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Epidemiological Evidence that Maternal Influenza Contributes to the Aetiology of Schizophrenia

An Analysis of Scottish, English, and Danish Data

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The epidemiological evidence that the offspring of women exposed to influenza in pregnancy are at increased risk of schizophrenia is conflicting. In an attempt to clarify the issue we explored the relationship between the monthly incidence of influenza (and measles) in the general population and the distribution of birth dates of three large series of schizophrenic patients – 16 960 Scottish patients born in 1932–60; 22 021 English patients born in 1921–60; and 18 723 Danish patients born in 1911–65. Exposure to the 1957 epidemic of A2 influenza in midpregnancy was associated with an increased incidence of schizophrenia, at least in females, in all three data sets. We also confirmed the previous report of a statistically significant long-term relationship between patients' birth dates and outbreaks of influenza in the English series, with time lags of −2 and −3 months (the sixth and seventh months of pregnancy). Despite several other negative studies by ourselves and others we conclude that these relationships are probably both genuine and causal; and that maternal influenza during the middle third of intrauterine development, or something closely associated with it, is implicated in the aetiology of some cases of schizophrenia.

There are sound reasons for suspecting that damage to the foetal brain *in utero* may contribute to the aetiology of schizophrenia, and that maternal influenza may be implicated in this. The excess of schizophrenic births found in the early months of the year in temperate latitudes strongly suggests that some seasonally varying agent, acting at or near the time of birth, is influencing the subsequent development of schizophrenia, and many viral infections have a characteristic seasonal variation. The accumulating evidence that schizophrenic patients have a reduced head circumference at the time of birth (McNeil *et al*, 1993) and the structural abnormalities found post-mortem in the brains of many schizophrenic patients, unaccompanied by any gliosis (Bogerts, 1989), both suggest that, whatever its cause, the damage was inflicted *in utero*. Against this background, the claim by Mednick *et al* (1988) that a Finnish birth cohort which had been in the second trimester of intrauterine life at the time of the 1957 epidemic of Asian (A2) influenza had an increased hospital admission rate for schizophrenia attracted immediate interest.

Unfortunately, the further studies which this report inspired have had conflicting results and the issue has become increasingly controversial. Three different types of study have been employed by those who have tried to test Mednick's hypothesis:

(a) studies of the influence of major epidemics of influenza A – either the 1957 epidemic of 'Asian flu' or the pandemic of 1918–19 – on the incidence of schizophrenia

(b) studies of long-term relationships between fluctuations in the distribution of schizophrenics' birth dates and fluctuations in the reported incidence of, or mortality from, influenza in the general population

(c) studies of populations for which there is documentary evidence that their mothers had influenza, or at least an influenza-like illness, during pregnancy.

Mednick *et al* (1988) studied the birth dates of patients admitted to psychiatric hospitals in Helsinki and showed that the proportion with a diagnosis of schizophrenia was significantly higher in those who would have been in the second trimester of intrauterine life during the five weeks in the autumn of 1957 in which the epidemic of A2 influenza ('Asian flu') was at its height than in those born at other times in the previous six years. Subsequently, Kendell & Kemp (1989) studied two Scottish data sets, one from the city of Edinburgh and the other from Scotland as a whole, using a similar experimental design. The Edinburgh data suggested that those who were in the sixth month of intrauterine development at the time of the 1957 epidemic were subsequently at increased risk of schizophrenia, but this was not confirmed in the much larger Scottish data set. These authors also pointed out that Mednick and his colleagues had been ill advised to study the *proportion* of psychiatric admissions with a diagnosis of schizophrenia. What mattered was the actual numbers of schizophrenics in successive birth cohorts, and if the

Helsinki data were reanalysed on that basis the significant relationship with the dates of the 1957 epidemic disappeared. Torrey *et al* (1991) also failed to find any evidence of an excess of schizophrenic births in association with the 1957 epidemic in a population of 44 000 schizophrenics, from ten American states, born between 1950 and 1959. Subsequently, however, Murray and his colleagues, in London, studied a large but incomplete data set derived from eight of the 15 health regions in England and Wales and found a significant excess of schizophrenics with birth dates early in 1958, corresponding to exposure to the 1957 epidemic in the fifth month of pregnancy (O'Callaghan *et al*, 1991*a*).

Only one study of the influenza pandemic of 1918–19 has been published, although this was the greatest and most virulent influenza epidemic of modern times. Kendell & Kemp (1989) examined the dates of birth of Scottish schizophrenics born between 1913 and 1922 and could find no clustering of birth dates attributable to the epidemic. Their case material was limited, however, to patients who had been in hospital after 1963, that is at a time when they would have been in their 40s or 50s.

After their original Helsinki study, Mednick *et al* (1988) examined the relationship between the dates of birth of 7239 Danish schizophrenics born between 1911 and 1950 and monthly notifications of influenza in Denmark during those 40 years (Barr *et al*, 1990). They found a highly significant relationship between influenza notifications and schizophrenic births with time lags corresponding to the sixth and seventh months of gestation. However, although the relatively simple statistical method they used made allowance for the spring excess of schizophrenic births, it made no allowance for the rising numbers of schizophrenics in their patient population in successive decades, and this may well have biased their findings. More recently, Murray and his colleagues have reported a similar study based on 14 830 English schizophrenics born between 1939 and 1960, and first admitted to hospital between 1970 and 1979 (Sham *et al*, 1992*a*). Although they had to use monthly numbers of deaths from influenza as an index of fluctuations in incidence, they employed more appropriate statistical techniques than Barr *et al* (1990). They used a generalised linear model with a Poisson-dependent variable and a logarithmic link to a linear predictor, and found a significant relationship between the monthly residuals for schizophrenic births and monthly influenza mortality with a time lag of -2 or -3 months, again indicating an influence during the sixth and seventh months of gestation.

One of the major weaknesses of investigations of birth cohorts exposed to maternal influenza *in utero* is that there is no way of knowing which individuals' mothers did develop influenza, for it is impossible to obtain accurate information in retrospect over 20 years later. By good fortune, the National Child Development Study (NCDS) was based on all births in England, Scotland or Wales from 3–9 March 1958, five months after the 1957 influenza epidemic, and within the four weeks in which O'Callaghan *et al* (1991*a*) found a highly significant increase in schizophrenic births. As maternal influenza during pregnancy had also been documented by midwives shortly after birth, Crow and his colleagues were able to compare the incidence of schizophrenia in members of the NCDS cohort whose mothers had contracted influenza during pregnancy with those whose mothers had not at a time when the effects of the 1957 epidemic should have been maximal (Crow *et al*, 1991; Crow & Done, 1992). Only three of the 945 cohort members with documented maternal influenza in the second trimester of pregnancy had a history of admission to a psychiatric hospital, even with broadly defined schizophrenia (0.3%), compared with 50 of the 14 153 cohort members with no history of exposure (0.4%). However, this apparently clear-cut negative result has been criticised by Murray and his colleagues on the grounds that diagnoses derived purely from case-note information are unreliable, and because the proportion of mothers recorded as having influenza during their pregnancy (5.9% in the second trimester and 12.5% overall) was so low as to suggest serious under-recording (O'Callaghan *et al*, 1991*b*).

