Invited commentaries on: Signs of asphyxia at birth and risk of schizophrenia/Obstetric complications and risk of schizophrenia†

DOES ASPHYXIA AT BIRTH CAUSE SCHIZOPHRENIA?

Further problems in case–control studies

I comment on these papers as a contribution to the long-standing debate about whether perinatal events contribute to the aetiology of psychosis. I argue, particularly in the light of the recent literature, that the evidence presented by Dalman *et al* (2001, this issue) is less compelling support for the authors' conclusion – that signs of asphyxia at birth are associated with an increased risk of schizophrenia in adults – than might at first sight appear. The problems relate to how the data were collected, who was blind to and responsible for critical aspects of data extraction, and how asphyxia was assessed.

Birth records (n=1567) were copied from the archives and given code numbers to conceal case or control status. Controls were selected from the parish register as the next two births in time of the same gender in the same hospital as the case. The first author (C.D.), who was not blind to case/control status, selected and retrieved the records. It is not stated which parts of the notes were copied. Is there a possibility that selective bias entered at this stage? The protocol did not exclude it.

The copied notes were then presented to a midwife for assessment. Two midwives (Gunilla Lilja and Åsa Weitzberg) are acknowledged as assessing records (1567 of them) but they are not co-authors and therefore have not been asked to take responsibility for this aspect of the investigation. One can ask how were the notes presented to the midwives and how blind were these assessors to case/control status? If the case notes were presented in trios (one proband and two controls), there was clearly a possibility that the assessment was not blind – the two controls were born later than the proband. If on the other hand case notes were presented to the assessor in bundles, there was the possibility that he or she may have discerned that a particular bundle related to cases or to controls. Thus, observer bias either at the stage at which the case notes were copied or when the copied notes were assessed has not been excluded.

There are further concerns about the assessments of asphyxia. Only 20.5% of the records in this study had an Apgar rating; the conclusions therefore depend on the assessment of asphyxia in the infants who did not have an Apgar rating. Exactly how was this done? Here we read: "All records that lacked an Apgar scoring were assessed by the midwife according to a protocol in which the five Apgar items (heart rate, breathing, colour, tone and excitability of the infant) were defined". No information is given on how often these items were recorded in the notes. The description that follows for the 40 records that were selected on the basis of an "estimated Apgar score" as showing signs of asphyxia implies that each of these items was recorded at 1 minute, 5 minutes and 10 minutes (32 cases selected at 1 minute, nine at 5 minutes and one at 10 minutes with two cases classified as "unknown" but nevertheless included). Were such detailed and timed assessments really available before the Apgar rating was introduced? If so why could not these rather than Gunilla Lilja's and Åsa Weitzberg's global judgement of the presence or absence of asphyxia have been used as an index?

To reassure the reader that the appraisal of asphyxia they have adopted was reliable the authors adopted two procedures. First, the authors state that "a random sample of 300 birth records for infants classified as having no signs of asphyxia was re-examined by the first author, and none was classified as false negative". Since, with a rate of 3.2%, nine to ten cases of asphyxia would be expected this clearly was not a random sample of the records available. If the records were selected for absence of signs of asphyxia, their re-examination by the first author cannot be considered a test of reliability. She already knew what to expect.

Second, examination by the midwife: it is stated that a second midwife scrutinised blindly the records of all the 44 cases that were originally classified as affected and a random sample of 120 classified as unaffected (in total, 164 birth records). The inter-record agreement is recorded as being excellent (0.95). This assessment constitutes the only appraisal of a mixed group of records previously classified as with and without signs of asphyxia. In that within this group it suggests that 7 or 8 cases (5%) out of 164 would have been re-classified it reveals a relevant rate of error. It is not clear at what stage (whether before or after completion of the study or submission and review of the paper) this assessment was carried out. No reliability study on an unselected sample of the original series of case notes was conducted.

