Eur Arch Psychiatry Clin Neurosci (1995) 245:255–259

ORIGINAL PAPER

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Prenatal exposure to influenza epidemics and risk of mental retardation

Received: 16 February 1995 / Accepted: 7 March 1995

Abstract This study was undertaken to determine whether prenatal exposure to influenza epidemics increases the risk of mental handicap. The monthly birth frequencies of 827 first-admission individuals (mean age at admission 13 years) with a primary diagnosis of non-specific mental retardation, discharged from psychiatric hospitals in England and Wales, were examined in relation to the monthly death rates from influenza over the period 1953–1980. The relative risk of developing mental handicap when exposed to influenza epidemics during mid-gestation was assessed by a generalized linear model. Increased death rates from influenza, a measure of prevalence of the infection, were significantly associated with an increase in births of mentally handicapped individuals 6 months later. For every 1000 female deaths from influenza there was a 17% increase in births of mentally handicapped individuals 6 months later. Maternal exposure to influenza at approximately the third to fourth month of gestation may be risk factor for developing mental handicap.

Key words Mental retardation · Influenza · Mid-pregnancy · Schizophrenia

Introduction

There has been much debate about the relationship between schizophrenia and mental retardation. Schizophrenia appears to be approximately three times more common among the mentally retarded than among the general population (Reid 1982; Rantakallio and von Wendt 1985; Turner 1989). A proportion of schizophrenics perform more poorly on intellectual tests than controls, both premorbidly (Offord 1974) and after the onset of psychosis (Aylward et al. 1984). A history of perinatal complications is found more frequently in both schizophrenic (Lewis and Murray 1987; Eagles et al. 1990; O'Callaghan et al. 1992) and mentally handicapped (Rantakallio and von Wendt 1985; Pasamanick and Knobloch 1966) individuals than in controls, and both show an excess of minor physical anomalies (Gualtieri et al. 1982; O'Callaghan et al. 1991; Smith and Bostian 1964; Firestone et al. 1978) suggestive of developmental impairment during gestation. Furthermore, both show an excess of births in the late winter and spring (Bradbury and Murray 1985; Pasamanick and Knobloch 1958; Häfner 1987).

The relationship between prenatal exposure to rubella, neurodevelopmental damage and subsequent mental retardation is well known (Chess et al. 1971). There is some evidence that other prenatal infections such as cytomegalovirus, syphilis and toxoplasmosis can also cause mental handicap (Dudgeon 1984; Rantakallio and von Wendt 1985). Recently, several, although not all (Torrey et al. 1991; Crow et al. 1992), studies have suggested that prenatal exposure to influenza epidemics may affect fetal brain development in such a way as to increase the likelihood of subsequent schizophrenia (Mednick et al. 1988; Barr et al. 1990; O'Callaghan et al. 1991; Sham et al. 1992; Kunugi et al. 1992; Takei et al. 1994). Given the similarity in clinical and epidemiological findings in schizophrenia and mental handicap noted previously, the question arises as to whether exposure to influenza infection during fetal life could also increase the risk of developing mental handicap.

In this study, therefore, we hypothesized a relationship between prenatal exposure to influenza and an increased risk of mental retardation. With rubella, the exact stage of development of the fetus when exposed to the virus has a significance; exposure at an earlier stage of development results in more profound consequences (Peckham 1985).

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Some schizophrenics show dysplastic abnormalities of the cerebral cortex (Zipursky et al. 1992; Harvey et al. 1993), but the brain abnormalities seen in schizophrenia are more subtle than those seen in severe mental handicap. It follows that if there is a link between mental retardation and prenatal exposure to influenza, then the crucial period of risk should be at an earlier stage of development than is the case for schizophrenia. Exposure at an intermediate stage of brain development could explain the higher prevalence of schizophrenia amongst the mentally retarded.