The series of studies reported here was conceived against this background. We assumed that confusion and controversy would continue until the same relationships were found in different data sets from different countries. For this reason we explored the relationship between fluctuations in the month of birth of people developing schizophrenia and the timing of epidemics of both influenza and measles in large series of English, Scottish and Danish schizophrenics using the same statistical methods in all three. The rationale for studying measles as well as influenza was to provide a type of control. Although there is no doubt that infection with the measles virus can result in brain damage in both children and adults, measles is rarely seen in pregnant women because the great majority of them, and also their new born infants, are protected by antibodies acquired from infection or immunisation in childhood. Consistent relationships should not, therefore, be found between the birth dates of schizophrenics and outbreaks of measles; and if they were found they would cast doubt on the aetiological significance of analogous relationships found for outbreaks of

influenza. In addition, we explored the relationships between fluctuations in the schizophrenic birth rate and variations in seasonal temperature in these three data sets. We did this because many viral infections, including influenza, have a well marked seasonal variation and because there have been reports of statistically significant relationships between fluctuations in winter temperature and birth rates for schizophrenia (e.g. Hare & Moran, 1981; Watson *et al*, 1984). In a previous study of our Scottish series we had also found a striking relationship between the magnitude of the spring excess of schizophrenic births and the mean temperature the previous autumn (Kendell & Adams, 1991).

Method and results

The three schizophrenic populations

The Scottish patients

The derivation of the series of Scottish schizophrenics has been described previously (Kendell & Adams, 1991). Briefly, it was derived from the total population of 38 363 patients admitted to psychiatric hospitals in Scotland between 1963 and 1989 who were either current (mostly long-term) in-patients with a diagnosis of schizophrenia or had received a discharge diagnosis of schizophrenia on at least one occasion (schizophrenia was defined as ICD-9 codes 295.0–295.9; World Health Organization, 1978). The series was restricted to patients born between 1 January 1932 and 31 December 1960 for two reasons: because births in Scotland were only recorded quarterly rather than monthly before 1932 it was not possible to calculate the monthly number of schizophrenics per 10 000 births before then; and too few people born after 1960 would have reached the main risk period for schizophrenia by 1989 when the data were extracted from the register.

Because it is commonplace for patients to be given a diagnosis of schizophrenia during one hospital admission and some other diagnosis during another, and it is impossible without access to the case notes to form an opinion about the validity of either diagnosis, we defined schizophrenia in two alternative ways in these Scottish data – patients receiving a discharge diagnosis of schizophrenia on any occasion (broad criteria, $n = 16\,960$) and patients receiving a discharge diagnosis of schizophrenia on at least two different occasions (narrow criteria, $n = 8229$). Long-stay in-patients with a diagnosis of schizophrenia were included in both; the 'narrow criteria' population was that studied previously by Kendell & Adams (1991).

The English patients

It was not possible to obtain a comparable series of English schizophrenics for two reasons. The Department of Health in England ceased collecting comprehensive data on psychiatric in-patients when the Mental Health Enquiry was terminated in 1974; and births in England were not recorded by month of birth until 1939, eight years later than in Scotland. Fortunately, one of us (EHH) had previously obtained from the then Department of Health and Social Security the dates of birth of all first ever admissions to English and Welsh mental hospitals between 1970 and 1979 who had been born in England or Wales (see Hare & Moran, 1981). Of these patients, 22 021 had been born between January 1921 and 1960, were aged 15–54 years at the time of admission, and had a diagnosis of schizophrenia (defined as ICD-8 codes 295.0–295.9; World Health Organization, 1967). Although, as explained, it was not possible to calculate the monthly number of schizophrenics per 10 000 live births in England before 1939, the 1971 census provided the dates of birth by month for a 1% sample of the population born in England and Wales. It was therefore possible to calculate a monthly rate for schizophrenia relative to the population at risk in 1971, and this is preferable to a rate relative to live births because distortions produced by varying numbers of infants and children dying before entering the risk period for schizophrenia are eliminated.

The Danish patients

The Institute of Psychiatric Demography in Aarhus, Denmark, holds a register of all patients treated for mental illness in Denmark, either as an in-patient (since 1 April 1969) or a day patient (since 1 April 1975). From this register we obtained details of all Danes known to the register on 31 December 1991, with a discharge diagnosis of schizophrenia (ICD-8 codes 295.0–295.9), who had been born between 1 January 1911 and 31 December 1965. Schizophrenia was defined in two alternative ways: patients with a main discharge diagnosis of schizophrenia on at least one occasion (broad diagnostic criteria; $n = 18\,723$); and patients with a main discharge diagnosis of schizophrenia on their most recent admission (narrow diagnostic criteria; $n = 14\,260$).

Between- and within-month variation in the 'incidence' of schizophrenia

In the Scottish data the number of schizophrenics per 10 000 live births was calculated for the 29 years from January 1932 to December 1960 (348 months). In the English and Welsh data the number of schizophrenics per 10 000 population was calculated for the 40 years from January 1921 to December 1960 (480 months). As births in Denmark were recorded by month from 1911, it was possible to calculate the number of Danish schizophrenics per 10 000 population for the whole 55 years from January 1911 to December 1965 (660 months). For convenience, these rates will be referred to as the 'incidence' of schizophrenia per month, and the data from England and Wales will be referred to as English data.

In all three data sets the log of the monthly rate was plotted against time and fitted to a polynomial in time using iteratively weighted least squares. A constant monthly effect was also estimated for each individual month to allow for seasonality. Fitting was done by maximum likelihood methods because variation about the line was Poisson, not

normal, in distribution. Because of the differences in the derivation of the three data sets the shapes of these fitted lines differed considerably in the three countries. (The Scottish patients were current in-patients or discharges at any time from 1963 to 1989; the English cohort was restricted to first admissions between 1970 and 1979 who had also been born in the country; and the Danish patients were in-patients or day patients between April 1969 and December 1991.) For our purposes, however, the shape of the line is unimportant. Indeed, the fitted lines can be regarded as a convenient means of adjusting all the data to a standard age, thereby eliminating age incidence effects. The crucial variables are the residuals about the fitted lines, for these measure the deviation of individual monthly 'incidence' rates from the expected value, and should reflect the influence, if any, of factors other than age on the monthly rate.

