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EDITORIAL

Birth cohort studies: past, present and future

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Life is to be understood backwards, but it is lived forwards.
[Livet skal forstaaes baglaens, men leves forlaens]
Søren Kierkegaard, Danish Philosopher, 1813–55

There is considerable interest in the suggestion that exposures acting in early life, together with those accumulating in adulthood, and even between generations, have long-term consequences for health in adulthood.[1] Potential early-life factors that might impact on adult health, include those acting during (or before) the period of fetal development (such as endocrine disruptors, maternal diet, smoking or alcohol), those in infancy (such as breast- or bottle feeding, exposure to moulds and damp) and those acting in childhood and adolescence (such as environmental toxins, diet and levels of physical activity, passive exposure to tobacco smoke and own initiation of smoking and alcohol consumption). Nearly all domains of later health experience, including cardiovascular disease, various cancers, respiratory disease, cognitive decline and psychological health, have been associated with early-life exposures of one kind or another.

These research interests began to some extent with the exploration of data from historical birth cohorts[2,3] and new uses of existing birth cohorts,[4,5] with the results from those studies providing a stimulus for the revitalization of more historical pregnancy/birth cohorts[6–8] and the establishment of new ones.[5,9–14] Birth cohorts are used for testing a wide range of hypotheses and there is evidence for a marked increase over the last decade in studies that use data from birth cohorts being published.[15] A quick glance through eight recent issues of the *International Journal of Epidemiology* from April 2008 to June 2009 shows that there is not one without a research paper using data from a birth cohort study and that of the total 270 research papers published in these volumes, 28 (10%) used data from a birth cohort study. In the most recent issue (June 2009), with a special theme on intergenerational influences on health, 7 (33%) of the 21 research papers used data from birth cohort studies.[16–22] In this August 2009 issue, two papers from recently established birth cohorts in India[23] and South Africa,[24] and a third that uses record linkage to establish a Norwegian birth cohort study, provide further examples.[25] In addition, the photoessay by Ian Beesley[26] and poem by Ian MacMillan[27] provide information on a new birth cohort—the Born in Bradford (BiB) Study.

Birth cohorts are expensive and several of the most recent National birth cohorts, including those from Norway, Denmark and the USA, have recruited, or plan to recruit, 100 000 parents and children[10,11,14] in order to determine the genetic and life-course influences on childhood health, development and/or common complex diseases in adulthood. In the UK, where there is a strong tradition of national birth cohort studies going back to the 1940s, funding has been earmarked from the Government's Large Facilities Capital Fund for a new birth cohort commencing around 2012, with the aim of supporting 'innovative research spanning the interface between the biomedical and social sciences'. The call specification requesting bids for the leadership team of this new cohort stipulates that data collection must be hypothesis driven (http://www.esrcsocietytoday.ac.uk/ESRCInfoCentre/opportunities/current_funding_opportunities/birthcohort2012.aspx). Given the investment of money and human resources in these new

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birth cohorts it is worth considering what the key research themes should be in new birth cohorts.

No doubt, if you asked 10 different researchers what the most important themes were to include in a new birth cohort you would get 10 different lists, so we have no intention of attempting to produce an exhaustive offering here. Similar to the UK government and funders' desire for the 2012 cohort to be hypothesis based, the US government wanted their new 100 000 birth cohort (the National Children's Study) to be driven by research questions that could be clearly justified. To this end, they organized a series of 'state-of-the-art' meetings and literature reviews over a number of years in order to produce a collection of scientific priorities, with justifications. Despite this extensive and evidence-based development process for the study (something many would consider essential for such an investment), decision making has been difficult and controversial, with a piece in *Science*, ironically stating: 'Researchers are planning a major study of mothers and children: after two years they've narrowed the possible objectives of the study down to 70'.[28] In contrast, in the UK, bidders have been given 3 months to develop their hypotheses and study methodology for peer review. But even with this short time-frame necessarily focusing the mind, it is difficult to design a study that will deliver short-term important objectives and be relevant for understanding the life-course determinants of common adult diseases that will peak in 70–100 years time, when these new birth cohorts will be entering old age.[5,29] What we will do here is advance some broad principles and ideas that we think are important to consider for future birth cohorts.

