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Schizophrenia Following Pre-natal Exposure to Influenza Epidemics Between 1939 and 1960

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We examined the relationship between the dates of births of schizophrenic patients admitted to hospitals for the first time in England and Wales between 1970 and 1979, and the occurrence of influenza epidemics between 1939 and 1960. Our results indicate that exposure to influenza epidemics between the third and seventh month of gestation is associated with schizophrenia in adult life. The hypothesis that maternal viral infection is an important cause of schizophrenia can explain many aspects of the enigmatic epidemiology of the condition.

Patients with schizophrenia show an excess of births in the late winter and spring (Murray *et al*, 1985; O'Callaghan *et al*, 1991*a*,*b*), suggesting a seasonal environmental factor which adversely affects foetuses or neonates (Hare, 1988; Murray *et al*, 1991). Influenza epidemics occur frequently in autumn and winter (Stuart-Harris & Smith, 1982), and two recent reports have described an increase in the number of births of future schizophrenic patients following the pandemic of A2 influenza in 1957 (Mednick *et al*, 1988; O'Callaghan *et al*, 1991*b*); such an effect was not detected in two other studies (Kendell & Kemp, 1989; Bowler & Torrey, 1990). A study of a cohort born in England and Wales in March 1958 did not find a significant association between maternal influenza and schizophrenia (Crow *et al*, 1991).

However, the A2 influenza pandemic was an unusual event. The more important question is whether influenza epidemics consistently have a schizophrenogenic effect. Investigations into the relationship between schizophrenic births and influenza epidemics over a period of years have yielded conflicting results (Watson *et al*, 1984; Torrey *et al*, 1988; Barr *et al*, 1990), possibly because of problems of method and inadequate statistical power. The present study clarifies this relationship by applying more sophisticated statistical methods to a larger data set than hitherto examined.

Method

We obtained, from the Department of Health, the dates of birth of all patients ($n = 14\,830$), born in England and Wales, who were first admitted to hospital in England and Wales between 1970 and 1979, and received an ICD-8 or ICD-9 diagnosis (World Health Organization, 1978) of schizophrenia. The average frequency of schizophrenic births per month from 1939 to 1960 is shown in Fig. 1(a). These monthly counts should reflect the monthly numbers of live births in England and Wales, which we obtained from the Office of Population Censuses and Surveys (OPCS) for 1939 to 1960. As a measure of the prevalence of influenza over time, we obtained the monthly numbers of deaths attributed to influenza in England and Wales from 1938 to 1960 from the Registrar General's *Annual Reviews of Statistics for England and Wales* (Fig. 1(b)).

The inverted U-shape of the curve for schizophrenic births (Fig. 1(a)) can be partly explained by the nature of our sample. Since all individuals in this sample were first admitted between 1970 and 1979, there is a simple relationship between date of birth and age at first admission. For example, an individual born in January 1940 must have his/her first admission between the ages of 30 and 39 years, and one born in January 1950 must have his/her first admission between the ages of 20 and 29 years, to be first admitted between 1970 and 1979. Thus, for each month of each year of birth, the probability of being included in the sample is equivalent to the probability of having a first admission within a corresponding 10-year age range. These probabilities, which we shall call sampling probabilities, for months of birth from 1939 to 1960, were estimated from a distribution of age at first admission for schizophrenia empirically derived from Mental Health Enquiry data on eight regions in England and Wales.

If there were an obvious relationship between influenza deaths and schizophrenic births, then visual inspection of Fig. 1(a) and (b) should be sufficient to detect this. However, if the relationship is obscured by random fluctuations in either or both series of data, then further statistical analyses are required. Since the relationship is not obvious, we proceeded first to graphical methods and then to model fitting.

