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The Interaction of Seasonality, Place of Birth, Genetic Risk and Subsequent Schizophrenia in a High Risk Sample

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Summary: Births occurring in winter months, which are high viral infection months, have been repeatedly shown to produce a slight excess of later-diagnosed schizophrenics. As a result, some researchers have speculated on the possible aetiological effect of viral infections on some forms of schizophrenia. The implications of the viral hypothesis were indirectly tested in the context of an ongoing prospective study of Danish children at high-risk (HR) for schizophrenia. A third-order analysis of variance interaction was hypothesized. Genetically vulnerable individuals, born in winter, in an urban environment (which increases the likelihood of the presence and transmission of viruses) would be more likely, as foetuses or neonates, to have suffered some CNS damage due to the infection; thus they would show higher rates of schizophrenia diagnoses. This hypothesis was supported. The rate of schizophrenia in the HR-urban-winter birth condition reached 23.3 per cent, considerably above population base rates (1 per cent) or rates for the HR subjects (8.9 per cent). Alternative explanations for the results were explored.

Winter births produce a slight excess of individuals later diagnosed as schizophrenic (Barry and Barry, 1961; Hare and Price, 1968). Of particular significance are large population studies (Dalén, 1968; 1975; Odegaard, 1974; Videbech *et al*, 1974), southern hemisphere studies (Dalén and Roche, in Dalén, 1975; Parker and Neilson, 1976), and equatorial studies (Parker and Balza, 1977), which have all yielded convergent results. This repeated observation has led to the hope that understanding of this relationship might suggest a useful aetiological hypothesis for at least some forms of schizophrenia. In view of the greater prevalence of viral infections during winter (Hope-Simpson, 1981) and other related evidence, some researchers have speculated on the possibility that viral infections are somehow involved in the aetiology of some forms of schizophrenia (Torrey and Peterson, 1976; Torrey, 1980).

An independent body of work has established that genetically transmitted characteristics combine in some way with environmental factors in the development of schizophrenia. This gene-environment interaction has received considerable attention in studies of the pregnancy and delivery of those who later became schizophrenic, and in studies of individuals born to schizophrenic mothers (McNeil and Kaij, 1978). Mednick (1970) has suggested that perinatal difficulties in deliveries involving high-risk children have unique consequences for their nervous system development. Pregnant schizophrenic women have been shown to produce an excess number of still-births and offspring with congenital anomalies (Sobel, 1961; Rieder *et al*, 1975). These perinatal deaths and anomalies perhaps are the extreme manifestation of a process attacking the high-risk foetus; in less extreme forms this process may result in some nervous system damage which predisposes some high-risk individuals to schizophrenia. Of some significance, in this context, are the results of population studies which indicate that maternal viral infections (Type A influenza) during pregnancy yield a modest excess of congenital anomalies; the most frequent foetal organ system damaged by the viral infection is the central nervous system (Campbell, 1953; Coffey and Jessop, 1959; Saxén *et al*, 1960).

Based on these bits of evidence, the general hypothesis was entertained that some forms of schizophrenia may result from perinatal viral infections which specifically attack the nervous system of genetically vulnerable foetuses. Some predictions of this general hypothesis were examined in the context of an ongoing, prospective study of Danish children at high-risk for schizophrenia. The Danish high-risk project unfortunately does not have a record of perinatal viral infections. In view of the marked seasonal variation of viral infections (particularly influenza), however, one

could safely hypothesize that such infections were more prevalent in the winter and early spring in the years the children were born (Hope-Simpson, 1981). Further, it was assumed that such viral infections were more likely in circumstances which favour the spread of the infection. Pregnant women who work and live in crowded urban conditions, who regularly use mass transportation and mass entertainment and who work in close proximity to others are much more likely to encounter the products of coughs and sneezes. Thus, they are more likely to be exposed to a viral infection while pregnant and/or more likely to transmit it to their newly born children.

The research hypothesis is: genetically vulnerable individuals, born in the winter or early spring months, in an urban area, are more likely to have been damaged by a viral infection and to show the results of these infections in poorer psychological adjustment and a higher likelihood of a schizophrenia diagnosis. In analysis of variance (ANOVA) terminology, a third-order interaction (genetic risk × urban v. non-urban birth place × season of birth) is hypothesized. It must be stressed that all three factors when present *in combination* will be related to later psychological impairment.