Data for now and the future

Funders and researchers who are committing themselves to a new birth cohort clearly want some early hits in terms of important research outcomes. However, it seems likely that much of the most interesting research will only emerge when the participants are entering older age and beginning to suffer health conditions such as cardiovascular disease, cancer, osteoporosis and cognitive decline. Thus, any new birth cohort has to be considered both in terms of the key research hypotheses relevant to pregnancy, infancy and early childhood outcomes and hypotheses relevant to understanding life-course determinants of adult health and well-being. To some extent this is true even if initial funding is only for a restricted age period or even where the initial intention is only to examine childhood health (the US National Children's Study is committed to finishing when the participants are aged 21 years, with no follow-up beyond that age). The recent revitalization of historical cohorts that had not been used since the participants were in childhood,[6–8] illustrate the potential for future researchers to similarly revitalize birth cohorts that are being established now even if they lay dormant for some years. A difficulty with conceiving current cohorts both as research resources for now and for many decades into the future is that we cannot imagine what data researchers will require in at least 50 years time.[5] For example, the Aberdeen Children of the 1950s cohort includes detailed family data that describes parental health, interests (including, for example, which newspapers or magazines they subscribed to) as well as perinatal and later childhood data, but has no information on parental smoking.[6] The Aberdeen Childhood Development Survey, the original study on which the revitalized birth cohort study is based, aimed to determine the prevalence and causes of mental sub-normality and developmental impairment.[6] Given the present-day knowledge of the impact of smoking during pregnancy on the fetus, and at other stages of the life course, on future health outcomes, it is inconceivable that smoking data would not be collected today in any birth cohort study, including one with an aim to investigate cognitive development. However, in the 1950s, smoking was only just emerging as a major health risk factor (the First Surgeon General's report of the deleterious effects of tobacco exposure did not appear until the early 1960s—Surgeon General. Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service. Public Health Service Publication No. 1103. Washington, DC: US Department of Health, Education and Welfare, 1964). Thus, it is important to consider collecting some data in new cohorts that may not be easy to justify with respect to specific research objectives or hypotheses, but for future epidemiologists may be essential. Such data, might include, for example, information on air travel by mothers during pregnancy and by the infants in early life, exposure to new licit and illicit drugs, use of electronic social communication networks, use of certain communication devices (e.g. mobile phones) or organic living.

Family matters

Recent intergenerational studies published in the *International Journal of Epidemiology* demonstrate the value of having parental[16–23] and even grandparental[22] data in birth cohorts. Such data are central to life-course epidemiology, which is concerned with the intergenerational transfer of health risk. They can provide methods for testing causal assumptions and unpicking mechanisms that underlie intergenerational associations.[30,31] The photoessay by Ian Beesley in this issue highlights the role of fathers in parenting.[26] New birth cohorts need to think of imaginative ways of involving fathers, traditionally a hard-to-reach, low-responding group, in these studies. In addition, including data on siblings in birth cohorts can provide

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a fuller understanding of life-course epidemiology and elucidate causal mechanisms.[31-33] Therefore, a focus on collecting high-quality measurements on family members who are more easily accessible and identifying innovative ways to efficiently engage all family members in the study are worth considering. Birth cohorts are traditionally recruited and initially assessed via health care facilities, such as antenatal clinics or labour wards. While these provide a useful means for examining and collecting data from mothers as well as offspring, they are unlikely to be ideal for recruiting fathers, who often do not attend antenatal clinics and who are unlikely to be interested in participating in research when they are with their partners in the labour ward. Thus, research centres that are not linked to service delivery but are open in the evening and at weekends might be a useful way of collecting data on both mothers and fathers during the pregnancy and on both parents and offspring post-pregnancy. Such an approach could be in addition to linkage to health care records and obtaining some data from health service clinic visits.

Birth cohorts in low- and middle-income countries matter

Currently, most existing birth cohorts are in high-income countries, with relatively few in low- and middle-income countries (LMIC). A recent review attempted to identify all existing birth cohorts in LMIC and noted that, as well as there being relatively few birth cohorts in these countries, in comparison with cohorts from high-income countries, those that existed in LMIC were, on average, of smaller sample size and less mature, although in general they were comparable in terms of the breadth and quality of data collected.[15,34] The review also noted the regions of the world with few or no birth cohorts, with none in North Africa or the Middle East and just one birth cohort identified in each of South Asia, East-Asia, sub-Saharan Africa and the former Soviet Union.[30,31] Given some of the methodological difficulties of establishing and maintaining birth cohorts even in affluent nations,[5] together with the likelihood that some risk factors may well be equally important in both industrialized countries and LMIC, one could argue that limited research funds should be preferentially directed towards studies that evaluate population-specific interventions aimed at reduction of risk factors for important causes of maternal, perinatal and infant mortality, as well as non-communicable diseases in LMIC (e.g. interventions for improving antenatal care, re-housing studies, smoking prevention programmes). While this approach has its obvious merits, we believe that there are several important reasons for supporting birth cohorts in LMIC. These include the possibility that the composition of exposures may differ between countries at varying stages of the economic transition (e.g. less leisure time and more occupational, physical activity in LMIC); some exposures, particularly occupational (e.g. occupational toxins and hazards), may be unique to LMIC; there may be between-country differences in confounding structure that can be used to test causality (see below); some exposure–disease associations, may realistically be expected to differ from those seen in higher income societies, economic transition may modify exposure–disease associations; and finally, replication of very well-established (in high-income populations) exposure–disease associations in populations from LMICs may have important positive political ramifications.[15]

