British Journal of Psychiatry (1994), **165**, 833–843

Correspondence

Prenatal influenza and schizophrenia

SIR: Crow & Done (1992) addressed the postulated association between maternal exposure to the 1957 epidemic of "Asian flu" and the risk of developing schizophrenia, by using a sample from the National Child Development Study (NCDS). Based upon the results of this study, Crow (*BJP*, May 1994, **164**, 588–592) dismisses the previously reported association between prenatal exposure to influenza and later schizophrenia (Mednick *et al*, 1988; Barr *et al*, 1990; O'Calloghan *et al*, 1991; Sham *et al*, 1992; Adams *et al*, 1993; Takei *et al*, 1994). However, we question whether the NCDS study was appropriate and had adequate statistical power to support Crow's conclusion.

In longitudinal studies like that by Crow & Done (1992), an estimate of rate ratio between the exposed and unexposed and 95% confidence interval (CI) are usually calculated. Crow & Done did not choose this standard approach, and instead applied 2×2 analysis to their data. Calculation of CIs is more informative than their method, since a CI describes the amount of sampling variability inherent in the estimate, reflecting the uncertainty of the observed estimate.

Applying the cohort approach in a situation where the endpoint is a rare outcome, like schizophrenia (life-time risk about 0.8%), is problematic. As the actual number of cases determines the width (uncertainty) of the CI of the rate ratio, a large sample (i.e. person-years at risk) is required to collect the adequate number of disease events.

We applied the standard epidemiological approach to the data presented by Crow & Done (1992). They identified one case of narrow schizophrenia among the 945 exposed (i.e. exposure to the 1957 influenza pandemic during the second trimester), and 33 cases among the remaining 15 323, considered as the unexposed. This yields an exact odds ratio of 0.49 with 95% CI of 0.12 to 2.95 (StatXact programme). In a rare disease, the rate ratio is equivalent to odds ratio. This indicates that the true relative risk lies between 0.12 and 2.95, and is therefore compatible with relative risk as high as 2.95 among the exposed.

We also calculated the power in the study by Crow & Done (1992). They estimated the risk of schizophrenia up to the age of 27 in their sample as about 0.36%. The relative risk for the exposed that they considered was 1.88, a value that was derived from the study by O'Callaghan *et al* (1991). If one wishes to have 80% power of detecting an effect of this magnitude with a significance level of 0.05, then a sample of 8700 is required for each of the unexposed and exposed groups (a total of 17 400 subjects). When the size is fixed, the power of detecting an effect is greatest at a 1:1 ratio of the number of unexposed and exposed. Among the total sample of 16 268 in the NCDS, the number of subjects Crow & Done regarded as exposed was only 945, as mentioned earlier. Even if the remaining sample, (i.e. 15 323) is considered unexposed, the power of their study is only 30%. This power indicates a 70% probability of accepting the null hypothesis (no association) even if a true association exists (Type II error). Needless to say, the power of the study is reduced further by random misclassification of the exposure status. Therefore, the study of Crow & Done (1992) did not have an adequate power to detect the effect, and Crow (1994) was incorrect in stating that the study "has considerable power to detect an effect of the size claimed by O'Callaghan *et al*. The findings are unequivocally negative."

References appear overleaf

NORIYOSHI TAKEI
ROBIN M. MURRAY
Institute of Psychiatry & King's College Hospital
Denmark Hill,
London SE5 8AF