The principle of our graphical methods was to 'filter out' random fluctuations by averaging. First, we examined whether there was, on average, an increase in schizophrenic births following influenza epidemics. Since the timing of epidemics varied from year to year, we calculated the average numbers of schizophrenic births in successive months following the month when the number of influenza deaths first exceeded 100 (an arbitrary value). These average

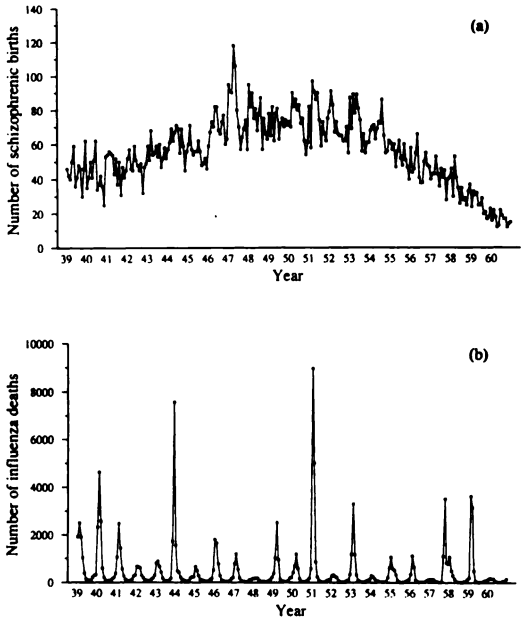

Fig. 1 (a) Average number of schizophrenic births in England and Wales per month, 1939–60. (b) Average number of deaths from influenza in England and Wales per month, 1939–60.

numbers were plotted to obtain an 'average response curve' to influenza epidemics.

Since most influenza epidemics occur in the autumn or winter, and schizophrenic births are more frequent in winter and spring months, there is possible confounding between the effects of influenza and season on schizophrenic births. To resolve this, we classified the 22 years from 1939 to 1960 into 11 high and 11 low influenza years, according to whether the peak of the influenza deaths in that year was above the median value for the 22 years. Since most influenza epidemics occur between November and April, the years were defined to start in November and end in October. The average numbers of schizophrenic births by month were calculated separately for the high and low influenza years and plotted to obtain 'average season-of-birth curves'.

To test the statistical significance and estimate the magnitude of the relationship between influenza deaths and schizophrenic births, we needed to make allowance for the changes in the population birth rate, the upward and then downward trend, and the seasonal variations, in schizophrenic births. Furthermore, it was necessary to regard the numbers of schizophrenic births by month as counts and not as a continuous variable. A generalised linear model (McCullagh & Nelder, 1979) with a Poisson-dependent variable and a logarithmic link to a linear predictor fulfilled all these criteria. The model assumes that there is a time-dependent underlying variable which determines the expected number of schizophrenic births, the actual number of schizophrenics being subject to randomness such that it follows a Poisson distribution around the expected number. The logarithm of the underlying variable is in turn determined by predictor variables which may include the population birth rate, trend and seasonality in schizophrenic births, as well as influenza deaths. Since the number of schizophrenic births was expected to be directly proportional to the number of births in the general population, the logarithm of this variable, with a coefficient of one, was included in the predictor. Such a term in the model is called an 'offset'. The numbers of schizophrenic births by month should also be directly proportional to sampling probabilities, and we therefore included sampling probabilities as another offset in the model. The coefficients of the other variables were estimated from the data by maximum likelihood, and were the parameters of the model. A mathematical description of the model is given in the Appendix.

A measure of how poorly the model fits the data is the scaled deviance, which is minus twice the logarithm of the maximum likelihood of the model. Hypotheses concerning model parameters (i.e. the fitted coefficients) were tested by likelihood ratio tests; the significance of a set of parameters conditional on the presence of another set of parameters was assessed by the decrease in scaled deviance associated with the inclusion of the first set of parameters by a model already containing the second set of parameters. Under the null hypothesis the decrease in scaled deviance has approximately a χ^2 distribution with degrees of freedom equal to the number of additional parameters estimated. When no further significant decrease in scaled deviance was possible, the model was selected as the 'best', and the residuals from this model were examined to check the assumptions of the model. We carried out these procedures on our data by using the program GLIM (Numerical Algorithms Group, 1985).

