Evidence Against Maternal Influenza as a Risk Factor for Schizophrenia

J.-P. C. J. SELTEN and J. P. J. SLAETS

We tested the hypothesis that second-trimester exposure to influenza is a risk factor for schizophrenia in the child. The dates of birth of Dutch schizophrenic in-patients were examined for any effect of the 1957 A2 influenza epidemic. Individuals who were in their second trimester of foetal life at the peak of the epidemic were at no greater risk of developing schizophrenia than controls. As the present study has a larger sample size than all previous European studies, and is supported by a large study in the USA, it provides strong evidence against the hypothesis that second-trimester exposure to influenza is a risk factor for schizophrenia.
British Journal of Psychiatry (1994), **164**, 674–676

The hypothesis that prenatal exposure to influenza can cause schizophrenia is a source of much debate. The evidence to support the hypothesis relates mainly to the 1957 pandemic of 'Asian' A2 influenza. Mednick *et al* (1988) noted a significant increase in schizophrenia in people from Helsinki, who were in their second trimester of foetal life during the epidemic. O'Callaghan *et al* (1991*a*) reported an increase in schizophrenic births in eight health regions of England and Wales. The increase occurred five months after the peak of the 1957 epidemic. When the authors analysed the results for men and women separately, the difference from controls was statistically significant for women but not for men. Recently, the same sex difference emerged in a study of data sets from Scotland, England and Wales, and Denmark (Adams *et al*, 1993). Again, the increase in schizophrenic births five months after the epidemic was greater for women than for men.

However, there are reasons to question the claim that prenatal exposure to the A2 influenza virus is a cause of schizophrenia. Firstly, the results of a large study in the USA were negative (Torrey *et al*, 1991). Secondly, in an examination of psychiatric admissions of people born in England and Wales in the week 3–9 March 1958, it was found that the children of mothers who reported having had influenza during the second trimester of their pregnancy were at no greater risk of developing schizophrenia than other children (Crow *et al*, 1991; Crow & Done, 1992). This last study was criticised for its small sample size and for the possibility that influenza was under-reported (O'Callaghan *et al*, 1991*b*).

Hence there is no conclusive evidence either in favour of or against an association between schizophrenia and A2 influenza (Cooper, 1992). In order to throw light on the issue we carried out an analysis of the Dutch register. A2 influenza arrived in the Netherlands in June 1957. As in England and Wales, the peak incidence of new infections occurred in September and October. The death tolls from influenza in the months of June, July, August, September, October and November 1957 were 10, 8, 13, 336, 778 and 113 respectively (Central Statistics Office). If second-trimester exposure to A2 influenza is a risk factor for schizophrenia, one would expect an increase in schizophrenic births in the first four months of 1958. If the five month lag reported by O'Callaghan *et al* (1991*a*) and Adams *et al* (1993), occurs, one would expect an excess of such births in February and March 1958.

Method

The Dutch psychiatric register provided us with data on the sex and month and year of birth (but not day of birth) of all Dutch-born patients who were admitted for schizophrenia in the period 1978–1991 and received an ICD-9 diagnosis of schizophrenia (World Health Organization, 1978).

The register collects information on a standardised form. If the entries 'diagnosis on admission', 'country of birth', 'municipality of birth', 'date of birth' and 'sex' have not been completed, the register returns the form to the psychiatric institute. This means that this information is always complete. The form has no entry for 'first admission' or 'readmission'. Nevertheless it was possible to distinguish first admissions from readmissions by means of computerised record linkage. Within the period 1978–91 patients could be recognised by their place and date of birth (day, month and year) and sex. This minimises the likelihood that the same patient is counted more than once.

The register does not record admissions to psychiatric wards of general hospitals, which receive about 14% of all admissions for schizophrenia. However, after discharge from these wards, schizophrenic patients, when in need of readmission, are usually referred to mental hospitals and are added to the psychiatric register. Schizophrenic patients admitted only to general hospitals are few.

