The risk of having a Down syndrome pregnancy is highly associated with a mother’s age. There have been many publications proposing different mathematical models to describe this association using the prevalence of Down syndrome in different populations from countries including America, Canada, Australia, the UK, Belgium, Sweden and Russia (personal communication) from 1958 to 2004. Although the mathematical models vary, it is striking...
how similar the underlying observed prevalence is according to maternal age. For example, the risk of a Down syndrome birth (in the absence of prenatal diagnosis and subsequent termination) for a 35-year-old woman is currently estimated to be 1 in 350 regardless of where she comes from, and the same risk was applicable in the 1960s. This would seem to imply that environmental factors are unlikely to be associated with the risk of Down syndrome. Several studies attempted to detect associations between environmental hazards and Down syndrome by seeking evidence of non-random occurrence of cases (clusters), but no such associations were found.3–5 These studies tended to have low power to detect clusters, due to their small size and/or their use of inefficient statistical methods.

In this issue of IJE, McNally et al.6 apply new, powerful statistical methods to eight years of data from a population of 30 000 births per year to investigate whether there is any evidence of space–time clustering of Down syndrome, Patau syndrome and Edwards syndrome. They find some evidence of space–time clustering for Down syndrome, but not for Patau or Edwards syndromes (possibly due to the latter two syndromes having far fewer cases and therefore less power to detect a clustering effect). They found that clustering of Down syndrome was associated with cases from more densely populated areas and was also present in women under 40 years of age. How do we reconcile this surprising result?

One explanation may be the magnitude of the effect. The effect of maternal age is so strong that the presence of environmental effects may not significantly alter the estimates of maternal age related risk. For example, the risk of a Down syndrome birth in the absence of prenatal diagnosis and subsequent termination increases over 40-fold between the ages of 20 and 45 (from 0.7/1000 births to 28/1000 births).1 If environmental effects are responsible for, increasing the background risk by say, an additional 0.07/1000 births (i.e. equivalent to an increase in risk of 10% amongst younger women), differences in rates of 0.07/1000 births between studies would not be detectable. However, the total number of Down syndrome births in a population would increase, because there are many more births to younger than older women. Therefore, although there does appear to be very striking agreement between the maternal age related risks in different studies, this does not mean that an environmental hazard may not be present. Unfortunately, space–time clustering analyses do not estimate the magnitude of the clustering effect.

An alternative explanation may arise from the methods of analysis. The space–time analysis works by examining how close together cases are in both space and time, compared with how close you would expect them to be if there was no clustering. No account is taken of the actual numbers of births that are occurring in each area, nor of the maternal age distribution. This is justified by the idea that even if there are areas where you would expect more Down syndrome births to occur, say due to more older mothers living there, you would still not expect these births to cluster in time. However, the establishment of new housing developments for example, may cause an underlying space-time cluster of births, which may then result in a space-time cluster of Down syndrome births. The authors state that there was little migration into or out of the region studied and few mothers changed residence between the time of booking and delivery. When the authors used the same methodology on a very similar data set (the same region for 1991–2003) to examine clustering of other congenital anomalies, they did not find a clustering effect despite the large number of cases.7 This may indicate that biases due to the distribution of births in the region did not occur in this study and the observed clustering is, in fact, real or due to some other unidentified source of bias.

McNally et al. have presented a very persuasive argument that transient environmental factors may play a role in the aetiology of Down syndrome. However, more work on estimating the magnitude of the effect is needed.

References