Determinants of child health and development: the contribution of ALSPAC—a personal view of the birth cohort study

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EDITOR'S
CHOICE

ABSTRACT

Britain has a unique experience of national longitudinal birth cohorts, but the Avon Longitudinal Study of Parents and Children differed in two major respects—it was based in one area rather than being a national sample, and it started in pregnancy rather than at birth or later in the first year. This paper outlines a personal selection of 10 topics, highlighting results from some of the 400+ papers that have already been published from this study. It indicates in particular how many childcare and domestic fashions were neither of benefit to the children (or their parents), the importance of pregnancy in regard to childhood conditions and the likely dangers of some common chemicals, whether in medications or domestic products.

INTRODUCTION

Three major British birth cohort studies were ongoing by 1985—comprising births occurring throughout the nation in 1 week of 1946,¹ 1958² and 1970.³ None of these studies had been initially designed as anything other than a study of births. On each occasion follow-up was an afterthought. Nevertheless the studies had provided much important information on the status of the nation's children, and how conditions varied with social status and region.

Although it would have been logical to start another national survey in 1982, politically it was a bad time to commit funding and no further major studies were initiated until the Avon Longitudinal Study of Parents and Children (ALSPAC) in 1990.⁴ Unlike its predecessors, it was designed to be a longitudinal birth cohort. Its stated aims were to determine ways in

which the individual's genotype combines with environmental pressures to influence health and development; it recognised the need to identify environmental factors prospectively during pregnancy. The advantage of an area-based study concerned the relative ease of contacting the pregnant women, collecting biological samples and providing facilities for hands-on examination of the study children under controlled circumstances.⁴

There were over 400 papers published by October 2009, with a steadily increasing rate over time (figure 1). Details of the publications can be found on the study website.⁵ Below I describe a few of the findings out of the many already published.

The puzzle of peanut allergy

In the early years of the study it became apparent that there was a growing proportion of children with peanut allergy. This was investigated in a number of ways within ALSPAC, by first identifying children likely to have this allergy by means of history and skin prick tests and confirmation using a double blind peanut challenge.⁶ We showed that the affected children were much more likely than other children to have had oozing crusted rashes early in infancy (OR 5.2,

$p<0.001$), with a trend such that the more severe the rash the higher the prevalence of subsequent peanut allergy.⁷ The risk was exceptionally high if oils or creams containing peanut oil had been used during infancy (OR=6.8, $p=0.02$), and the hypothesis was raised that the child was likely to have become sensitised by having peanut oil containing lotions administered onto broken skin.^{7,8}

The prenatal antecedents of asthma

Although it is generally known that the severity of asthma is strongly influenced by environmental factors such as outdoor air pollution, studies within ALSPAC have produced evidence that the prenatal environment has a strong influence on the development of asthma. Maternal anxiety in pregnancy, and the taking of paracetamol by the mother have both been shown within ALSPAC to have dose-response relationships with later asthma.^{9–11} Other factors believed by some to cause the onset of wheezing, such as immunisation, have been shown not to be true.¹²

The domestic physical environment

Within the home there have been a number of ALSPAC studies carried out on the levels of air pollution. Although environmental tobacco smoke is well known as a threat to respiratory health, this study has also looked at other sources of air pollutants, mainly related to cleaning products. A scale was developed concerning the frequency with which 12 different products were used within the home. This scale was shown to be strongly related to the onset of wheezing in early childhood,¹³ and a later study showed strong relationships with persistent wheeze and reduced lung function by age 8.5 years.¹⁴ Other ALSPAC studies have concentrated on features of hygiene, and demonstrated that children whose mothers kept them excessively clean were at increased risk of developing eczema and wheezing by age 3.5 years.¹⁵

Figure 1 Number of publications based on ALSPAC, by year of publication.