Method

Subjects

The sample is drawn from a prospective, longitudinal study begun in Denmark in 1962 by Mednick and Schulsinger (1968). The high-risk (HR) group (at risk for schizophrenia) is composed of 207 offspring of chronic and severely schizophrenic mothers. The low-risk (LR) group comprises 104 children with no known mental illness in their family for two previous generations. Individuals in both groups, normally functioning at the start of the project, had an average age of 15.1 years (range 9–20). The subjects were contacted during 1972–74 and underwent an extended clinical and diagnostic interview. In the HR and LR groups respectively, 173 (83.6 per cent) and 91 (87.5 per cent) completed the full assessment and diagnosis protocol (Schulsinger, 1976).

Measures

Two criterion variables were used: (a) one was the dichotomous diagnosis of schizophrenia and not-schizophrenia. For this purpose, three techniques contributed to the diagnosis of schizophrenia: (1) the current section of the CAPPS (Current and Past Psychopathology Scales) and its corresponding computer-processed programme Diagno II (Endicott and Spitzer, 1972); (2) the PSE (Present State Examination, 9th Edition) and its computer-processed programme CATEGO (Wing *et al*, 1974); (3) a clinical diagnosis based on an extensive interview. A consensus diagnosis, based on agreement of at least two of the three diagnostic methods, became the basis for a diagnosis of schizophrenia.

In view of the relatively small number of subjects, it was decided to use an additional, *continuous* measure of psychopathology, namely (b) level of adjustment or severity of mental illness. For this purpose, the PSE Index of Definition of Syndromes ("Caseness") and CAPPS Severity of Illness (item no.471) scales were used. The PSE "Caseness" measure indicates (on a scale of 1–9) the extent to which a subject resembles a hospitalized psychiatric patient. The CAPPS Severity is a rating (on a 1–6 scale) made by the interviewer of the degree of mental illness shown by the subjects. A higher score on both scales reflects greater severity of mental illness. Inter-rater reliability for the CAPPS Severity of Illness scale is 0.77 (Endicott and Spitzer, 1972). In this study, the PSE "Caseness" (a computer rating) and CAPPS Severity (rated by trained interviewers) scales correlated 0.70.

Season of birth was defined as winter versus non-winter birth, taking January, February, and March as winter and the rest of the year (April through December) as non-winter months. The first quarter of the year (January–March) was most appropriate for the present purposes; the work of Hope-Simpson (1981) has suggested that these months are dramatically and reliably high viral epidemic months, particularly for influenza. The Hope-Simpson data are from England; Dr Mednick's work with Danish Health statistics indicates that these findings apply equally to Denmark.

Urban births were defined as those occurring in the greater Copenhagen area. Copenhagen was the only Danish city in the late 1940's with a population of approximately one million. The second largest city in Denmark, Aarhus, had only a population of 110,000 (Hammond and Co., Inc., 1949). Births occurring in the remainder of Denmark were therefore considered not-urban.

Results

It is hypothesized that certain pregnancy conditions (genetic risk-urban environment-winter delivery) will increase the probability of outcomes with poor mental health, including schizophrenia.

Schizophrenia-not schizophrenia analysis

Only the HR group was considered in this analysis since only one LR subject had a diagnosis of schizophrenia. The per cent of consensus-diagnosed schizophrenics in each condition is given in Table I. Note that urban births (12 per cent) yielded a marginally higher rate of schizophrenia than the not-urban births (4 per

TABLE I

Per cent high-risk subjects diagnosed schizophrenic distributed by place and season of birth

Urban births 12.0%		Not-urban births 4.2%	
Winter	Not-winter	Winter	Not-winter
23.3%	8.4%	0%	6.3%
(7 of 30)	(8 of 95)	(0 of 16)	(2 of 32)

Note: Of these HR subjects, 8.9 per cent were diagnosed schizophrenic (Schulsinger, 1976).

cent) (Fisher's exact probability test, $P < .078$, one-tailed).

As hypothesized, the highest rate of schizophrenia is observed in the high risk-urban-winter births (23.3 per cent). These three factors increase the risk of schizophrenia considerably over the general population base rate of approximately 1 per cent, or the HR base rate of 8.9 per cent. Among the urban births, significantly more schizophrenics result from winter births (23.3 per cent) as opposed to not-winter births (8.4 per cent) (Fisher's exact probability test, $P < .028$, one tailed). It may be worth pointing out that among the urban births, about as many schizophrenics were born in the three winter months (7) as were born in the remaining nine months (8). The differences among the not-urban births are not significant.

Severity of mental illness analyses

Table II presents the mean CAPPS Severity and PSE "Caseness" scores as a function of place and season of birth for the HR and LR groups. As hypothesized, the highest degree of psychopathology is found for the HR urban-winter births.

Analyses were performed using the General Linear Model (GLM) supplied by Statistical Analysis System (SAS Institute Inc., 1979) on both the PSE "Caseness" score and the CAPPS Severity rating. The GLM programme is appropriate for analyses with unbalanced cell sizes. It uses a regression approach to the analysis of variance.