The pattern of month-to-month or between-month variation in the 'incidence' of schizophrenia in the three populations is shown in Figure 1. All three show an excess of schizophrenic births in the winter or spring and a corresponding deficit in summer or autumn – the well known season of birth effect (Bradbury & Miller, 1985). The Scottish patients have the most interesting and abnormal distribution. There is a significant excess of births in the four consecutive months February, March, April, and May, accompanied by a significant increase in 'incidence' between January and February and a significant fall between May and June. There is also excessive ($P<0.05$) within-month variation (i.e. from year to year between 1932 and 1960), whether this is assessed by the χ^2 test or by Cox's dispersion statistic, in March, April and May, three of the four months in which the 'incidence' of schizophrenia is significantly raised. This pattern was substantially the same whether the broad or the narrow definition of schizophrenia was used. The pattern with the latter and the means of testing for overdispersion have already been reported (Kendell & Adams, 1991).

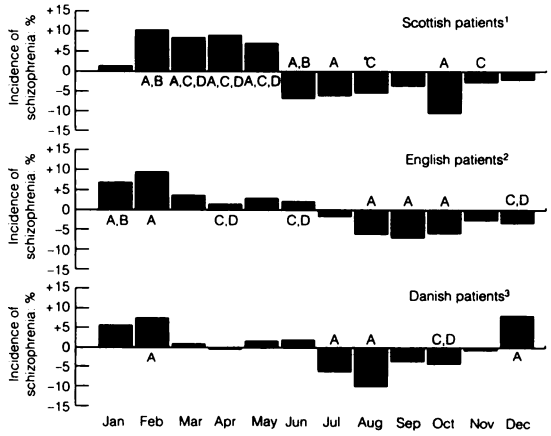

Fig. 1 Between- and within-month variation in the 'incidence' of schizophrenia in Scottish, English, and Danish cohorts (A = significant deviation from mean monthly incidence; B = significant change in incidence from preceding month; C = excessive within-month (i.e. year to year) variation (χ^2 test); D = excessive within-month (i.e. year to year) variation (dispersion statistic); $P<0.05$ in all cases).
1. Scottish patients: $n = 16960$ (1932–60).
2. English patients: $n = 22021$ (1921–60).
3. Danish patients: $n = 14260$ (1911–65).

The English patients show a significant excess of schizophrenic births in only two months – January and February – and although there is a significant increase in 'incidence' between December and January, a month earlier than in Scotland, the season of raised 'incidence' does not have a sudden end; it lingers until June. More importantly, and disappointingly, the months in which within-month (i.e. year to year) variation is excessive (April, June, and December) are not those in which 'incidence' is significantly raised; nor are they consecutive months.

The Danish patients show a distribution of 'incidence' which is closer to that of the English than of the Scottish patients; but they show less between-month or within-month variation than either, despite the fact that Denmark has hotter summers and colder winters than either Scotland or England. Although the 'incidence' of schizophrenia is significantly raised in both December and February there is no sudden month-to-month change in 'incidence', and October is the only month in which within-month variation is excessive. As in Scotland, the pattern was substantially the same whether the broad or the narrow definition of schizophrenia was used.

Long-term relationships between the 'incidence' of schizophrenia and outbreaks of influenza and measles

If maternal influenza during pregnancy contributes to the aetiology of schizophrenia there ought to be detectable relationships between the timing of outbreaks of influenza in the general population and the birth dates of schizophrenics, and indeed such relationships have been reported in Denmark (Barr *et al*, 1990) and England (Sham *et al*, 1992*a*). Using a variety of different statistical methods we examined the relationship between the monthly 'incidence' of schizophrenia and outbreaks of both influenza and measles in all three populations.

In the Danish series we were able to examine the relationship between the monthly 'incidence' of schizophrenia and the reported monthly incidences of influenza and measles in the Danish population, because the Danish State Serum Institute has kept comprehensive records of monthly notifications of a wide range of infections ever since the 19th century. As no comparable incidence figures are available for Scotland or England for the requisite time periods, we used monthly mortality figures for influenza and measles (obtained from the Annual Reports of the Registrars General of the two countries) instead. Because the introduction of antibiotics greatly reduced mortality from both infections between the 1920s and 1960s, and so changed the relationship between incidence rates and mortality rates, we used the ratio of actual mortality to average mortality over a moving five-year period instead (2.5 years before and 2.5 years after the month in question) as an index of population incidence.

The first method of analysis was an attempt to detect relationships between the monthly 'incidence' of

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schizophrenia and fluctuations in the incidence of influenza and measles over the whole time period available, that is 1932–60 for the Scottish patients, 1921–60 for the English patients, and 1911–65 for the Danish patients. We used a simple regression and included the indices of the incidence of influenza or measles described above as covariates when fitting the age curve for the 'incidence' of schizophrenia. The results are shown in Table 1 in the form of standardised regression coefficients for a series of time lags ranging from −8 (the first month of pregnancy, assuming that birth always occurs in the ninth month of pregnancy) to +2. Apart from a few scattered negative relationships, implying an unusually *low* 'incidence' of schizophrenic births in association with outbreaks of infection, the only statistically significant relationships obtained for either influenza or measles are for influenza in the English patients with time lags of −2 and −3 months (i.e. in the sixth or seventh months of pregnancy). There is, however, no analogous relationship in the Scottish or Danish series, using either broad or narrow diagnostic criteria for schizophrenia. Indeed, in the Scottish series almost all the regression coefficients are negative.

Further analyses were based on comparisons of the residuals from the fitted line for the 'incidence' of schizophrenia of months associated with an outbreak of influenza or measles (using a variety of different ways of defining an 'outbreak') with those of months associated with a low population incidence of these infections. The first such method involved identifying times of rapidly increasing or decreasing population incidence of infection (usually the beginning or the end of an outbreak) by identifying pairs of months 30 days apart (i.e. January and March, September and November, etc.) for which the difference in the reported number of cases exceeded some arbitrary

Table 1

Simple regression: standardised regression coefficients representing the influence of the monthly incidence of influenza or measles on the monthly 'incidence' of schizophrenia

Time lag: months	Influenza		Measles	
Scottish patients 1932–60	$n=8229$	$n=16960$	$n=8229$	$n=16960$
−8	−0.97	−0.95	−0.81	−0.78
−7	0.27	−0.36	−0.19	−1.09
−6	−1.48	−2.00*	−0.45	−1.51
−5	−1.44	−1.42	0.58	−0.53
−4	−1.34	−1.71	−0.15	−1.30
−3	−1.28	−1.31	0.53	−0.56
−2	−1.49	−0.91	0.63	−0.57
−1	−1.81	−1.34	1.20	0.18
0	−1.09	−0.49	1.21	0.52
+1	−0.81	−0.93	0.62	0.36
+2	−0.61	−1.46	−0.64	−0.97
English patients 1921–60				
−8		0.93		−0.99
−7		0.63		−0.78
−6		−0.95		−1.40
−5		−0.74		−0.65
−4		0.90		−0.09
−3		2.62*		0.16
−2		2.79*		1.26
−1		1.58		1.17
0		0.09		0.50
+1		1.07		−0.25
+2		0.98		−0.61
Danish patients 1911–65	$n=14260$	$n=18723$	$n=14260$	$n=18723$
−8	−0.49	0.21	0.54	0.64
−7	0.11	0.03	0.00	0.23
−6	0.38	−0.37	−0.13	0.47
−5	0.22	0.24	−1.03	−0.19
−4	0.80	0.87	−1.53	−0.48
−3	1.12	1.07	−2.13*	−0.71
−2	−0.29	−0.48	−2.20*	−0.84
−1	−0.17	−0.16	−1.76	−0.75
0	−0.91	−0.56	−1.63	−0.64
+1	−0.76	−0.52	−1.30	−0.08
+2	0.85	0.65	−0.45	0.80

*Statistically significant at $P<0.05$.