Results

The 'average response curve' to influenza epidemics (Fig. 2(a)) shows an obvious increase in the average number of schizophrenic births after the start of influenza epidemics. Fig. 2(b) shows that the effect of influenza is not due to its covariation with season, since the spring excess of schizophrenic births is more marked following the 11 winters with an above median number of influenza deaths than the 11 winters with a below median number of influenza deaths.

We fitted a series of generalised linear models with different combinations of predictor variables, always including the offsets. Variables which were not of direct interest (the trend and seasonality of schizophrenic births) were entered first, so that their effects could be allowed for when the effect of influenza deaths was being considered. The general shape of Fig. 1(a) suggested that a linear function of time (measured in years from 1939) would not fit the data, and indeed we found that the reduction in scaled deviance associated with the successive inclusions of linear, quadratic, cubic and quartic terms in time were 50.30, 44.98, 61.99 and 0.14, respectively, each on 1 degree of freedom (d.f.). This indicated that a cubic

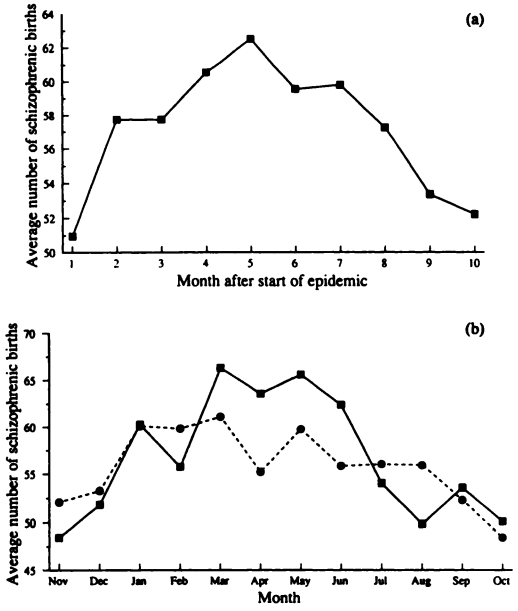

Fig. 2 (a) 'Average response curve' of schizophrenic births to influenza epidemics. (b) 'Average season-of-birth curves' for high (-■-) and low (--●--) influenza years.

polynomial was sufficient to model the long-term variation in schizophrenic births.

Next, we included the 12 months of the year into the model, which reduced the scaled deviance by 38.03 on 11 d.f., indicating significant ($P<0.0005$) seasonal variation in schizophrenic births. We were now able to include influenza deaths as a predictor variable. However, since an influenza epidemic could in principle affect the foetus at any month of gestation, we carried out ten separate analyses, the first relating schizophrenic births to influenza deaths in the same month, the second relating schizophrenic births to influenza deaths one month previously, and so on to the tenth, which related schizophrenic births to influenza deaths nine months previously. Influenza deaths two months and three months before birth reduced the scaled deviance by 4.98 and 5.33 respectively (d.f. = 1, $P=0.02$). We therefore defined the sum of influenza deaths two and three months before birth as a measure of the 'total exposure' to influenza deaths in the vulnerable period. Inclusion of this 'total exposure' alone reduced the scaled deviance by 7.46 on 1 d.f., indicating a significant ($P=0.007$) effect. The removal of the effect of the different months of the year from this model increased the scaled deviance by 27.41 on 11 d.f. ($P<0.005$), indicating that there was significant seasonal variation in schizophrenic births not explained by influenza deaths. The inclusion of the interaction between months and influenza deaths two to three months before birth reduced the scaled deviance by only 8.11 on 11 d.f., confirming that the effect of influenza on schizophrenic births was independent of season.