Data were analysed for each month of birth in the period August 1957 up to and including July 1958. Schizophrenic patients born in the same months of the previous two and the next two years (August 1955–July 1957 and August 1958–July 1960) were used as controls.

https://doi.org/10.1192/bjp.164.5.674 Published online by Cambridge University Press

Table 1
Distribution of affected births in the index year (August 1957–July 1958), compared with average for control years (August 1955–July 1957 and August 1958–July 1960)

Month (1957–58)	All		Men		Women	
	1957/58	Control[1]	1957/58	Control[1]	1957/58	Control[1]
August	67	75.25	34	47.25	33	28.00
September	68	71.75	38	41.25	30	30.50
October	84	73.00	56	51.75	28	21.25
November	79	79.25	54	51.50	25	27.75
December	66	74.50	36	45.25	30	29.25
January	72	77.00	45	50.75	27	26.25
February	72	68.75	44	42.00	28	26.75
March	80	81.75	57	51.50	23	30.25
April	66	84.25	44	57.75	22	26.50
May	80	86.75	53	53.75	27	33.00
June	64	80.25	49	53.25	15	27.00
July	75	77.00	44	48.00	31	29.00

1. Multiply by 4 for total births in 4 control years studied.

Results

During the index year (August 1957–July 1958) 873 schizophrenic patients were born and a total of 3761 were born in the four control years. We compared the numbers of index and control patients for each of the 12 months (see Table 1).

The numbers of schizophrenic births in January, March and April 1958 were lower than the average numbers for the same months in the control years. The rate of schizophrenic births for February 1958 (0.00386; 95% confidence interval (CI) 0.00297 to 0.00475) was similar to that for the control years (0.00362; 95% CI 0.00319 to 0.00414). This also applied to the birth rate of female schizophrenics in that month.

Our results cannot be explained by fluctuations in the Dutch population birth rate, because the number of births in the first four months of 1958 (78 553) is similar to the average for the same months in the control years (79 468). Likewise, the number of births in February 1958 (18 646) approximates to the average number in the control years (19 004).

The age range during the period for which admission data were collected for subjects born in the index year is different from that of subjects born in the control years. After adjustment for the range of ages of onset in index and control groups we reanalysed our results. They remained essentially unchanged.

Discussion

As our study is larger than all previous European studies and is supported by a large study in the USA (Torrey *et al*, 1991) it provides strong evidence against the hypothesis that second-trimester exposure to the 1957 A2 influenza epidemic is a risk factor for schizophrenia. (The numbers of schizophrenic births in 1958 in the Adams *et al* (1993) study were as follows: Scotland, broad and narrow diagnostic criteria: $n = 341$ and $n = 157$ respectively; Denmark, broad and narrow diagnostic criteria: $n = 407$ and $n = 297$ respectively; England: $n = 418$. Data kindly provided by Professor Kendell.)

We cannot exclude the possibility that our findings are biased by the diagnostic habits of Dutch psychiatrists. We receive the impression that Dutch psychiatrists use a narrow definition of schizophrenia and reserve this diagnosis to severe cases, but this is uncertain.

The possibility that prenatal influenza contributes to the aetiology of schizophrenia cannot be ruled out. Barr *et al* (1990), Sham *et al* (1992) and Adams *et al* (1993) examined the relationship between influenza epidemics and schizophrenic births over several decades. In most of the data sets they obtained weak but statistically significant associations. Any causal relationship, however, remains to be demonstrated.

Acknowledgement

This research was supported by the Dutch Inspectorate of Mental Health.

References

ADAMS, W., KENDELL, R. E., HARE, E. H., *et al* (1993) Epidemiological evidence that maternal influenza contributes to the aetiology of schizophrenia. An analysis of Scottish, English and Danish data. *British Journal of Psychiatry*, **163**, 522–534.

https://doi.org/10.1192/bjp.164.5.674 Published online by Cambridge University Press

BARR, C. E., MEDNICK, S. A. & MUNK-JØRGENSEN, P. (1990) Exposure to influenza epidemics during gestation and adult schizophrenia. *Archives of General Psychiatry*, **47**, 869–874.