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figure. Because this figure was arbitrary it was given five alternative values. In the case of influenza in Denmark, for example, it was given five values ranging from 5000 to 25 000 cases per month and the analysis was performed with each. The effect on the 'incidence' of schizophrenia of these sudden changes in the incidence of influenza or measles was estimated by creating an artificial covariate with a value of +1 for the high incidence month and −1 for the preceding or following low incidence month. (All other months were given a value of zero.) When this variable is included in the regression the regression coefficient becomes a measure of the difference in the 'incidence' of schizophrenia between the two contrasted sets of months. The same procedure was used for periods of increasing and decreasing incidence and the two were also combined to provide a third regression coefficient covering both. The results of one set of these five alternative analyses (the middle of the range in each case) are shown in Table 2. In most respects they confirm the results of the original simple regression described above and in Table 1.

As before, significant positive relationships emerge in the English cohort between outbreaks of influenza and a raised 'incidence' of schizophrenia with time lags of −2 and −3, but not with any other time lag, and not with measles. Again, however, there is no analogous relationship in the Scottish or Danish data. Indeed, influenza generates no significant relationships with any time lag in either. In the Scottish data, measles generates a significant, positive relationship with a time lag of zero (and also an inexplicable reversing relationship with a lag of −5), but nothing comparable was to be found in the Danish data. Although Table 2 only shows the results obtained with one of the five

Table 2
Standardised regression coefficients representing the difference in the 'incidence' of schizophrenia between pairs of months in which the incidence of influenza or measles is increasing or decreasing

Time lag: months	Influenza			Measles		
	Increasing	Decreasing	Combined	Increasing	Decreasing	Combined
Scottish patients (n = 16 960)						
−8	−0.06	−1.18	−0.76	0.05	1.12	0.84
−7	−0.51	1.75	0.68	1.44	0.06	1.05
−6	1.03	−0.09	0.68	−0.98	−1.00	−1.39
−5	−0.01	−0.36	−0.22	−3.03*	2.78*	−0.37
−4	−1.43	−1.17	−1.71	0.31	−1.47	−0.74
−3	0.03	−0.51	−0.29	0.02	−2.27*	−1.47
−2	−0.19	0.92	0.43	−0.15	0.75	0.38
−1	0.56	−0.43	0.12	0.47	0.18	0.46
0	1.91	−0.10	1.23	2.85*	0.76	2.59*
+1	−0.41	1.02	0.38	0.71	0.74	1.02
+2	−1.61	0.20	−0.95	−2.06*	0.54	−1.07
English patients						
−8	1.74	0.72	1.59	0.41	−1.00	−0.28
−7	0.23	−0.56	−0.24	−1.04	1.18	−0.12
−6	−1.38	−1.67	−2.00*	−1.41	1.19	−0.44
−5	−1.34	−1.08	−1.59	−0.62	−1.34	−1.24
−4	−0.41	0.91	0.34	1.96	−0.07	1.53
−3	0.93	2.97*	2.59*	1.90	−0.69	1.12
−2	0.41	3.36*	2.55*	0.75	−1.15	−0.06
−1	−0.51	0.37	−0.06	1.33	1.19	1.72
0	−0.52	−3.50*	−2.76*	−1.22	0.26	−0.79
+1	0.09	−2.87*	−1.96	−1.82	0.67	−1.00
+2	1.45	0.03	0.92	−0.72	1.49	0.33
Danish patients (n = 14 260)						
−8	−1.31	−0.95	−1.31	0.19	−0.67	−0.34
−7	−0.25	−0.64	−0.52	−0.39	0.38	−0.01
−6	0.77	0.85	0.94	1.16	1.57	1.87
−5	0.22	1.29	0.87	1.61	−1.03	0.43
−4	0.63	−0.30	0.20	0.36	−1.29	−0.61
−3	0.58	−0.28	0.17	−1.61	0.85	−0.56
−2	0.43	−0.17	0.15	−2.22*	−0.54	−1.91
−1	−0.55	−1.67	−1.29	−0.15	0.18	0.02
0	−1.43	−1.27	−1.56	0.08	−0.46	−0.26
+1	−0.53	1.03	0.31	−0.79	−1.84	−1.82
+2	0.46	1.42	1.10	0.05	0.43	0.34

*Statistically significant at $P < 0.05$.

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alternative definitions of an outbreak of influenza or measles, and all five analyses were also performed with the narrow as well as the broad Scottish and Danish definitions of schizophrenia (and with the Scottish data for male and female patients separately as well), the results shown here are representative. When all these various analyses are considered together there is a consistent tendency for the English patients to generate significant relationships with influenza with time lags of −2 and −3 and for the Scottish patients to generate positive coefficients which are frequently large enough to be statistically significant with a time lag of −7 with influenza and of 0 or +1 with measles. The Danish patients, on the other hand, yielded no significant relationships with either influenza or measles with any time lag.

