# Correspondence

EDITED BY TOM FAHY

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## 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) × 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 × 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 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.

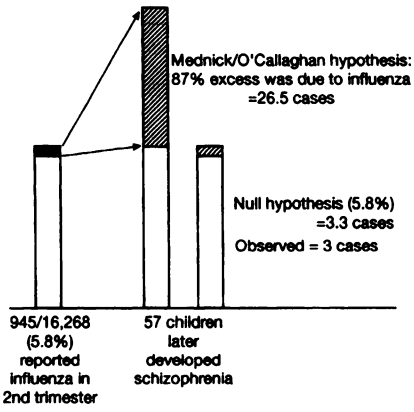



**Fig. 1** Relationship between exposure to influenza in the 1957 epidemic and the births of schizophrenic patients in March 1958 according to the hypothesis of Mednick *et al* (1988) and O'Callaghan *et al* (1991), and the null hypothesis, together with the numbers actually observed.

**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.

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

**—, — & Johnstone, E. C. (1991)** Schizophrenia and influenza. *Lancet*, **338**, 116–117.

**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., Takei, 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, 1996*a*) 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, 1966*b*), they had too few



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schizophrenic offspring in their cohort to be capable of refuting hypothesis (b); and if contracting influenza in mid-pregnancy does indeed double the child's risk of developing schizophrenia, that would surely be important both to our understanding of schizophrenia and as a public health issue.

**Adams, W. & Kendell, R. E. (1996*a*)** Influenza and schizophrenia (letter). *British Journal of Psychiatry*, **169**, 252–253.

**— & — (1996*b*)** Influenza and schizophrenia (letter). *British Journal of Psychiatry*, **169**, 791–792.

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## Early detection of schizophrenia

**Sir:** The detection of pre-schizophrenia using "at risk mental states" (Birchwood *et al*, 1997) is crucially dependent on (a) the prevalence of the hypothesised 'pre-clinical' schizophrenia disease state, and (b) the specificity and positive predictive value (PPV) of the risk indicator. Pre-clinical schizophrenia is, by definition, a state of transition, and its prevalence in the population will therefore approach (low) schizophrenia incidence. The specificity of detection criteria such as ideas of reference is also low, because these symptoms are much more prevalent in the general population than is pre-schizophrenia (e.g. Eaton *et al*, 1991). Let us assume that (a) as many as 50% of pre-schizophrenics have easily detectable ideas of reference; (b) the pre-clinical disease state has a prevalence of 0.05% in the population; and (c) the specificity of ideas of reference is as high as 90%. Even these values will yield an unworkably low PPV of 0.3% (of 1000 having 'at risk' mental states, only three have disease).

Combining criteria (Birchwood *et al*, 1997) in a parallel fashion will further decrease the already low PPV, and although serial combination of criteria may increase the specificity somewhat, the number of undetected cases will increase with each serial step, so that eventually one is left with an insignificant proportion of the cases that one had set out to detect (Hennekens & Buring, 1987).

McGorry's group also used trait indicators of risk, such as family history, claiming high schizophrenia transition rates in groups with serially combined state and trait indicators (Yung *et al*, 1996). However, most cases had already been referred to a psychosis service before 'transition', and individuals without state/trait indicators were not followed-up for their transition rate (thus making it impossible to establish the PPV of the detection criteria). In addition, application of categorical decision rules (case/non-case) on dimensional scale structures (sub-case) is confusing, and subject to a statistical 'transition' artifact similar to the one that generates regression to the mean. Only 20% of schizophrenics have a first-degree relative with the same diagnosis (low sensitivity), and only 10% of first-degree relatives of schizophrenics will develop the disease (low specificity), resulting in a very low PPV if the possibility of early detection in non-selected populations is examined.

**Birchwood, M., McGorry, P. & Jackson, H. (1997)** Early intervention in schizophrenia. *British Journal of Psychiatry*, **170**, 2–5.

**Eaton, W. W., Romanowski, A., Anthony, J., *et al* (1991)** Screening for psychosis in the general population with a self-report interview. *Journal of Nervous and Mental Disease*, **179**, 689–693.

**Hennekens, C. & Buring, J. (1987)** *Epidemiology in Medicine*, pp. 334–335. Boston, MA: Little Brown & Company.

**Yung, A. R., McGorry, P. D., McFarlane, C. A., *et al* (1996)** Monitoring and care of young people at incipient risk of psychosis. *Schizophrenia Bulletin*, **22**, 283–305.

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## Terminology of learning disability

**Sir:** I agree wholeheartedly with Reid (1997) that the term 'learning disability' is confusing. This is a particular problem among professionals working with children. Some use the term of children with mental retardation, some use the term of children with normal intelligence who have specific development disorders of scholastic skills, while others use it to describe children who are failing to achieve their academic potential whatever the reason. It is important that we all use a clear diagnostic term, whatever this is to be. It is also important that this diagnostic term is decided upon by doctors and not by politicians. My preference is for the term 'mental retardation', which is used in both ICD–10 and DSM–IV.

**Reid, A. H. (1997)** Mental handicap or learning disability. A critique of political correctness. *British Journal of Psychiatry*, **170**, 1.

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**Sir:** Reid (1997) suggests that rejecting old labels may be about denying the very existence of difference and may thus allow denial and dismissal of need. I agree that this can be an unhealthy part of the dismissal of labels but examining our labels for difference is ultimately about a healthy and maturing dynamic in society.

It is interesting that Reid describes awareness in labelling starting with race, then gender, then disability. I feel this is an evolution in society. Why did we have race and gender discrimination acts in the 1970s with strong powers of enforcement but no disability discrimination act until the 1990s and with only weak enforcement powers? In the fight for racial de-segregation in schools, minorities were often told it was better for them to be placed in segregated schools where their needs were understood – an argument that would be seen as outrageous today. Within contemporary families such arguments are often used to deny their 'different' child with disability a place in a mainstream school.

Reid criticises the term learning disability as containing no suggestion of medicine. Surely this is an example of the arrogance for which the medical profession is criticised. People living with the difference of learning difficulties would perhaps reject terms which define them as a medical grouping rather than as different but true members of our community.

The words 'learning disability' are not perfect, but debate about this can only be healthy. I would suggest that an even more important issue is that attitude and provision are even less perfect and that challenging our labels helps us grapple with these very issues.

**Reid, A. H. (1997)** Mental handicap or learning disability. A critique of political correctness. *British Journal of Psychiatry*, **170**, 1.

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## Confidential Inquiry Into Suicide and Homicide by Mentally Ill People

**Sir:** The Confidential Inquiry into Suicide and Homicide by People with Mental Illness now enters a new stage (Appleby *et al*, 1997). Much emphasis will now be placed upon establishing a complete and representative sample of all relevant suicides, identified through data obtained from local Directors of Public Health, to whom HM coroners routinely notify inquest verdicts.

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