar to that observed in Brazil (de Messias et al., 2001) where schizophrenic births were significantly associated with rainfall levels 3 months earlier. These collective results tentatively raise the possibility that one or more factors associated with rainfall (such as a virus) could cause brain injury to the fetus during the second trimester of pregnancy. Our climatic analyses also reveal a significant correlation (after Bonferroni correction) between the rate of schizophrenic births to births in the general population and temperature 5 months earlier.

The significant blip in the February schizophrenic-to-control birth ratio and the lack of a comparable effect in the months adjacent to February seems to weaken the biological plausibility of any candidate. However, it must be noted that after the September peak, rainfall begins to drop steadily and temperatures cool down, which in turn leads to less than ideal conditions for the propagation of viral agents. It must also be noted that when health hazards become widely known, whether by word of mouth among the population or by government information campaigns (such as when a dengue or influenza epidemic or pandemic begins), many people tend to take measures to minimize risk of infection (such as discarding empty containers and/or repositories where rain water may accumulate and serve as breeding habitats for the vectors).

Hurricanes, which cause torrential downpours, are common in the Caribbean Sea from June to November. One may wonder if the increase in rainfall observed during some periods in our study might be due to a hurricane rather than to an increase in the number and severity of the rainshowers that are normal during those months. According to the United States National Oceanic and Atmospheric Administration (NOAA), there were only three catastrophic hurricanes in Puerto Rico during our period of study (1932, 1956 and 1960). Tropical storms and depressions are very common in this area, and there are dozens of those reported by NOAA during our period of study, most of them in September and October.

Given the very subtle seasonal changes in temperature in Puerto Rico, is it reasonable to even hypothesize any such temperature variations might have a measurable effect on the risk of schizophrenia? Recent

evidence indicates that even subtle temperature changes may increase or decrease risk of viral infection. For example, in regions where dengue is already present, a mean temperature increase of about 1 °C appears to increase the aggregate epidemic risk of this disease by an average of 31–47% (Patz et al., 1998). Taken together, our results lead us to suggest an alternative explanation on the issue of weather as a risk factor for schizophrenia: perhaps it is not simply level of precipitation or temperature but rather a combination of climate conditions specific to each region that cause, or contribute to, an excess of schizophrenic births. In our case, we see indications that warmer temperatures 5 months before birth and increased rainfall 4 months before birth are strongly associated with increased rates of schizophrenic births. As noted, the combination of heat and humidity create an optimum environment for many viruses to reproduce and propagate in the tropics, which in turn could lead to the prenatal injuries that have been suggested as the possible causes of schizophrenia. We suggest that climatological factors need to be studied jointly to try to understand the complete effect of weather in schizophrenic births in every specific region. That way, we may be able to identify the specific element or elements associated with weather that could make it a risk factor for schizophrenia.

Our study strived to overcome the most common methodological problems found in the literature. We did so through careful, individualized review of each record, which avoided problems with the accuracy of birth data and duplication of subject counts, and through standardized diagnostic procedures; through the use of appropriate controls (all general population births) and climatic data specific to the area under study (less than a 15-mile radius), for every month from January 1932 to December 1967; and through the use of statistical tests that have been shown to be appropriate for the modeling of rare occurrence events such as schizophrenic births.

A limitation of this study is the size of our sample of schizophrenic patients ($n=710$). However, the careful and meticulous procedure utilized to decide which records would be included or excluded from the study ensures a diagnostic accuracy seldom found in epidemiological studies of this size.

Finally, as Torrey et al. (1997) point out, it should be noted that most individuals with schizophrenia are

not born during the month of highest risk that we found in this study (February), and most people born in February do not develop schizophrenia later on in life. Our findings do not reflect any specific assessment of individual risk, but rather risk for the population we studied, as a whole.

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