Subjects and methods

We obtained the dates of birth of all first-admission individuals, born in England and Wales between 1953 and 1980, who were discharged between 1976 and 1986 with an ICD-8 primary diagnosis (WHO 1978) of mental retardation (MR; 310: borderline MR; 311: mild MR; 312: moderate MR; 313: severe MR; 314: profound MR; 315: unspecified MR) or ICD-9 (317: mild MR; 318.0: moderate MR; 318.1: severe MR; 318.2 profound MR; 319: unspecified MR) (n = 827: 478 males and 349 females) from psychiatric hospitals in nine Regional Health Authorities in England and Wales: North–West Thames (1980–1984), South–East Thames (1980–1986), South–West Thames (1976–1984, 1986), Oxford (1980–1986), Mersey (1980–1981), Yorkshire (1980–1984), North (1980–1985), West Midlands (1980–1982) and East Anglia (1980–1981). Because our sampling procedure used the first diagnosis for each patient recorded by the Mental Health Enquiry, those mentally handicapped individuals whose condition had a known organic basis such as epilepsy, chromosome abnormalities (e.g. Down's syndrome) or metabolic disorders were likely to have been excluded. Furthermore, because our data concerned those individuals admitted to psychiatric hospitals, by definition we were studying mentally handicapped individuals likely to have shown behavioural disturbance.

The demographic characteristics of the sample are shown in Table 1. The mean age at first admission was 13 (SD 10; range 1–31 years). The mean duration of hospitalization was 39 days (SD 221; range 1–3943 days). Of the sample, 99.4% was discharged within 1 year.

To allow for variations in the population birth rate, we obtained the numbers of live births in England and Wales for each month between 1953 and 1980 from the Office of Population Censuses and Surveys (OPCS). As a measure of the number of pregnant women exposed to influenza, we used the total number of female deaths attributed to influenza in England and Wales each month between 1952 and 1980. Although these deaths consist mainly of elderly persons, it is fairly reasonable to assume that changes in these death rates reflect fluctuations in the prevalence of influenza.

Analysis

The method is described in detail elsewhere (Sham et al. 1992; Takei et al. 1993). Briefly, for each month in the period 1953–1980, we investigated the relationship between the number of births of mentally handicapped (MH) individuals in the sample (the response variable) and the number of influenza deaths, allowing for the fluctuations in the general population birth rates, and for the long term, and seasonal, variation in MH births (the predictor variables). We assumed a model in which the response variable (MH births) had a Poisson distribution, with a mean value determined by the anti-logarithm of a linear function of the predictor variables. The Poisson regression model is a member of the class of generalized linear models (McCullagh and Nelder 1989). For these models an appropriate measure of fit between model and data is the *scaled deviance,* which is a constant minus twice the logarithm of the maximum likelihood of the model. The significance of the effect of a predictor variable is tested by the reduction of scaled deviance associated with the addition of the variable to the model, which has a χ^2 distribution under the null hypothesis that the variable has no effect. Our primary hypothesis was that fetuses, who encountered an influenza epidemic during the late first or early second trimester, would be at greater risk of developing mental handicap, but we tested the relationship of mentally handicapped births to death rates from influenza during the same months as, 1 month before and up to 9 months before, birth. These procedures were implemented by the GLIM programme (Baker and Nelder 1978).

After testing the statistical significance and estimating the magnitude of any relationship between prenatal exposure to influenza and MH births, we looked for any temporal association between birth rates of MH individuals and those of schizophrenics. The rationale for this examination was that, if maternal influenza infection plays a causal role in subpopulations of both mental handicap and schizophrenia, there should be a temporal correlation between birth rates of the two disorders. For this purpose the sample of MH individuals was restricted to those born between 1953 and 1965 to control for the birth period of the schizophrenic sample that was available to us. Similar data on all dates of birth of schizophrenics of first admission (n = 2369) born in England and Wales during this period were provided by the same nine Regional Authorities described previously. To examine the correlation between the two series of monthly births of schizophrenic and MH individuals, we performed a cross-correlation function analysis (SPSS Inc 1988) using the Statistical Package for Social Sciences, PC version (SPSS.PC). The first-order differences of the series were used for the analysis, so that changes in birth rates were highlighted for the analysis. Differencing is a commonly used transformation prior to time series analysis to eliminate local temporal trends and "noise" (Gottman 1981). In this analysis time lags of MH birth occurrences that we examined were confined to nil (i.e. the same month), and one and two months following the schizophrenic births.