The third method of analysis involved comparing months in which the population incidence of influenza or measles was highest with the remainder. This was done by creating a binary variable for which the months with the highest incidence of infection were given a score of +1 and all other months a score of zero. If the 'incidence' of schizophrenia is higher in these high incidence of infection months a significant regression coefficient will be obtained when this binary variable is included in the regression as a covariate. As before, several alternative cut-off points were used – the highest 2.5% versus the other 97.5%, the highest 5% versus 95%, the highest 10% versus 90%, the highest 20% versus 80%, and the highest 50% versus 50%. The results are summarised in Table 3. Once again, the English series shows significant relationships with influenza with time lags of −2 and −3 (i.e. in the sixth and seventh months of pregnancy) and also, less convincingly, with a lag of −1, although it should be noted that there are also significant

Table 3
Standardised regression coefficients representing the difference in the 'incidence' of schizophrenia between months with a high and with a low incidence of influenza or measles

Time lag: months	Influenza			Measles		
	20% v. 80%	10% v. 90%	5% v. 95%	20% v. 80%	10% v. 90%	5% v. 95%
Scottish patients (broad diagnostic criteria, $n=16\,960$)						
−8	0.93	−0.07	1.30	−0.16	2.05*	1.93
−7	0.20	0.59	1.87	−0.42	1.19	1.50
−6	−1.11	−0.77	−0.19	−0.46	0.31	0.85
−5	−0.90	−1.24	−1.47	−0.26	−0.38	−0.58
−4	−1.95	−1.45	0.70	0.26	0.13	0.28
−3	1.38	−1.33	0.20	0.31	2.23*	0.65
−2	−2.31*	1.22	1.60	−0.01	−0.20	1.46
−1	0.56	−1.73	−1.02	1.87	1.40	−0.68
0	−1.15	0.17	−0.07	0.15	0.49	0.83
+1	0.32	−0.07	0.51	1.49	1.32	1.64
+2	−0.13	−0.01	−1.92	−0.97	0.99	1.32
English patients						
−8	0.24	0.43	0.78	−0.22	−0.42	−0.42
−7	−0.81	−0.42	0.13	−0.42	0.91	−0.36
−6	−0.73	−0.90	−1.82	0.08	0.33	−0.44
−5	−0.55	−1.96	−0.78	−1.37	0.83	−0.75
−4	−0.18	0.75	0.52	0.29	1.28	1.17
−3	3.02*	2.06*	1.44	1.19	2.22*	2.59*
−2	1.27	3.20*	2.58*	2.34*	1.70	2.17*
−1	2.77*	−0.96	−0.09	2.41*	3.32*	0.81
0	0.67	0.53	−0.33	−0.13	2.29*	2.27*
+1	−0.35	0.81	0.16	−0.45	0.37	0.01
+2	−0.11	0.01	1.27	−2.12*	−1.66	−0.09
Danish patients (narrow diagnostic criteria, $n=14\,260$)						
−8	0.02	−0.99	−0.38	1.54	−0.13	−0.12
−7	−0.40	0.38	0.28	0.35	0.44	−0.34
−6	0.04	0.81	0.66	1.15	0.19	−1.79
−5	2.23*	0.23	1.40	−0.70	0.34	−1.11
−4	−0.28	0.77	0.55	−1.80	0.03	−1.72
−3	0.83	0.74	1.15	−2.27*	−1.75	−2.30*
−2	−0.02	−0.72	−1.42	−2.23*	−1.51	−2.40*
−1	−0.27	−1.22	−0.84	−1.30	0.34	−1.32
0	−1.02	−0.85	−1.13	−0.48	−0.05	−1.61
+1	−0.14	0.02	−1.33	−0.09	−0.64	−1.78
+2	0.20	0.50	1.12	−0.13	−0.29	−0.45

*Statistically significant at $P<0.05$.

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relationships with measles with time lags of −3, −2, −1, and 0. The Scottish series showed no significant relationships with influenza, with either the broad or the narrow diagnostic criteria. With measles, there were a few significant relationships with time lags of −3, 0 and +1, particularly with the narrow definition of schizophrenia. The Danish series produced one isolated significant relationship with influenza – with the narrow diagnostic criteria and a time lag of −5. For measles there were significant, negative relationships with time lags of −2 and −3, but only with the narrow diagnostic criteria.

In summary, all three methods of analysis show a positive relationship in the English patients between the 'incidence' of schizophrenia and outbreaks of influenza with time lags of −2 and −3 months. But no analogous relationship can be found, even weakly or inconsistently, in the Scottish or Danish patients. There are several other statistically significant relationships, negative as well as positive, between the 'incidence' of schizophrenia and the population incidence of influenza or measles in all three series. With so many different relationships being explored (even the summary data shown in Tables 1 to 3 contain over 500 regression coefficients), this is hardly surprising. It is instructive to examine the relationships with measles, which were included as a form of control. There are actually more statistically significant, positive regression coefficients in Tables 1 to 3 between the 'incidence' of schizophrenia and measles than there are for influenza (13 v. 12). But those for influenza are nearly all with time lags of −2 or −3, whereas those for measles are much more scattered, and often accompanied by similar numbers of negative coefficients. The only relationship which emerges with any consistency, apart from that with influenza in the English data, is a tendency for both the English and the Scottish data to generate positive relationships between the 'incidence' of schizophrenia and the population incidence of measles with a time lag of zero.

The 1957 'Asian flu' epidemic

The chances of demonstrating the effect of a single, well documented major epidemic on the 'incidence' of schizophrenia are probably better than those of demonstrating the influence of a series of lesser epidemics over a period of many years, and indeed a significant effect attributable to this 1957 epidemic has already been reported in Helsinki (Mednick *et al*, 1989) and England (O'Callaghan *et al*, 1991*a*).

All three series were investigated using a similar approach to that described by O'Callaghan *et al* (1991*a*), although these authors were forced to examine the crude numbers of schizophrenics born in successive four-week periods rather than rates, as their patients were not drawn from a finite population. The age curve for the 'incidence' of schizophrenia was derived in the same way as before for the four years 1956–59. The 'incidence' of schizophrenia in each of the 14 months from July 1957 to August 1958 was then compared with the 'incidence' in the three other corresponding months in that four-year period (i.e. July 1957 v. July 1956, 1958 and 1959; January 1958 v. January 1956, 1957 and 1959, etc.) by introducing a covariate with a score of +3 for the index month and of −1 for the other three. This gives a comparison which is adjusted for year-to-year changes in the 'incidence' of schizophrenia as well as for month-to-month variation. The *t*-values for the equality of these rates are shown in Table 4. Five of the nine statistically significant, positive differences (i.e. those in which 'incidence' is higher in the index month than in the other three) are in March 1958. Two of the others are in February 1958 and one in April 1958. In the English patients the only significant *t*-value is for March 1958,