Conclusions

The conclusion that "signs of asphyxia at birth are associated with an increased risk of schizophrenia" that Dalman *et al* draw is subject to the following reservations. First, two possible sources of observer bias (copying of sections of case records by a non-blind observer, and a possible order effect in the assessment of records) have not been eliminated. Second, responsibility for blindness of key assessments has not been acknowledged by co-authorship of the workers involved. Third, the reliability with which asphyxia was detected in retrospectively scrutinised case notes that lacked Apgar ratings has not been established.

The paper by Thomas *et al* (2001, this issue) on the same data-set casts the conclusions of Dalman *et al* in doubt. Across a range of obstetric complications (including complications of delivery, eclampsia, and low birth weight) no differences between cases and controls were detected, whether in the group as a whole or (as the authors emphasise) in subgroups identified by gender or age of onset. Asphyxia (assessed as described in Dalman *et al*)

†See pp. 403–414, this issue.

https://doi.org/10.1192/bjp.179.5.415 Published online by Cambridge University Press

stands out as the sole correlate of schizophrenia. Yet Table 2 of Thomas *et al* indicates that abnormalities of foetal heart rate (<100 or >160 b.p.m.), a quantifiable component of the Apgar score, did not distinguish cases from controls in any of the subgroups examined. In other words, the heart rate was unchanged in the cases the authors judged to be asphyxiated at birth.

Two recent case–control studies cast doubt on the pathogenic influence of asphyxia that Dalman *et al* claim to have detected. Kendell *et al* (2000) found no evidence that an Apgar score of <7 distinguished the birth records of 156 cases of schizophrenia from 156 matched controls (nor did the Apgar score distinguish cases from controls in their study of 217 probands with affective psychoses; Bain *et al*, 2000). Byrne *et al* (2000) found that the assessments of 'incubator/resuscitation/blue' and 'asphyxiation', both of which would appear to have qualified a case for the category of 'asphyxia' as defined by Dalman *et al*, did not distinguish 431 individuals with schizophrenia from 431 gender-matched controls. Both the studies of Kendell *et al* and of Byrne *et al* drew negative conclusions regarding the role of a range of labour and delivery complications in the aetiology of schizophrenia. The negative findings of Thomas *et al* add to this consensus, while the positive claims regarding asphyxia of Dalman *et al* stand in contrast to other recent studies and may be attributable to observer bias.

Bain, M., Juszczak, E., McInneny, K., *et al* (2000) Obstetric complications and affective psychoses. Two case–control studies based on structured obstetric records. *British Journal of Psychiatry*, **176**, 523–526.

Byrne, M., Browne, R., Mulryan, N., *et al* (2000) Labour and delivery complications and schizophrenia. Case–control study using contemporaneous labour ward records. *British Journal of Psychiatry*, **176**, 531–536.

Dalman, C., Thomas, H. V., David, A. S., *et al* (2001) Signs of asphyxia at birth and risk of schizophrenia. Population-based case–control study. *British Journal of Psychiatry*, **179**, 403–408.

Kendell, R. E., McInneny, K., Juszczak, E., *et al* (2000) Obstetric complications and schizophrenia. Two case–control studies based on structured obstetric records. *British Journal of Psychiatry*, **176**, 516–522.

Thomas, H. V., Dalman, C., David, A. S., *et al* (2001) Obstetric complications and risk of schizophrenia. Effect of gender, age at diagnosis and maternal history of psychosis. *British Journal of Psychiatry*, **179**, 409–414.

T. J. Crow University Department of Psychiatry, Warneford Hospital, Oxford OX3 7JX, UK

MORE LARGE STUDIES NEEDED

We need more large studies and cumulative meta-analyses of individual obstetric complications and their effects on the neonate

Obstetric complications are 'one' of the few putative causes of schizophrenia for which there is relatively good evidence (Geddes & Lawrie, 1995), but only a few particular obstetric complications are likely to be important (Geddes *et al*, 1999) and they may have at most non-specific effects, for example in bringing forward the age at onset (Verdoux *et al*, 1997). The importance of the papers by Dalman *et al* (2001, this issue) and Thomas *et al* (2001, this issue) is that they attempt to relate obstetric complications to their effects on the neonate, and to the subsequent development of schizophrenia. They are a valuable contribution to the ongoing debate about the role of obstetric complications in schizophrenia, despite some inevitable methodological limitations.