Table III presents the three-way ANOVA for the CAPPS Severity and PSE "Caseness" scores. The hypothesized three-way interaction is significant. As a main effect, high risk status results in more severe psychopathology scores on both dependent measures while urban birth place is significant only for CAPPS Severity rating.

Appropriate *t* test comparisons were performed on the relevant means of the significant three-way interaction found in Table III. The HR-winter-urban birth group evidenced a higher severity of illness (on both CAPPS Severity and PSE "Caseness" scales) than all the LR groups (all comparisons $P < .02$), and when compared to the other HR groups, differed only from the HR-winter-not-urban group ($P < .03$).

ANOVAs leaving out the schizophrenics

There was concern that the disproportionate number of schizophrenics in the HR-urban-not-winter birth condition (see Table I) was accounting entirely for the significant third-order interaction presented in Table III. ANOVAs were performed leaving the schizophrenics out of the analyses. The third-order interaction remained, but it was only marginally significant ($F(1,238) = 2.93$, $P < .08$). These results suggest that the seasonality-place of birth effect may not simply relate to the diagnosis of schizophrenia but also has relevance to lesser degrees of psychological disturbance.

Discussion

Within the context of a high-risk for schizophrenia project, the implications of the viral hypothesis were considered, and some specific predictions were made. In part, the predictions expressed themselves in the form of a third-order ANOVA interaction which was significant. Genetically vulnerable individuals born in winter months (in which there are high frequencies of viral infections) in an urban setting had the highest rates of schizophrenia and the poorest level of psychological adjustment. It is worth emphasizing that the rate of schizophrenia for the genetically vulnerable, winter-urban born reached 23.3 per cent which is considerably above population base rates of schizophrenia (1 per cent), or rates for HR subjects in this population at this time (8.9 per cent). The specific predictions of the viral hypothesis were not rejected. It must be quickly pointed out that these predictions were indirect in the sense that it was not known whether the foetuses or neonates actually suffered a viral attack.

Kinney and Jacobson (1978), working with a subgroup of Kety and Rosenthal's Danish adoption population, have examined the relationship between season of birth and risk and later schizophrenia. Unfortunately, it is difficult to compare both sets of findings. While the present study's criterion of risk involves having a severely schizophrenic mother, their criteria also included post-natal brain damage. It is also difficult to determine whether the perinatal circumstances surrounding an adoption in some way interacted with the rural-urban or season of birth factors. During the time of these adoptions the adoption agency had a stated policy of attempting to place adoptees at some geographical distance from their biological parents (Mothers Aid Organization for Copenhagan, Copenhagen County and Frederiksborg Country, Annual Report for 1946–47). Thus, while Kinney and Jacobsen studied adoptees in the Greater

TABLE II

Mean level of severity of mental illness[1] for high- and low-risk subjects, distributed by place and season of birth

Scale	Risk group	Urban births		Not-urban births	
		Winter	Not-winter	Winter	Not-winter
CAPPS	High	3.47 (n=30)	3.13 (n=95)	2.63 (n=16)	2.97 (n=32)
	Low	2.13 (n=16)	2.55 (n=44)	2.43 (n=7)	2.17 (n=24)
PSE	High	4.33 (n=30)	3.67 (n=95)	2.94 (n=16)	3.63 (n=32)
	Low	2.88 (n=16)	3.27 (n=44)	3.29 (n=7)	2.54 (n=24)

Note: A higher score on both scales reflects greater severity of mental illness.
[1]Based on CAPPS severity and PSE "Caseness" scores.

TABLE III

ANOVA of severity scores by risk status, place and season of birth

Effects	CAPPS severity scores			PSE "caseness" scores		
	MS	F	P	MS	F	P
Risk (R)	31.54	28.38	0.0001	26.35	6.50	0.011
Season (S)	0.001	<1.0	N.S.	1.02	<1.0	N.S.
Birth-place (BP)	5.0	4.49	0.035	11.01	2.72	0.10
R×S	1.20	1.08	N.S.	0.84	<1.0	N.S.
R× BP	0.24	<1.0	N.S.	0.02	<1.0	N.S.
S× BP	0.53	<1.0	N.S.	2.85	<1.0	N.S.
R×S× BP	4.56	4.11	0.044	15.28	3.77	0.053
Error term (df=254)	1.11			4.17		

For all effects, df=1.

Copenhagen area, it is not clear what proportion were actually born outside of Copenhagen. This would influence the results, since without consideration of place of birth the present study would not have found a seasonality effect.