Table 4
Comparisons between the 'incidence' of schizophrenia in July 1957 to August 1958 and the corresponding control months in 1956–59

		t-values for equality of rates												
		English patients	Scottish patients						Danish patients					
			Broad criteria			Narrow criteria			Broad criteria			Narrow criteria		
Month	Year		Male	Female	Both	Male	Female	Both	Male	Female	Both	Male	Female	Both
Jul	1957	1.94	0.11	−0.92	−0.50	0.06	−0.80	−0.44	−1.68	−0.33	−1.58	−2.16*	−0.30	−1.99
Aug	1957	1.26	−0.02	−2.16*	−1.37	0.08	−1.45	−0.83	0.23	1.52	1.03	0.36	0.88	0.76
Sep	1957	0.60	−0.47	0.19	−0.23	−0.87	0.99	−0.04	−0.20	0.42	0.07	0.14	1.00	0.64
Oct	1957	−1.45	1.15	−1.33	0.06	0.71	−1.52	−0.38	0.63	−0.57	0.20	−0.42	−0.72	−0.75
Nov	1957	−0.08	0.80	−0.24	0.48	0.50	0.39	0.64	0.29	1.34	0.88	0.53	−1.72	−0.48
Dec	1957	0.02	0.87	0.36	0.91	1.28	1.17	1.74	−0.29	0.71	0.15	−0.13	0.84	0.31
Jan	1958	1.25	0.79	−0.76	0.14	0.42	−2.18*	−1.01	−0.06	0.95	0.48	−0.14	−0.56	−0.44
Feb	1958	−0.93	−2.09*	0.61	−1.22	−1.98	0.32	−1.35	−0.62	2.43*	0.87	−0.25	2.37*	1.10
Mar	1958	2.49*	1.18	2.75*	2.66*	1.84	2.98*	3.30*	1.45	0.94	1.72	1.50	1.13	1.88
Apr	1958	−0.17	−1.86	−1.50	−2.38*	−1.74	−1.20	−2.10*	−0.50	1.40	0.39	−0.20	2.19*	1.06
May	1958	−0.46	−0.23	0.43	0.11	0.02	−0.31	−0.17	−0.31	−0.66	−0.63	0.01	0.70	0.41
Jun	1958	−0.62	2.08*	0.22	1.77	0.68	−1.89	−0.61	−1.22	0.79	−0.54	−1.96	0.38	−1.39
Jul	1958	0.24	−1.03	1.70	0.27	−0.87	1.28	0.10	0.63	−0.39	0.30	1.44	−0.51	0.93
Aug	1958	−0.62	−0.07	−0.31	−0.25	−0.10	−0.44	−0.35	−0.26	−0.07	−0.25	−0.05	−0.42	−0.26

*Statistically significant at $P<0.05$.

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almost identical to the increase in the schizophrenic birth rate between 15 February and 14 March reported previously by O'Callaghan *et al* (1991*a*). In the Scottish patient population there are also highly significant ($P<0.01$) *t*-values for March 1958 with both the narrow and the broad diagnostic criteria, both for women, and for men and women combined. In the Danish patients significant positive *t*-values are generated only by women. In February 1958 with the narrow diagnostic criteria, and in both February 1958 and April 1958 with the broad criteria. We were unable to examine men and women separately in our English patients as sex had not been recorded when the data were originally collected, but O'Callaghan *et al* (1991*a*) commented that the difference between index and control years in their study was significant for women ($P=0.011$) but not for men ($P=0.227$). As the same striking sex difference emerges in all three countries it is difficult to dismiss this as a chance finding.

In both England and Scotland influenza deaths were greatest in October 1957, and the epidemic was at its height between mid-September and late October 1957. In Denmark, the epidemic occurred a few weeks later and reported cases were maximal in October and November 1957. This implies a time lag of −5 months (the fourth month of intrauterine development) in England and Scotland and of either −3 or −5 months (the sixth or fourth months of intrauterine development, but the evidence is stronger for the former) in Denmark.

The 1918–19 pandemic

A similar analysis was performed with the Danish data for the six-year period from 1916–21. As the pandemic occurred in two waves starting in July 1918 and continuing until March 1919, the 'incidence' of schizophrenia in each of the 19 months from June 1918 to December 1919 was compared with the average 'incidence' in the corresponding months in 1916, 1917, 1920, and 1921. Despite having substantial numbers of patients with birth dates in those six years (an average of 239 per year) none of the *t*-values approached statistical significance with either the broad or the narrow criteria (see Table 5). It was not possible to do the same with the English or Scottish data because the birth rate was only recorded quarterly before the 1930s in these countries. However, it has already been shown in the Scottish cohort that there is no increase in the annual 'incidence' of schizophrenia attributable to the 1918–19 pandemic (Kendell & Kemp, 1989).

Temperature

In a previous study of the Scottish series we had found a striking relationship between the 'incidence' of schizophrenia in February, March, April, and May (the four months in which the 'incidence' of schizophrenia was highest and the year-to-year variation greatest – see Fig. 1) and the mean temperature six months before; the lower the temperature in the autumn the higher the 'incidence' of schizophrenic births the following spring (Kendell & Adams, 1991). For this reason we looked for an analogous relationship in our English and Danish data sets, using the appropriate mean monthly temperatures and mean maximum and minimum temperatures for each country. We also searched for other possible relationships between monthly variations in the incidence of schizophrenia and monthly variations in temperature. The results were disappointing. We could not find the striking relationship we had found in our Scottish data in the English or Danish data, and although a number of other statistically significant time-lagged relationships between temperature and schizophrenic births emerged in individual data sets, none of these could be replicated in either of the other two.

Table 5
Comparisons between the 'incidence' of schizophrenia in June 1918 to December 1919 and the corresponding control months in 1916–17 and 1920–21 (Danish patients)

Month	Year	*t*-values for equality of rates $n=14\,260$	$n=18\,723$
Jun	1918	−0.06	0.09
Jul	1918	−0.06	0.40
Aug	1918	0.69	0.72
Sep	1918	−0.88	−0.63
Oct	1918	−1.38	−1.15
Nov	1918	−0.14	0.08
Dec	1918	−0.96	−0.87
Jan	1919	0.50	1.04
Feb	1919	0.66	0.32
Mar	1919	0.14	−0.07
Apr	1919	0.26	−0.17
May	1919	−0.66	−1.05
Jun	1919	0.50	0.72
Jul	1919	0.18	0.20
Aug	1919	0.31	−0.18
Sep	1919	1.40	1.40
Oct	1919	−1.71	−1.02
Nov	1919	−0.05	−0.56
Dec	1919	−0.81	−1.00

Discussion

Our original motive for studying three large schizophrenic data sets simultaneously, and in a variety of different ways, was the hope that we would find similar relationships in all three: either the same relationship between the timing of outbreaks of influenza and the 'incidence' of schizophrenia in all three, or no significant relationships at all. Despite some inconsistencies we believe that we have largely succeeded.

The results are most clear cut for the studies focused on the 1957 epidemic of 'Asian' (A2) influenza. Previous investigators had reported an increased hospital admission rate for schizophrenia in association with this epidemic in Helsinki (Mednick *et al*, 1988), England (O'Callaghan *et al*, 1991*a*) and Edinburgh (Kendell & Kemp, 1989), but not in the USA (Torrey *et al*, 1991), or Scotland as a whole

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(Kendell & Kemp, 1989). The temporal relationship between the peak of the epidemic and the birth dates of the at-risk cohort suggested a pathogenic effect either in the second trimester (Helsinki), or the fifth (England) or sixth (Edinburgh) month of pregnancy. We have now confirmed these reports by finding a sharply defined excess of schizophrenic births in March 1958 in both England and Scotland, suggesting a pathogenic effect in the fourth month of pregnancy, and a similar excess of schizophrenic births in February and April 1958 in Denmark, suggesting a pathogenic effect in the fourth or sixth month of pregnancy (the epidemic was at its height a few weeks later in Denmark).