Besides these statistical analyses, a simple graphical approach was also employed. We determined to see whether MH births would increase after exposure to the peak-prevalence of influenza in each year over the study period 1953–1979. The timing of an increase in the MH births was expected in the month 6 months after the peak of influenza deaths (see *Results* section), which corresponds to approximately the fourth month of gestation, i.e. late-first to early-second trimester.

Table 1 Demographic characteristics of mentally handicapped subjects

Gender distribution (m/f, m proportion)	478/349 (57.8%)
Age at admission (years, SD)	13.0 (7.0)
Duration of admission (days, SD)	39.0 (221.0)

Results

Because the number of MH births in any month should be directly proportional to the number of births in the general population in that month, we first entered the logarithm of the monthly numbers of population births with a coefficient constrained to unity (called *offset*). To model the long-term variation of MH births over the years 1953–1980, we fitted polynomial functions of year (Y) and found that a quadratic polynomial was adequate to model this trend: The change in scaled deviance of inclusion of Y, Y^2, Y^3 and Y^4 was 5.41, 38.22, 0.85 and 2.05, respectively, each with 1 *df* (degree of freedom). We then included a seasonal term for the 12 months of the year, which reduced the scaled deviance by 6.90 with 11 *df*.

This reduction was not statistically significant, but the seasonal term was left in the model to make the test for any effect of influenza as rigorous as possible.

Figure 1 shows the monthly female influenza death rates in England and Wales between 1953 and 1980. When the monthly number of deaths attributable to influenza was included in the model, we found that the number of influenza deaths 6 months before birth reduced the scaled deviance by 5.65 ($df = 1$; $P = 0.02$). There were no other months before birth whose inclusion significantly improved the model. The estimates and standard errors of the parameters for seasonality and influenza effect (6 months before birth), which were obtained from the final model, were converted to give the relative risk by exponentiating them (Table 2). The effect of influenza was found to correspond to a 16.9% increase (95% confidence interval: 3.7–31.7%) in the number of births of mentally handicapped individuals for every 1000 female deaths from influenza 6 months previously. The scaled deviance in the final model was 425.03 with 321 *df*. When the standardized residuals in this model were examined, 15 (4%) of the total 336 months studied had a residual above 2.00. All these 15 months had a positive residual indicating that there are still fluctuations in births that cannot be explained by the present model.

We next tested for the possibility of a sequential correlation between the birth occurrences of schizophrenic ($n = 2369$) and MH individuals ($n = 415$) over the 156 months between 1953 and 1965. When cross-correlation function analysis was applied to these first-order differenced series, there was indeed a trend, although weak and not significant, towards schizophrenics births preceding by 2 months those of MH individuals (cross-correlation 0.136; SE 0.081; P 0.092; Table 3).

As graphically shown in Fig. 2, there was an increase in births of MH in the month 6 months after the peak of deaths from influenza, i.e. there were more mentally handicapped individuals among those exposed to epidemics during approximately the fourth month of gestation.

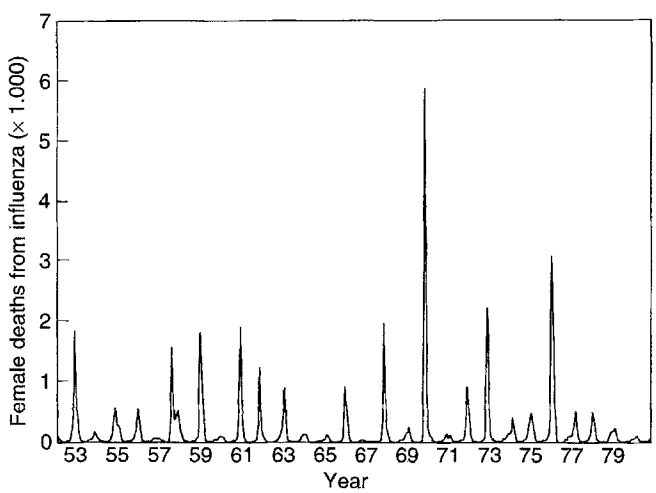

Fig. 1 Female deaths from inflluenza per month between 1952 and 1980 in England and Wales