COOPER, S. J. (1992) Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic. *British Journal of Psychiatry*, **161**, 394–396.

CROW, T. J., DONE, D. J. & JOHNSTONE, E. C. (1991) Schizophrenia and influenza. *Lancet*, **338**, 116–117.

—— & —— (1992) Prenatal exposure to influenza does not cause schizophrenia. *British Journal of Psychiatry*, **161**, 390–393.

MEDNICK, S. A., MACHON, R. A., HUTTENEN, M. O., *et al* (1988) Adult schizophrenia following prenatal exposure to an influenza epidemic. *Archives of General Psychiatry*, **45**, 189–192.

O'CALLAGHAN, E., SHAM, P., TAKEI, N., *et al* (1991*a*) Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic. *Lancet*, **337**, 1248–1250.

——, ——, ——, *et al* (1991*b*) Schizophrenia and influenza. *Lancet* **338**, 118–119.

SHAM, P., O'CALLAGHAN, E., TAKEI, N., *et al* (1992) Schizophrenia following prenatal exposure to influenza epidemics between 1939 and 1960. *British Journal of Psychiatry*, **160**, 461–466.

TORREY, E. F., BOWLER, A. E. & RAWLINGS, R. (1991) An influenza epidemic and the seasonality of schizophrenic births. In *Second World Congress on Viruses and Mental Health* (ed. E. Kurstak), pp 109–116. New York: Plenum.

WORLD HEALTH ORGANIZATION (1978) *Mental Disorders: Glossary and Guide to their Classification in accordance with the ninth revision of the International Classification of Diseases (ICD–9)*. Geneva: WHO.

*Jean-Paul Selten, MD, *Psychiatrist, Rosenburg Psychiatric Hospital, PO Box 53019, 2505 AA The Hague, The Netherlands*; J. P. J. Slaets, MD, *Geriatrician, Leyenburg Hospital, The Hague, The Netherlands*

*Correspondence

(*First received September 1993, final revision December 1993, accepted January 1994*)

A Ratio Estimation Method for Determining the Prevalence of Cocaine Use

MICHAEL GOSSOP, JOHN STRANG, PAUL GRIFFITHS, BEVERLY POWIS and COLIN TAYLOR

This paper presents an approach to estimating the prevalence of cocaine use, based upon a new ratio estimation technique. This method can be applied to random samples of overlapping populations for which no sampling frames exist. When the ratio estimation method is applied to the two study samples (drawn from populations of people using cocaine and people using heroin) the ratio of cocaine users to heroin users (*C*/*H*) was 1.55, with a 95% confidence interval of ±0.48. Such estimates should be applied with caution. However, if used with reference to national estimates of about 75 000 heroin users, application of the present estimate suggests that there may be about 116 000 cocaine users in the UK.

British Journal of Psychiatry (1994), **164**, 676–679

People who use illicit drugs are, for obvious reasons, a largely hidden population and it is difficult to obtain valid estimates of the size of this population. Various research methods have been used for this purpose. In the United States a national household survey is conducted regularly, providing valuable information about patterns and trends in drug taking. No such survey exists in the UK, where estimates are often based on data drawn from secondary indicator sources, institutional and professional authorities, and from indigenous informants (Wiebel, 1990). Among the secondary indicators used for such purposes are admission records from casualty departments, coroners' reports, the Home Office Addicts Index, treatment admissions for drug dependence, prescription tracking systems, data on arrests and seizures, and laboratory analyses of controlled substances (Ghodse, 1977; Hartnoll *et al*, 1985; Das Gupta, 1990).

Estimates using a 'capture–recapture' method (Andima *et al*, 1973) have been made in the UK by Hartnoll *et al* (1985). This is one method which can appropriately be used when no sampling frame exists, though it does presume the availability of at least two independent samples of the same hidden population. While the capture–recapture method has provided useful information for the development of services, the true independence of the samples that have been used (e.g. arrest and treatment samples) is doubtful – as the authors themselves acknowledge.

https://doi.org/10.1192/bjp.164.5.674 Published online by Cambridge University Press