Finding a statistically significant excess of schizophrenic births in relation to this 1957 epidemic in Scotland when Kendell & Kemp (1989) had failed to do so using the same data obviously requires some comment. The statistical methods used in the two studies were different and so were the controls. Kendell & Kemp's analysis was based on numbers of births per month rather than birth rates relative to the general population, and their controls were the two previous years rather than a combination of earlier and later years. Moreover, their study did generate a statistically significant excess of schizophrenic births in women exposed in the fifth month of pregnancy ($P<0.05$ for a one-tailed t-test), but they dismissed this as a chance finding because it did not hold for men, or men and women combined. It is therefore particularly intriguing that we again find an effect which is largely restricted to women both in our Scottish and our Danish patients just as O'Callaghan *et al* (1991*a*) did in their English patients.

Our failure to find any comparable increase in schizophrenic births in association with the pandemic of 1918–19 can be plausibly attributed to the fact that both the data sets examined were restricted to patients still under psychiatric care after January 1963 (Scotland) or April 1969 (Denmark). All patients who had either died or ceased requiring psychiatric treatment before their mid-40s would therefore have been lost. This epidemic was also less sharply delineated than the one in 1957. In Britain it came in three waves extending from July 1918 to March 1919 (Ministry of Health, 1920), and in Denmark in two waves over the same nine-month period.

The results of the investigations of long-term relationships between fluctuations in the 'incidence' of schizophrenia and fluctuations in the incidence of influenza in the general population were less clear cut, despite the fact that the two previous studies of this kind, based on Danish (Barr *et al*, 1990) and English (Sham *et al*, 1992*a*) case material, had both found significant relationships between the two with time lags of -2 or -3 months. There was no hint of any comparable relationship in our Scottish data. Our English data were similar to those studied by Sham *et al* (1992*a*). Both were based on the cohort of native born first admissions to English and Welsh mental hospitals between 1970 and 1979 originally studied by Hare & Moran (1981). Both studies also used the Registrar General's mortality data and similar regression techniques. There were, however, two important differences: Sham *et al* only used the 14 830 patients born between 1939 and 1960, whereas we used all 22 021 born between 1921 and 1960; and we calculated rates per 10 000 population from 1971 census data rather than from live births. Even so, we also found convincing evidence of an increased 'incidence' of schizophrenia in association with exposure to influenza in the sixth and seventh months of pregnancy.

Our Danish data were also similar to those studied by Mednick and his colleagues (Barr *et al*, 1990). We and they both obtained the birth dates of Danish schizophrenics from the case register held by the Institute of Psychiatric Demography in Aarhus, which covers all Danes treated for mental illness in Denmark as an in-patient since April 1969, or as a day patient since April 1975. We also used the same sources – the State Serum Institute in Copenhagen and the Danish statistical office – for monthly notifications of influenza and monthly totals of live births in Denmark. In addition we both defined schizophrenia as ICD–8 code 295; and Barr *et al* used the patients' most recent diagnoses, the same as our narrow diagnostic criteria. The only important difference in the two data sets is that we studied all 14 260 (narrow diagnostic criteria) and 18 723 (broad diagnostic criteria) schizophrenics born between 1911 and 1965, whereas Barr *et al* studied only the 7239 born between 1911 and 1950. It is therefore somewhat disconcerting that we found no evidence of any relationship between the 'incidence' of schizophrenia and the incidence of influenza, whereas Barr *et al* found a highly significant relationship between the two in the sixth month of gestation, with a weaker relationship in the seventh month as well (P values of 0.001 and 0.014).

Because of this disparity we carried out further analyses using a technique modelled on theirs. Each month was divided into three equal quantiles (thirds) based on the 55 values for the incidence of influenza between 1911 and 1965. An artificial covariate was then created, as before, with scores of $+1$ and -1 for high and low quantiles, and included in the regression equation. In this way it was possible to compare the top third with both the bottom third and the bottom two-thirds. As Table 6 shows, none

Table 6
Standardised regression coefficients representing the difference in the 'incidence' of schizophrenia between months grouped into three equal quantiles according to their incidence of influenza or measles (Danish patients)

	Influenza		Measles	
Time lag	$n=14\,260$	$n=18\,723$	$n=14\,260$	$n=18\,723$
Highest quantile v. lowest quantile				
−8	−0.18	0.56	1.16	1.57
−7	0.21	0.23	1.13	1.31
−6	0.54	0.34	0.36	0.75
−5	−0.07	0.11	−0.20	0.55
−4	0.38	0.41	−0.39	0.34
−3	1.88	1.61	−0.07	0.61
−2	0.88	0.90	−0.60	0.27
−1	−0.27	−0.23	−0.68	0.24
0	−0.28	0.11	−0.76	0.49
+1	−0.93	−0.42	−0.31	1.16
+2	0.51	0.74	−0.23	0.95
Highest quantile v. middle and lowest quantiles				
−8	0.69	1.58	1.81	2.29*
−7	0.64	0.67	1.29	1.91
−6	1.56	0.81	0.56	0.71
−5	0.69	0.48	−0.63	0.34
−4	1.09	1.10	−0.57	−0.07
−3	1.16	0.92	−0.59	0.07
−2	0.12	0.41	−1.08	−0.11
−1	−0.95	−0.59	−0.65	−0.20
0	−0.21	0.64	0.00	1.02
+1	0.28	0.73	0.80	2.10*
+2	1.16	1.26	0.80	2.02*

*Statistically significant at $P<0.05$.

of the standardised regression coefficients for influenza generated in this way is statistically significant, although it is worth noting that for the comparison of the highest and lowest quantiles the coefficients approach statistically significant levels (1.88 and 1.61) with a time lag of −3. Measles, on the other hand, yields significant regression coefficients with time lags of −8, +1, and +2, but only with the narrow diagnostic criteria. Finally, we repeated these analyses for each month individually. When we did this, a few significant coefficients did emerge for influenza with time lags of −2 and −3, but only for April and November.

Our failure to find anything more substantial to confirm the clear-cut relationship that Barr and his colleagues (1990) reported cannot be attributed to the insensitivity of our statistical methods. For one thing, we used identical methods for the analysis of our English data and the same relationships between the 'incidence' of schizophrenia and influenza mortality emerged unambiguously in every analysis. It is equally unlikely that our decision to study the 55 years from 1911–65 rather than the 40 years from 1911–50 was responsible. Although patients born in the 1950s and early 1960s would still have been at risk of developing schizophrenia at the end of 1991 when our data were extracted from the Aarhus register we had over 300 patients in every birth year other than 1965 during that period, compared with an average of 340 per year over the whole 55 years. We think it likely, therefore, that the relationship reported by Barr *et al* (1990) was seriously exaggerated by the deficiencies of their statistical methods. They compared incidence rates using analyses of variance (ANOVA) and assumed an underlying normal distribution of variation. This is inappropriate because, by their nature, the data are discrete and Poisson in distribution. This normality assumption may have underestimated the residual variation, and hence produced a significant result which would not have been obtained had maximum likelihood methods been used.