The investigators identified the obstetric records of 524 cases and 1043 controls ascertained from the Stockholm County In-Patient Register, thus avoiding the potential pitfalls of maternal recall bias. Apgar scores were recorded at the time of delivery in only 20.5% of the sample and the majority of the scores were therefore calculated retrospectively, albeit blind to case/control status. An Apgar score of 6 or less at 1, 5 or 10 minutes was taken as evidence of asphyxia and found in 44 obstetric records. These 'positive' records were then scrutinised by experienced paediatricians, although negative records were not subject to the same scrutiny. Interrater reliability was high. The methodological limitations may have resulted in some bias but are unlikely to have lead to a false positive result.

Sample characteristics for cases and controls differed in a few important respects. A higher proportion of cases were unmarried or divorced, many received inadequate antenatal care and cases were more likely to have a history of maternal psychotic illness. The risk each complication contributed to the development of schizophrenia was calculated using the odds ratio (OR) by conditional logistic regression.

Most obstetric complications were not found to contribute any additional risk, with the exception of signs of asphyxia which were found significantly to increase the odds of the subsequent development of schizophrenia (OR 2.7, 95% CI 1.5–4.8). This result remained significant and was in fact strengthened once potential confounders (maternal history of psychotic illness, maternal age, socio-economic class, marital status, attendance at antenatal care) were taken into account (OR 4.4, 95% CI 1.9–10.3). Notably, however, no dose–response relationship was found between the severity of asphyxia and the risk of schizophrenia. This does not support an aetiological relationship, but one could argue that collapsing Apgar scores of less than seven over three time points (presumably to increase statistical power) added 'noise'. A large or consistent effect of gender, age at diagnosis or maternal history of psychosis was not found.

These results are in keeping with the results of meta-analyses suggesting that obstetric complications are not simply a manifestation of genetic risk and may be pathogenic via a potential final common pathway of hypoxic brain damage (Verdoux *et al*, 1997). Although the age at onset effect was not significant, the results are in the expected direction. Single studies are often underpowered, frequently fail to find significant differences between cases and controls and tend to rely on summary scales of mainly maternal complications. The current studies avoid the problems of summary scales and their uncertain interpretation. It is, however, sobering to realise that despite a total sample of over 1500 they may have been too small to detect some important effects. More large studies of specific complications, and cumulative meta-analyses of them, are required before the case for or against the potential role of obstetric complications in schizophrenia is conclusive.

Dalman, C., Thomas, H. V., David, A. S., *et al* (2001) Signs of asphyxia at birth and risk of schizophrenia. Population-based case–control study. *British Journal of Psychiatry*, **179**, 403–408.

Geddes, J. R. & Lawrie, S. M. (1995) Obstetric complications and schizophrenia: a meta-analysis. *British Journal of Psychiatry*, **167**, 786–793.

___, Verdoux, H., Takei, N., *et al* (1999) Schizophrenia and complications of pregnancy and labor: an individual patient data meta-analysis. *Schizophrenia Bulletin*, **25**, 413–423.

Thomas, H. V., Dalman, C., David, A. S., *et al* (2001) Obstetric complications and risk of schizophrenia. Effect of gender, age at diagnosis and maternal history of psychosis. *British Journal of Psychiatry*, **179**, 409–414.

Verdoux, H., Geddes, J. R., Takei, N., *et al* (1997) Obstetric complications and age at onset in schizophrenia: an international collaborative meta-analysis of individual patient data. *American Journal of Psychiatry*, **154**, 1220–1227.

A. M. McIntosh, S. M. Lawrie Edinburgh University Department of Psychiatry, Kennedy Tower, Royal Edinburgh Hospital, Edinburgh EI0 5HF, UK

https://doi.org/10.1192/bjp.179.5.415 Published online by Cambridge University Press