Table 2 Effect of season of birth and influenza exposure on births of mentally retarded individuals

Parameter (month of birth)	Relative risk[b]	95% CI of relative risk
Jan[a]	1	–
Feb	1.073	0.754–1.528
Mar	1.252	0.900–1.743
Apr	1.071	0.757–1.515
May	1.085	0.770–1.529
Jun	1.080	0.761–1.532
Jul	0.896	0.617–1.300
Aug	1.106	0.781–1.565
Sep	1.268	0.906–1.774
Oct	1.034	0.726–1.473
Nov	0.970	0.673–1.399
Dec	1.156	0.817–1.635
Influenza[c]	1.169[d]	1.037–1.317

[a] January was arbitrarily chosen as the standard month. The effects of other months were evaluated in comparison with this month
[b] Relative risk was obtained by exponentiating the "raw" estimates
[c] Female death rates attributable to influenza infections 6 months before birth
[d] Relative risk was obtained by multiplying the raw estimate by 1000 and then exponentiating it. The value thus corresponds to a 16.9% increase in the number of births of mentally handicapped individuals for every 1000 female deaths from influenza 6 months previously

Table 3 Cross-correlation function analysis between a series of birth occurrences of mental handicap and schizophrenia

Time lag	Cross-coefficient	SE	P
None	0.014	0.080	ns
1 months[a]	–0.035	0.081	ns
2 months[b]	0.136	0.081	0.092

[a] Correlation between birth occurrences of schizophrenia and mental handicap with 1 month time lag, the former preceding the latter by 1 month
[b] Correlation between birth occurrences of schizophrenia and mental handicap with 2 month time lag, the former preceding the latter by 2 months

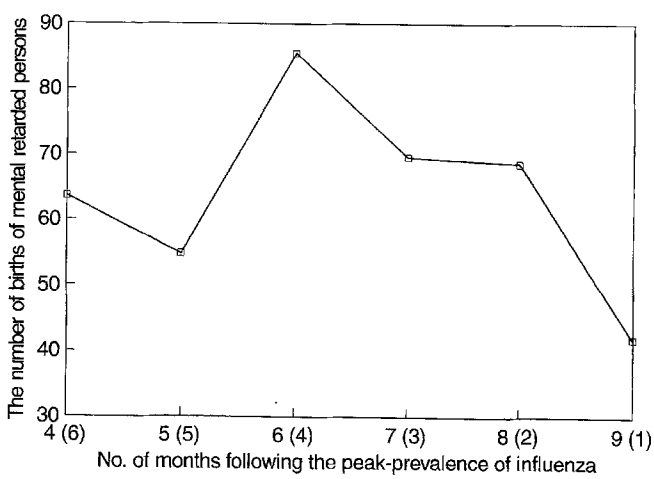

Fig. 2 "Birth response curve" of mental retarded persons to influenza epidemics

Discussion

The results of this investigation are consistent with the hypothesis that there is an increase in the risk of mental retardation among those individuals who are exposed to influenza epidemics 6 months before birth. Because the real peak-prevalence of influenza infections may precede by several weeks the peak of deaths from influenza, the corresponding vulnerable period may be around the third to fourth month of gestation. Recent studies have linked prenatal exposure to influenza in the fourth to sixth month of gestation, with an increased risk of later developing schizophrenia (Mednick et al. 1988; Barr et al. 1990, O'Callaghan et al. 1991; Sham et al. 1992; Kunugi et al. 1992; Takei et al. 1994). If influenza epidemics contemporaneously exert an adverse effect on fetuses at an earlier developmental stage than this, then those individuals should be born later than those destined to become schizophrenic. Indeed, there was a trend for mentally handicapped individuals to be born 2 months later than schizophrenics, although this did not reach statistical significance (P = 0.092).