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The importance of eating fish

There has been a variety of advice to the pregnant woman as to how much seafood she should eat, with caution being advocated because of the contamination by mercury and various persistent chemicals found in those seafoods at the top of the food chain such as tuna, shark and whale. On the other hand, it was recognised that omega-3 fatty acids were beneficial. The key question relates to the balance between the potential harm and benefit of various types of seafood. Information had been collected by ALSPAC during the study pregnancy concerning the amount of different types of seafood that the mother was eating. From this the amount of omega-3 fatty acids was calculated and shown to relate well to the mothers' blood levels of docosahexaenoic acid.¹⁶ Comparison of the amount of fish eaten by the mother prenatally with the outcome of the child has shown beneficial effects on visual stereoacuity,¹⁶ early child development,¹⁷ child behaviour and verbal IQ.¹⁸

Maternal depression and anxiety

ALSPAC was one of the first studies to document the fact that, in general, mothers had more signs of depression and anxiety during pregnancy than postnatally.^{19–21} A series of studies led by Tom O'Connor and Vivette Glover have shown that prenatal anxiety and mood disturbance appears to have a relationship with child outcomes such as hyperactive behaviour, disturbed sleep in childhood and a different pattern of diurnal salivary cortisol.^{22–26} These findings were independent of postnatal mood disorders which were also shown to have effects on the developing child.

The importance of the father

A number of studies within ALSPAC have looked at paternal depression and shown that children whose fathers had depression in the postnatal period were more likely to have behaviour problems at age 3 and a half and, in particular, (for boys) conduct problems at age 7. This was shown to be independent of factors such as maternal depression and paternal depression at other periods of the child's life.²⁷ Further analysis showed an association with psychiatric disorders in the child at age 7, particularly if the father had been depressed both during the prenatal period and postnatally. The disorders of the child were particularly of oppositional defiant/conduct disorders (OR 1.97, $p=0.03$).^{28, 29}

Patterns of parenting

At the time of the initiation of ALSPAC the local population had already been informed of the dangers of putting the young baby to sleep prone in regard to sudden infant death syndrome. However there was still considerable disquiet as to the safety and possible dangers of putting the baby to sleep on his/her back. ALSPAC was able to show that babies placed prone, and to a lesser extent, those placed on their side had more respiratory infections and were less healthy than those put to sleep on their back,³⁰ but there was some evidence that those placed prone had slightly more advanced development at 6 months; this however was no longer evident at 18 months of age.³¹ These findings reassured policy makers on both sides of the Atlantic, who subsequently campaigned for children to be placed on their backs with consequent reductions in sudden infant death syndrome.

Other studies within ALSPAC that have been used to advise parents include the finding that potty training of the child is far more effective if started relatively early (<2 years), as leaving it until later results in an increased risk of persistent daytime wetting (OR=1.52, $p<0.001$) and of relapse in daytime wetting (OR=1.52, $p<0.001$).³² ALSPAC has published details of normal infant defecation patterns concerning frequency, consistency and colour,³³ and shown that contrary to popular belief there is very little difference in the first 3 years between these patterns for children who have an autistic spectrum disorder.³⁴ Additional studies by the nutritionists on the study have shown that introduction of lumpy rather than pureed foods early in infancy resulted in less feeding difficulties at 15 months.³⁵ Follow-up of these children showed that the reduction in feeding difficulties persisted and at 7 the children eating lumpy foods early were more likely to be consuming healthy foods such as fruit and vegetables.³⁶

The importance of biomarkers

Blood and other biological samples were collected from the mother during pregnancy, at delivery and from the child at a variety of time points.⁵ Consequently a number of studies have been undertaken which would not otherwise have been possible. As well as being able to harvest DNA for genetic studies, the ALSPAC biomarkers have shown: (a) the population variation in haemoglobin in children aged 8, 12 and 18 months,^{37, 38}

