Unravelling prenatal influences: the case of smoking in pregnancy

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The adverse health outcomes of maternal smoking in pregnancy are long-established: prenatal smoking retards fetal growth, depresses infant birthweight and is associated with increased risks of pregnancy loss.1 More recently, epidemiological evidence has also linked prenatal smoking with children’s behavioural outcomes, and with impairments in their memory and learning. A quite extensive body of findings now documents increased risks of aggression, conduct problems and hyperactivity in the offspring of mothers who smoked while pregnant.2 Links with children’s cognitive functioning are evident early in development, but may diminish with age. Associations with behavioural difficulties appear more long lasting, with some studies pointing to heightened risks of aggression and criminality persisting well into adult life.2

Do these observational findings reflect a causal influence? Identifying the causal status of environmental risk factors poses major challenges in many areas of epidemiological research;3 when those risks occur prenatally, the challenges can be especially acute.4 Three papers in this issue of IJE highlight differing approaches to tackling these questions in relation to prenatal smoking, and underscore the complexity of the issues involved.

Probably the most central stumbling block to causal inference in this field lies in the problem of confounding.2,5,6 Mothers who smoke in pregnancy are not a random sample of mothers. Maternal smoking is known to be associated with, and probably influenced by, a wide range of social and individual characteristics, including maternal genotypes. Roza and colleagues7 approach the problem in two different design features, to move the debate forward. Instead, we need a range of approaches, utilizing different design features, to move the debate forward. Roza and colleagues7 approached the problem in two ways: through statistical adjustment for a wide range of well-selected confounders, and through the additional strategy of examining effects of fathers’ smoking during the mother’s pregnancy. Studies of adverse

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birth outcomes suggest that effects of passive smoking are much weaker than those of active smoking. Assuming a similar pattern of effects here, Roza et al.7 reasoned that if maternal smoking is indeed causally related to children’s behaviour problems, links with active maternal smoking should be markedly stronger than those with passive exposure to fathers’ smoke.

The findings of their study are clear and consistent. In unadjusted models, continued smoking in pregnancy was associated with a 60% increase in risk for toddler behaviour problems. Adjusted for demographic confounders and parental psychopathology that effect was reduced to just 8%. Effect estimates for fathers’ smoking were closely similar to those of mothers’, suggesting that they too owed more to correlated parental characteristics than to effects of passive smoking. Taken together, the pattern of the findings suggests that prenatal smoking may primarily be a marker for other vulnerability factors for offspring behaviour problems, rather than itself constituting a causal risk.

Obel and colleagues10 focused on a more specific outcome: parent- and teacher-rated measures of hyperactivity inattention. Recent evidence suggests that some differences in brain morphology in children with attention deficit hyperactivity disorder (ADHD) are already evident at birth, making prenatal exposures especially strong candidates for environmentally mediated risks. In this instance, however, there are particular concerns over the possibility of genetic confounding. ADHD (and the related dimensional measures of hyperactivity used here) is quite highly heritable; in addition, the well-documented effects of nicotine on attention mean that mothers who themselves have problems with inattentiveness may be especially likely to smoke.

Rather than attempting direct measurement of these confounders, Obel et al.10 made use of international comparisons. Rates of pregnancy smoking differ quite widely between European countries. Given these variations, Obel et al.10 advanced the plausible argument that in populations where smoking is less socially acceptable, and where the prevalence of pregnancy smoking is low, a larger proportion of mothers who continue to smoke in pregnancy may have an underlying ADHD pathology than in populations where smoking is more normative. Following that logic, we would expect associations with ADHD-related outcomes in offspring to be higher in countries with lower rates of pregnancy smoking. If, on the other hand, the strength of the association is similar in societies with very different rates of smoking, genetic confounding is less likely to be a concern.

In essence, that second scenario is what the investigators found. Comparing findings in a large Finnish cohort (where only 16% of women reported smoking in pregnancy) with those from two Danish cohorts (where rates of smoking were between 29% and 36%), Obel et al.10 documented very similarly increased risks for offspring hyperactivity in all three samples; on the basis of these findings, then, we might conclude that confounding may not be such a major problem after all.

In microcosm, these contrasting findings reflect the divergent conclusions currently emerging from a range of studies in this field. How can these apparent contradictions be resolved? Writing in the IJE some months ago, Michael Rutter outlined a series of possible strategies for testing the causal status of environmental risks, some focusing on statistical approaches and others on the use of designs capable of disambiguating effects.11 Where—as here—genetic confounding is likely to be implicated, design features may be especially important, as genetic confounds cannot necessarily be dealt with satisfactorily through reliance on statistical controls. Two other recent studies illustrate the types of ‘natural experiment’ likely to prove most informative. The first, studying multiple offspring in the same families, compared outcomes for siblings with varying exposure to smoking in utero.12 The second made ingenious use of the possibilities offered by in vitro fertilization (IVF) to examine effects of smoking in mother–child pairs differing in their genetic relatedness.13 Both studies tested associations with birthweight as well as with behavioural outcomes. In relation to birthweight, both sets of findings were consistent with much past research in pointing to environmentally mediated effects of prenatal smoking. In the behavioural domain, the pattern was quite different. In the sibling study, sibs varying in exposure to prenatal smoking had closely comparable behavioural outcomes. In the samples conceived via IVF, associations between pregnancy smoking and offspring behaviour problems were only observed when mothers and offspring were genetically related. Once again, unique effects of pregnancy smoking proved hard to detect.

A third study reported in this issue approached the problem in a quite different way. Morales and colleagues14 examined the extent to which variations in children’s metabolic genes affect their susceptibility to maternal smoking. To do this, they focused on polymorphisms of GSTMI and GSTT1, genes that encode phase II xenobiotic metabolizing enzymes involved in the detoxification of tobacco smoke. Recent studies have reported associations between fetal growth and maternal gene variants likely to modify the effects of smoking; Morales et al.14 applied this same paradigm to early childhood cognitive outcomes. Because deletion of these genes, resulting in loss of functional activity, is quite common, the authors argued that tests for interactions with these polymorphisms should highlight whether maternal smoking does indeed have neurotoxic effects. As they report, adverse cognitive outcomes in offspring whose mothers smoked in pregnancy were only
found in children lacking the GSTM1 allele; these results were robust to controls for post-natal maternal smoking, maternal education and social class, and were not evident in tests involving fathers' smoking. As the authors also point out, they did not study maternal genotypes, nor the possibility of maternal–fetal gene interactions and their findings could be confounded by effects of other gene variants. If replicated, however, their results clearly add an important new piece to the jigsaw puzzle, and one that may require re-evaluation of past findings.

In this field as in others, apparent inconsistencies in findings will doubtless act as a spur to further enquiry. At this stage, for example, we still lack a clear understanding of the mechanisms whereby prenatal smoking could influence neurodevelopment, and more focused studies in this area are likely to show rich rewards. Investigators are now beginning to harness the possibilities of brain imaging in this task, and preclinical studies provide persuasive evidence of epigenetic processes that in time may provide the key links between exposure to environmental pathogens and risk for adverse behavioural and cognitive outcomes in offspring. The public health significance of maternal smoking in pregnancy is beyond doubt; studies such as those reported in this volume highlight the vigour and innovation already evident in research in this area, and the challenges still to be overcome.

References