When the results of all our analyses are considered, together with the findings reported previously both by ourselves and other investigators, it is clear that, despite many negative findings, there is substantial evidence that epidemics of influenza are frequently associated with an increased 'incidence' of schizophrenia. There are, however, two problems that must be addressed before confident conclusions are drawn.

The first problem is the wide variation in the stage of pregnancy at which maternal influenza appears to exert its harmful effects. Studies of the sequelae of the 1957 epidemic indicate harmful effects in the fourth, fifth, or sixth months of intrauterine development, whereas those based on long-term relationships between fluctuations in schizophrenic births and in the population incidence of influenza indicate harmful effects in the sixth or seventh months. For a number of reasons, all these estimates are imprecise. Births occurring on the first and 31st days of a month will both be attributed to the same month, although they are more than four weeks apart. Sickness notifications may lag several days behind the actual onset of influenza, and death may occur several weeks after the onset if it is the result of secondary bacterial infection. As a result, measures of the population incidence of influenza based on mortality data will underestimate time lags more than those based on sickness notifications. In reality, the duration of pregnancy is variable, yet we and others have arbitrarily assumed in our time-lagged studies of long-term relationships that birth always occurs in the ninth month of pregnancy, so that a time lag of −3 is equated with the sixth month of pregnancy. For all these reasons it is probably a mistake to draw any more precise conclusion than that the crucial time is in the second trimester of pregnancy. This does not mean, however, that the vulnerable stage

of intrauterine development might not be quite brief, perhaps as short as a week or two.

The second problem is the failure of Crow & Done (1992) to find any hint of a pathogenic influence in the only study in which it was recorded at the time which mothers had had influenza-like illnesses during their pregnancies. One of the criticisms of this study is probably unjustified. The fact that only 5.9% of mothers were recorded as having had influenza in the second trimester of pregnancy, and only 12.5% at any stage of pregnancy, is not evidence of serious under-reporting. Although it is true that in densely populated urban areas up to a third of the inhabitants may develop clinical symptoms of influenza during major epidemics (e.g. see Horne, 1957), the proportion will always be lower for an entire country. In Denmark, for example, there were 328 262 notifications of influenza in October and November 1957 when the Asian flu epidemic was at its height, an attack rate of only 7.5% overall. The other criticisms of Murray and his colleagues still have some force. Crow's methods of case detection were imperfect, the total numbers of identified schizophrenic offspring were small, and the confidence limits are therefore wide (O'Callaghan *et al*, 1991*b*).

Particularly in view of these shortcomings, greater weight must be given to the many studies which have found a statistically significant relationship between maternal influenza and the risk of schizophrenia. We are also aware of a recent report that Mednick and his colleagues have now traced the antenatal records of many of the patients involved in their original study of the sequelae of the 1957 epidemic of Asian influenza in Helsinki, and found that an attack of influenza in the second trimester of pregnancy was recorded in the charts of schizophrenics' mothers significantly more often than in those of control mothers (Sham *et al*, 1992*b*). Whether or not this is accurate, we ourselves are now convinced that the relationship between maternal influenza and schizophrenia is genuine, and probably causal. It should also be recognised that it is unlikely that further epidemiological studies will resolve the issue until a future major epidemic provides an opportunity to mount prospective studies. There are comparatively few large, adequately documented and population-based schizophrenic populations in existence and most have now been studied. It is unlikely, too, that there exists another birth cohort like the National Child Development Study in which maternal influenza during pregnancy was both common and recorded at the time. This suggests to us that the most fruitful approach for the foreseeable future will be to assume that influenza A probably does contribute to the aetiology of schizophrenia, and that other less common viral infections may well do the same. It presumably does so by interfering with cellular migration or other developmental processes in the foetal brain and there is no lack of more or less plausible mechanisms to explore, despite the evidence that the influenza virus rarely, if ever, reaches the foetus, or even the maternal blood stream (Smith & Sweet, 1988).

We cannot suggest any plausible explanation for the striking sex difference we observed, but as it emerges unambiguously in three different data sets, we are reluctant to accept it as a chance finding. There are, of course, other well established sex differences in schizophrenia (Lewis, 1992). Premorbid intellectual and social deficits are more often found in boys than in girls and the age of onset is substantially earlier in men than in women. The long-term prognosis is worse in men as well. The cause of these differences is unknown and it may be that the greater liability of the female nervous system to intrauterine damage which our findings suggest is related to them. Coffey & Jessop (1959) found more congenital abnormalities of the central nervous system in the female than in the male offspring of mothers who had had Asian influenza during pregnancy. McNeil *et al* (1993) have also reported recently that 'preschizophrenic' female, but not male, infants have a reduced head circumference at birth. Both these findings are consistent with ours. Even so, we have to admit that we would have found it easier to account for a predominantly male effect of maternal influenza than the largely female effect we found.

As only a small fraction of the variance in the 'incidence' of schizophrenia is explained by exposure to maternal influenza, it is unlikely that influenza is implicated in the aetiology of more than a small minority of cases. (Sham *et al* (1992*a*) estimated that 1–2% of all schizophrenic births in England could be explained by the number of influenza deaths in the preceding months.) Even so, there is a public health dilemma to be faced. If the pathogenic mechanism depends on maternal infection with live virus, pregnant women should be offered immunisation against influenza, particularly if their second trimester is going to coincide with the high-risk winter months. If, on the other hand, the pathogenic mechanism depends on the mother's immune response rather than infection itself – which seems more likely – immunisation is positively contraindicated.

Finally, it must be recognised that, even if it is assumed that maternal influenza does contribute to the aetiology of some cases of schizophrenia and that the fifth or sixth months of pregnancy are the crucial, or most susceptible, time this still does not account

for the winter/spring excess of schizophrenic births. The relationship between maternal influenza and schizophrenia is best established in English data covering the period from 1921 to 1960. Most outbreaks of influenza in England during these 40 years were in January and February with a few in December or March. (The 1957 epidemic in September and October was very unusual.) If maternal influenza in the fifth or sixth month of pregnancy were the cause of the winter/spring excess of schizophrenic births, the high incidence months should come at least three months later, that is they should be May and June, or June and July. In fact, at least over the 40 years in question, they are January and February and, although the peak months vary from time to time and country to country, they are invariably in the winter or spring, never in the summer (see Fig. 1).

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