Table 1
Parameter estimates of 'best' generalised linear model

Parameter	Estimate	s.e.
Constant	-5.373	0.05218
Year	-0.08193	0.01592
Year squared	0.01024	0.001618
Year cubed	-0.0003590	0.00004791
January	(0)	(0)
February	0.01412	0.04010
March	-0.02388	0.03992
April	-0.06893	0.04165
May	-0.04537	0.04042
June	-0.02577	0.03997
July	-0.09419	0.04053
August	-0.09624	0.04098
September	-0.09308	0.04099
October	-0.1390	0.04179
November	-0.07616	0.04169
December	-0.1007	0.04125
Influenza	0.00001403	0.000005158

The 'best' model therefore contained an offset, a cubic polynomial in year, a seasonal effect, and an effect of influenza two to three months before birth. This model had a scaled deviance of 257.53 on 248 d.f., indicating an adequate fit to the data. Furthermore, the serial correlation of the residuals was 0.036, suggesting that any autocorrelation in schizophrenic births was explained by the model. When the coefficient of the offsets was not constrained to unity, its fitted value of 0.778 with a standard error of 0.116 justified the assumption that schizophrenic births were proportional to total population births and sampling probabilities. Residual plots did not suggest any mis-specification of the model.

The estimates and standard errors of the parameters of the best model are presented in Table 1. The polynomial in year describes the long-term variation in the number of schizophrenic births. The zero value for January is due to the arbitrary choice of January to be the standard month against which the effects of other months were evaluated. The estimates for February to December indicate that there was an excess of schizophrenic births in the early months of the year. The estimate for influenza corresponds to an increase by a factor of $e^{0.000014}$ in the number of schizophrenic births for every death attributed to influenza two to three months previously.

The number of deaths attributed to influenza two to three months before birth was therefore significantly associated with an increase in the risk of schizophrenia in later life. The effect of influenza, as indicated by parameter estimates of the final model, corresponds to a 1.4% increase in the number of schizophrenic births for every 1000 deaths attributed to influenza in the two to three months before birth. For each month in the year, the fraction of schizophrenic births accounted for by influenza deaths was estimated by subtracting the number of schizophrenic births predicted by the model if there were no influenza deaths from the number of observed schizophrenic births, and then

Table 2
Months with large residuals

Year	Month	Schizophrenic births		Residual
		observed	fitted	
1939	December	62	41.55	3.172
1940	June	62	45.03	2.528
1940	December	53	40.09	2.038
1941	February	56	42.49	2.072
1942	October	32	46.46	-2.122
1947	April	118	87.09	3.312
1947	August	57	74.90	-2.068
1948	August	87	69.78	2.062
1954	August	86	60.49	3.279

dividing this difference by the number of observed schizophrenic births. The percentages of schizophrenic births accounted for by influenza deaths for the months January through to December were estimated to be 0.60%, 1.26%, 2.75%, 3.83%, 3.19%, 1.68%, 1.61%, 0.22%, 0.11%, 0.07%, 0.13%, 0.38%, respectively. Since the spring excess of schizophrenic births is approximately 10%, about one-third of this could be explained by the prevalence of influenza as measured by monthly influenza deaths.

Table 2 shows the months for which the fit between model and data was poor, as indicated by standardised residuals of less than -2 or greater than 2. Of the 264 months of the study period, only nine months had standardised residuals outside the range (-2 to 2), and seven of these were positive. The most significant residual was for April 1947, following a pandemic of influenza with relatively low mortality (Kilbourne, 1987).

Discussion

Our results indicate that 1–2% of all schizophrenic births can be explained by the number of influenza deaths in the preceding months. However, the true contribution of maternal influenza to schizophrenic births may be far greater than this estimate suggests. Deaths attributed to influenza, which occur mainly in the elderly, are an extremely indirect measure of the prevalence of influenza in pregnant women. Deaths related to influenza are subject to considerable under-reporting; 'hidden influenza deaths' may be greater than those recorded by a factor varying between 1.8 and 8.9 in different epidemics (Curwen *et al*, 1990). These inaccuracies in the data are likely to have diminished the observable association between influenza and schizophrenia.