Plausible alternative explanations

The complexity of the third-order interaction has made it difficult to find alternative explanations of these results. However, some plausible hypotheses will be considered which could explain, in part, the present findings:

1. Procreational patterns by parents of schizophrenics, which might differ from those of the general population, have been proposed as the grounds for the excess of winter schizophrenic births (Huntington, 1938; Hare and Price, 1968; James, 1978). No support for this hypothesis was found. High-risk individuals (27 per cent) did not have significantly more winter births than low-risk individuals (25 per cent).

2. Lewis and Griffin (1981) have devised a correction technique and have shown that the reported excess of winter-born schizophrenics can be explained on the basis of the age-prevalence effect, a methodological artifact. This effect, the authors show, has a negligible influence after age 23. In the present study, the sample of individuals assessed in 1972 had a mean age of 23.7 years and the group diagnosed schizophrenic was somewhat older (mean age of 24.5 years). Thus, these results cannot be explained by the age-prevalence effect.

Watson *et al* (1982) applied the suggested correction technique for the age-prevalence effect and failed to replicate Lewis and Griffin's findings. These authors speculated that the effects of the age-prevalence factor are minimal, at least when severe climates prevail. The source of both the present data (based on a Danish

sample) and that of Watson *et al* (based on a Minnesota sample) are similar in that severe winters prevail in these places; Lewis and Griffin's findings are based on data from Missouri, which is affected by a relatively milder climate.

3. It was assumed that an urban environment (interacting with HR and winter birth) favoured the contracting of a viral infection by the mother or infant due to increased likelihood of contact with other people. Other conditions which are associated with urban living, like greater noise, crowding, air pollution, and psychological stress could possibly interact with genetic risk. However, it is not immediately apparent why these urban factors should have a greater influence in January, February, and March. These data do not permit a closer study of the urban—not-urban variable.

4. The assumption was made that a birth occurring during the winter season would increase the likelihood of the foetus or neonate (directly or indirectly through the mother) contracting a viral infection. However other *non-viral* factors, seasonal in nature, could in fact account for the observed seasonality of schizophrenic births (Torrey, 1980). Certain protein deficiencies, commonly occurring during the summer months (the crucial first trimester for the winter births) could be reasonably hypothesized as producing the brain damage which eventually leads to some forms of schizophrenia. In the same manner other nutritional deficiencies (like vitamins C and K) which are more common during the winter have been proposed as explaining the seasonality effect. These alternative, non-viral hypotheses could just as well explain the observed findings, although it is not clear why they would restrict themselves to an urban environment.

5. Carter and Watts (1971) have shown that the relatives of schizophrenics tend to be more resistant to viral infections than people in the general population. Predictions based on their findings would suggest that the season of birth effect should be more dramatic in the present study's *low-risk* group, where these mothers would be more susceptible to viral infections than their high-risk counterparts. The results are not in agreement with these predictions since the effect was greatest in the high-risk group. It is worth noting that Carter and Watts' data are based on a much broader definition of relative which pools not only mothers (the only relative to form the present investigation's high risk group) but other family members as well. The results of both studies are therefore not directly comparable. At the same time, one could entertain the hypothesis that the nonschizophrenic relatives of schizophrenics were protected from the illness because of their greater resistance to viral infections. Thus the findings of this study may not be entirely inconsistent with those of Carter and Watts.

6. It was hypothesized that a child born during the winter months was more susceptible to suffering CNS damage due to a viral infection than someone born in a non-winter month. But a majority of this latter group (the non-winter born) also would have passed some earlier stage of foetal development during the high viral infection months. Theoretically, then, they would be just as likely to have been damaged by the viral infection; yet the findings did not support this hypothesis. Why was a viral infection during the winter perinatal period more crucial in terms of predicting schizophrenia than an infection earlier in pregnancy (non-winter birth)? One might speculate that, once born, the infant is no longer protected by the mother's immune system and is therefore more susceptible to the damaging effects of an infection. In addition, infections at earlier stages of pregnancy, particularly the first trimester, are associated with gross congenital malformations (Saxén *et al*, 1960; Torrey and Peterson, 1976). Infections occurring later in pregnancy might be associated with more subtle, and less readily noticeable CNS damage. This in turn might produce effects on behaviour which are delayed until higher level functioning is demanded of the developing individual. Unfortunately, again, the nature of the present data do permit a closer inspection of these and other plausible hypotheses.

In summary, several predictions from a viral hypothesis of the aetiology of schizophrenia have been tested. The results have not disconfirmed the hypothesis. It must be stressed, though, that this investigation represented only an indirect test. It was not known in each individual case whether a perinatal viral infection was contracted. However, the probability of such viral infections are remarkably higher in the months of January, February, and March in Denmark. We are planning a population study to make a more direct test of the viral hypothesis of schizophrenia.

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