We tentatively suggest that exposure to influenza epidemics at approximately, the third or fourth month of gestation increases the risk of more global cerebral damage (and consequent mental handicap), whereas exposure at a later stage increases the risk of subtler consequences (and subsequent schizophrenia). The effect of influenza that we found corresponds to a 16.9% increase (95% confidence interval: 3.7-31.7%) in the number of births of mentally handicapped individuals for every 1000 female deaths from influenza 6 months previously.

There are, however, some limitations to our study: Firstly, our data do not cover the whole of England and Wales, and some of the nine regions only provided data for some of the years between 1976 and 1986. This imperfection, however, would not have systematically biased the results towards a temporal correlation between the fluctuations in the prevalence of influenza and fluctuations in births of MH individuals some months later. Secondly, because our sample was based on hospital discharges, the mentally handicapped individuals we studied may not be representative of all such persons admitted to the hospital. However, few first-admission cases of mentally handicapped are institutionalized permanently. Indeed, 99.4% of our sample had a hospitalization of less than 1 year; the mean duration of admission with standard deviation (SD) was 39 days (SD 221 days). There was a single patient who was discharged over 10 years after first hospitalization. One could argue that if the most severely mentally handicapped tend not to be discharged, our sample would consist mainly of patients with a milder form of mental retardation. Nevertheless, when our sample was broken down according to the ICD classification, the severely mentally retarded group comprised 31%. Thirdly, our results cannot be extended to the majority of mildly educationally subnormal individuals who are socially and psychiatrically stable, and never admitted to a psychiatric hospital. Indeed, because our sample contains only psychiatric-hospital admissions and not mental-handicap hospital admissions, the present finding may not be generalized to patients admitted to mental-handicap hospitals. It is likely that many of the individuals we studied were admitted to the hospital because of behavioural or psychiatric disturbances. Fourthly, the monthly female deaths due to influenza are at best an indirect measure of the prevalence of influenza infection among expectant mothers, and as noted previously; there may be a time-lag between contraction of the infection and ensuing death. Finally, the date of birth was used to estimate the period of gestation when exposure to influenza occurred. Not all babies are born at full-term delivery; thus, the duration of pregnancy may have been less than 40 weeks in a proportion of patients in our sample, and in those the exposure may have occurred earlier than we estimated.

These methodological limitations may be taken as undermining any conclusions that can be drawn from our findings, but one could also argue that such limitations may be masking a stronger association. Indeed, the limitations considered previously seem to minimize, rather than exaggerate, the possible association.

Certainly, the significance of the level of association in this study is not as high as our previous finding concerning prenatal influenza and schizophrenia: 0.02 as opposed to 0.003 (Takei et al. 1993). One possible reason for this is the smaller size of the present sample. Ten tests examining the correlation of prenatal exposure to influenza at the time of birth and before birth, with mentally handicapped births, were performed, so one might argue that the critical P-value should perhaps be reset at 0.005. By this stringent criterion our results would not be significant. We previously discussed whether such an adjustment is appropriate (Sham et al. 1992). In fact, we had a specific hypothesis that the association would be found concerning the 1 or 2 months preceding the vulnerable period for schizophrenia, which appears to be the fifth-sixth month of gestation (O'Callaghan et al. 1991; Barr et al. 1991). The association between mentally retarded births and prevalence of influenza was found to involve a time scale consistent with this specific hypothesis.

Because our findings could cause anxiety in pregnant women, we need to be cautious about their interpretation. To our knowledge, this is the first study to have demonstrated an association between the prevalence of influenza and birth frequencies of mentally handicapped persons. Any single study reporting a finding, whether positive or negative, requires replication. Despite the reservations, we think that the possible role of maternal influenza in the aetiology of mental retardation is worthy of further investigation.

Acknowledgements We are grateful for financial support from the Wellcome Trust, and to Drs. R. Goodman, A. Holland, P. Bolton, and Professor C. Peckham for their valuable comments. N. Takei was a Wellcome Training Fellow in Clinical Epidemiology and is now supported by the Stanley Foundation (Stanley Research Fellow).

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