Our findings suggest that foetuses are susceptible to the 'schizophrenogenic' effect of influenza deaths two to three months before the month of birth. For a full-term birth at the end of a calendar month, this period corresponds to the sixth and seventh months of gestation. However, it is well known that the rise in deaths attributed to influenza occurs some weeks after the start of an epidemic. Taking into account this time lag, the window of susceptibility is probably somewhere between the third and seventh months of gestation.

We hypothesise that influenza infection of the mother during a vulnerable period adversely affects the development of the foetal brain, resulting in damage which predisposes the individual to schizophrenia. The damage is evidenced by the pattern of neuropathological abnormalities observed in schizophrenia (Roberts, 1991): reduced cortical volume, enlarged cerebral ventricles, and abnormal cytoarchitecture in the entorhinal cortex. The possible mechanisms of the effect of influenza include: (a) the direct cytopathic effect of the virus, (b) the effect of a component of the virus, such as neuraminidase (Conrad & Scheibel, 1987), (c) elements of the body's response, such as the production of autoantibodies (Laing *et al*, 1989) and interferons (Taylor-Papadimitriou & Rozengurt, 1985), and (d) non-specific effects of the respiratory infection, such as fever (Edwards, 1986) and hypoxia (Kreusser & Volpe, 1984). Several of these effects are not unique to influenza, and may result from other viral infections. Thus the importance of viral infections to the aetiology of schizophrenia may be far greater than we have demonstrated.

Other possible explanations of the association between influenza and schizophrenia should also be considered. Medications taken during epidemics may adversely affect foetal brain development. Influenza may decrease appetite and cause inadequate nutrition. Influenza may predispose to other infections.

The hypothesis that pre-natal viral infection increases the risk of schizophrenia can explain many previously enigmatic epidemiological features of schizophrenia. The increase in viral infections, including influenza, during urbanisation in the 19th century (Kilbourne, 1987) coincided with the reported increase in admissions for 'insanity' in Western Europe and North America (Torrey, 1980). The fact that viral infections are more prevalent in overcrowded conditions (Kilbourne, 1987) is consistent with the relatively high incidence of schizophrenia in economically deprived, overcrowded urban areas (Torrey & Bowler, 1991), and with the recent decline in the incidence of schizophrenia reported from several countries which have experienced an improvement in living conditions in recent decades (Der *et al*, 1990). Mothers

with young children suffer more viral infections (Hennessy *et al*, 1964), which explains the observation that schizophrenia is commoner in the younger members of large sibships (Farina *et al*, 1963).

This report adds to the current evidence for an association between pre-natal exposure to influenza epidemics and the later development of schizophrenia. We believe that the hypothesis that influenza is causally related to a subset of schizophrenia should be further investigated.

Appendix

The generalised linear model

Let the schizophrenic births in month j of year i be y_{ij}, where $i = 1 \ldots 22$ represents the years 1939 . . . 1960, and $j = 1 \ldots 12$ represents the months January . . . December. Let the number of deaths attributed to influenza at time t be x_t, where $t = 12(i-1)+j$, so that $t = 1$ for January 1939, $t = 2$ for February 1939 . . . $t = 264$ for December 1960. We regard y_{ij} as having a Poisson distribution, which leads to a log-linear model of the form:

$$\log(\mu_{ij}) = \log(b_{ij}p_{ij}) + \sum_{m=0}^{M} \beta_m i^m + \gamma_j + \delta_k x_{t-k}$$

where μ_{ij} is the value predicted for y_{ij} by the model, $\log(b_{ij}p_{ij})$ is an 'offset' allowing μ_{ij} to be directly proportional to b_{ij} and p_{ij}, $\Sigma\beta_m i^m$ is a polynomial in year which allows for long-term variation, γ_j is the effect of month j, and $\delta_k x_{t-k}$ is the effect of influenza deaths k months previously. A series of models incorporating an increasing number of terms were fitted by GLIM.

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