

Correspondence

EDITED BY TOM FAHY

Contents ■ Influenza and schizophrenia ■ Early detection of schizophrenia ■ Terminology of learning disability ■ Confidential Inquiry into Suicide and Homicide by Mentally Ill People ■ Measuring cognitive deterioration in Alzheimer's disease ■ CYP2D6 genotype and tardive dyskinesia ■ Dissociative pathology discriminates between bipolar mood disorder and dissociative disorder

Influenza and schizophrenia

Sir: Readers of this debate may be at a loss to understand how two analyses (Adams & Kendell, 1996; Crow, 1966) of the same data set (the psychiatric subsample of the National Child Development Study (NCDS) cohort) can be used to reach such discrepant conclusions.

Common ground is that (a) from their own earlier epidemiological studies Mednick *et al* (1988) and O'Callaghan *et al* (1991) had concluded that an 87% (or 88%) increase in births of children who later developed schizophrenia was attributable to exposure in the second trimester of pregnancy to the 1957 influenza epidemic; and (b) in the NCDS cohort (Crow *et al*, 1991; Crow & Done, 1992) of the 945 births to mothers who (out of a total of 16 268) are recorded as suffering from influenza in the second trimester, three children later suffered from schizophrenia (by broad criteria).

Where Adams & Kendell and I differ is in calculating how many cases would be predicted on the basis of Mednick *et al* and O'Callaghan *et al*'s hypothesis of an 87–88% increase. Adams & Kendell calculate the expected figure on the basis of the number (54) of children born to 15 323 mothers who did not report a flu-like illness in the second trimester, to arrive at an expectation ("the base rate in the cohort") of one schizophrenic birth per $15\,323/54=283.8$ mothers. They then calculate that this figure gives an expectation on the null hypothesis (no increase due to second trimester influenza) of $945/283.8=3.33$ schizophrenic offspring, and on the Mednick/O'Callaghan hypothesis of an 87% increase of $(945/283.8) \times 1.87=6.23$ schizophrenic offspring. The actual observation of three cases rather than the 6.23 predicted could be a chance finding, and Adams & Kendell conclude that the Mednick/O'Callaghan hypothesis is not disproved.

Conversely, I calculate the figure predicted by Mednick/O'Callaghan on the assumption that if the hypothesis had been

true, a substantial proportion (0.87/1.87) of the total number (57) children born in the week 3–9 March 1958 who later became schizophrenic did so *because* their mothers had been exposed to influenza in the second trimester. Therefore, this number would, on the Mednick/O'Callaghan hypothesis, have been born to the 945 mothers who reported suffering from influenza in the second trimester. On this basis I calculated that an additional 26.5 ($57 \times 0.87/1.87$) cases would be predicted among the births to these 945 mothers and that the highly significant discrepancy between the predicted and actual observation (three cases) constituted a decisive refutation of the Mednick/O'Callaghan hypothesis. The figure makes clear this prediction and its implications.

In summary, Adams & Kendell interpret Mednick, O'Callaghan and co-authors as having claimed that if a mother suffered from influenza in the second trimester, there was an 87% increase in the probability that her child would develop schizophrenia. I interpret them as claiming that there was an 87% increase in births of schizophrenia in

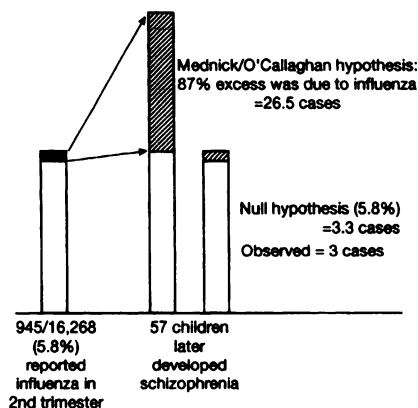


Fig. 1 Relationship between exposure to influenza in the 1957 epidemic and the births of schizophrenic patients in March 1958 according to the hypothesis of Mednick *et al* (1988) and O'Callaghan *et al* (1991), and the null hypothesis, together with the numbers actually observed.

March 1958 and that this was attributable (by infection of some mothers in the second trimester) to the 1957 epidemic.

The issue deserves careful consideration by those who are interested in the question of whether prenatal exposure to influenza causes schizophrenia, and what the evidence originally claimed for this hypothesis was and what it now is.

Adams, W. & Kendell, R. E. (1996) Influenza and schizophrenia (letter). *British Journal of Psychiatry*, **169**, 791–792.

Crow, T. J. (1996) Influenza and schizophrenia (letter). *British Journal of Psychiatry*, **169**, 790–791.

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Mednick, S. A., Machon, R. A., Huttunen, 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., Takai, N., et al (1991) Schizophrenia after prenatal exposure to the 1957 A2 influenza epidemic. *Lancet*, **337**, 1248–1250.

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Authors' reply: Crow and we have been talking at cross-purposes and misunderstanding one another. The proposition that maternal influenza in the second trimester of pregnancy results in a doubling (or an 87% increase) of the risk of schizophrenia in the offspring conceals two quite different hypotheses: (a) that the offspring of the entire population of women in the second trimester of pregnancy at the time of an influenza epidemic will be twice as likely to develop schizophrenia as the offspring of an unexposed population; and (b) that the offspring of women who actually contract influenza during the second trimester of pregnancy will be twice as likely to develop schizophrenia as the offspring of women who do not. Hypothesis (a) was proposed by O'Callaghan (but not, incidentally, by Mednick) and tested by Crow & Done. We made it clear in our original contribution to this correspondence (Adams & Kendell, 1996a) that we were concerned with hypothesis (b). We were wrong to suggest that Crow & Done's arithmetic was faulty; it was appropriate to the hypothesis they were testing. They were wrong to entitle their article 'Prenatal exposure to influenza does not cause schizophrenia'. As we have demonstrated (Adams & Kendell, 1966b), they had too few