but that there was no detectable adverse effect on development at 18 months³⁹; (b) an association between the mother's prenatal blood levels of testosterone and an increase in her daughter's more masculine behaviour⁴⁰ but a reduction in levels of total IgE in the boys ($p<0.0001$)⁴¹; (c) assays of the child's blood at age 7 for biomarkers for coeliac disease showed a prevalence of 1.0%, and that the prevalence was twice as common among girls (OR 2.12, $p=0.0001$)⁴²; (d) lead levels in the child's blood at age 2 and a half is associated with reduction in reading ($p=0.006$) and writing ability ($p=0.003$) at age 7 and increased risk of antisocial behaviour (OR=2.9, $p=0.04$) and hyperactivity (OR=2.8, $p=0.03$).⁴³ Importantly this study indicates that the threshold for harmful effects should be reduced to 5 $\mu\text{mol/g}$ or lower.

The development of visual abilities

The various components of visual ability are important for the ultimate ability of the child socially and educationally. There are a number of studies led by Cathy Williams *et al* using the cohort to study the ways in which the child's vision may be helped by screening early using trained orthoptists,^{44, 45} and showing that early treatment for amblyopia results in better outcome in regard to vision.⁴⁶ She was also able to demonstrate that for children with amblyopia, those who had had patches were more likely to have been bullied unless the treatment had ceased prior to starting primary school.⁴⁷ The study was able to demonstrate that there were higher prevalences of a number of visual problems (hypermetropia, amblyopia and convergent strabismus) in the more deprived social classes,⁴⁸ and that these children were also less likely to be taken to eye care centres. This suggests that special efforts may need be made to screen and treat children in deprived areas for these visual problems.

Genetic effects

One of the first genetic studies undertaken within ALSPAC, long before the advent of genome-wide association studies, concerned the relationship between the insulin glucose kinase gene and fetal growth—this showed a relationship between the mother's (but not the infant's) genotype and birthweight.⁴⁹ Subsequently, studies with other genes were carried out, particularly relating to obesity,^{50, 51} bone mineralisation⁵² and child behaviour.⁵³ Although the sizes of

the effects demonstrated were relatively small, it is worth noting the large effects produced by the filaggrin gene. This gene had been shown elsewhere to be closely related to ichthyosis and eczema, but further studies within ALSPAC have shown that there were also strong relationships with childhood asthma, especially when associated with eczema (OR 3.2, $p=1.4 \times 10^{-11}$), and with sensitisation to aeroallergens (OR=2.1, $p=5.4 \times 10^{-27}$).⁵⁴

DISCUSSION

In this paper I have indicated some of the ways in which ALSPAC has contributed towards the wealth of knowledge required in order to push the evidence base forward so that appropriate advice can be given, and interventions initiated to improve the health, wellbeing and development of children. A number of these studies have influenced policy on both sides of the Atlantic, particularly in regard to the initiation of 'Back to Sleep' campaigns, and the recognition that it is important for a woman to eat fish during pregnancy.

In regard to contributing to parenting advice it is remarkable that many of the details we have uncovered are exactly what our own grandmothers used to advise such as putting the baby to sleep supine, introducing lumpy solids early, starting toilet training early and ensuring that the pregnant mother is as free from stress as possible. Rediscovering the wheel in this way is as important as revealing unexpected relationships. That with chemical exposures in the home is something with which our grandmothers did not have much contact; however, if the effects demonstrated within ALSPAC on wheezing and lung function are causal, this exposure may have important consequences for adult health as well as that in childhood.

I have only been able to touch on a few of the topics that are being explored within ALSPAC. Many studies of the data already collected are being undertaken by scientists throughout the world. These include topics such as environmental factors related to the onset of puberty, obesity, markers of cardiovascular disease as well as the development of psychiatric disorders in adolescence. Genetics studies are changing in emphasis and extent from candidate genes to genome-wide association studies, copy number variation to methylation. The likelihood is that the study will continue long into the future and contribute to the information from other cohort studies concerning the influence of prenatal and

childhood environments on adult disorders of various kinds.

ALSPAC has shown the value of in-depth information collected over time in a birth cohort study. The results to date and in the future are likely to continue to identify practical ways in which the health and development of children can be improved.

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