Establishing causality matters

Establishing whether exposures acting in early life (during the intrauterine period and in infancy and childhood) are truly causally related to disease outcomes in later life is essential to determining whether interventions to improve population health should primarily focus on this stage of the life course. However, determining causality for these early exposures is potentially more difficult than it is for risk factors assessed in mid-life in relation to later disease outcomes, not least because the exposure is more distant from the endpoint.[35] Family-based study designs, using genetic variants as proxies for exposures during these key periods (so-called Mendelian randomization studies) and cross-cohort comparisons are all key ways in which this might be achieved in birth cohorts.[31,34-36] Several recently published papers in the *International Journal of Epidemiology* illustrate these points. Thus, in the papers by Roza *et al*.[16] and Horta *et al*.,[21] risk factors assessed in both mothers and fathers during the mother's pregnancy are examined in relation to offspring outcomes. In the former, the similarity in magnitude of association of mothers smoking during pregnancy with offspring behavioural problems to fathers smoking with offspring behavioural problems, together with the marked attenuation of both associations with adjustments for potential confounding factors, suggests that maternal smoking in pregnancy is not causally related to offspring behavioural problems via an intrauterine mechanism.[16] In contrast, in the study by Horta *et al*.,[21] maternal birthweight and growth in infancy were positively associated with offspring birthweight, whereas paternal birthweight and infancy growth was not associated with offspring birthweight, leading the authors to suggest that the association of maternal birthweight with offspring birthweight seen in this and other studies is likely to be causal and that interventions to prevent undernutrition in early infancy (particularly in females) is potentially 'a valuable investment that will influence future generations as well as the present one'.[21]

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Both Morales *et al*.[17] and Kramer *et al*.[20] use genetic variants to shed light on possible causal mechanisms in their studies. Morales *et al*.[17] examined whether the association of maternal smoking in pregnancy with offspring cognitive function is modified by polymorphisms of *GSTM1* and *GSTT1*. These genes code for two major phase II xenobiotic metabolizing enzymes that are involved in detoxification of components of tobacco smoke. Deletion of these genes results in loss of functional activity of their enzymes and hence prolonged toxic effects of xenobiotics in cigarette smoke. If exposure to xenobiotics *in utero* affects neurodevelopment of the developing fetus and hence later cognitive function then one might expect associations of maternal smoking with offspring cognitive function to be stronger in women with the deletion of the polymorphisms than in those without this deletion. The findings from the study were mixed, with some weak evidence of a stronger association in mothers with the deletion (null allele) for *GSTM1*, compared with those without the deletion, but no such evidence in relation to polymorphisms in *GSTT1*.[17] The relatively small sample size and frequent lack of replication of other published gene–environmental associations mean that replication in larger studies is required before strong conclusions can be drawn about the causal effects of *in utero* exposure to xenobiotics. In a nested case–control study in a pregnancy cohort, Kramer *et al*.[20] used genetic variants, plasma homocysteine, folate, lipids, thrombin–anti-thrombin complexes and histological features of the placenta to examine the extent to which the association of pre-term birth with maternal cardiovascular risk might be explained by underlying maternal problems with vascular function. They found high maternal homocysteine concentrations to be associated with both placental vasculopathy and pre-term birth, but none of the genetic variants, including variation in *MTHFR*, which affects homocysteine metabolism, was associated with pre-term birth.[20] Here again, the study is of relatively small sample size for genetic associations to be robustly assessed and further larger studies are required to examine the hypotheses proposed.

Lastly, Obel *et al*.[18] used cross-cohort comparisons to examine the extent to which 'genetic confounding' might explain the association between maternal smoking during pregnancy and offspring hyperactivity inattention. They reasoned that one explanation for the association of maternal smoking in pregnancy with offspring risk of attention deficit hyperactivity disorder (ADHD) might be that mothers with a genetic predisposition for ADHD may be more likely to smoke as a means of controlling their symptoms and that their offspring would be at increased risk of inheriting ADHD from their mothers.[18] Furthermore, they suggested that, in populations where smoking was more socially acceptable, there would be a higher prevalence of smoking during pregnancy and also that only a small proportion of these smokers would be doing so to 'treat' 'hyperactivity–inattention symptoms'.[18] Thus, they argued that genetic confounding would be less problematic in these populations than in populations with low pregnancy smoking prevalence, They hypothesized that if the association of maternal smoking with offspring ADHD was explained by genetic confounding then the association should be weaker in populations with high maternal smoking prevalence and stronger in populations with low maternal smoking prevalence, and explored this by comparing the association in three birth cohorts: the national Finnish birth cohort of 1985–85, the Danish Aarhus Birth cohort (1990–92) and the Danish Healthy Habits birth cohort (1984–87), with maternal pregnancy smoking prevalences of 16, 29 and 36%, respectively. They found that maternal pregnancy smoking was positively associated with offspring ADHD in all three cohorts and also that there was no evidence that the magnitude of association differed by cohorts. As a result, they concluded that the association was unlikely to be explained by genetic confounding.[18] A similar approach could be used for non-genetic confounding, which is arguably more common than genetic confounding. For example, breastfeeding has been found to be associated with obesity and a number of vascular and metabolic risk factors in observational studies, though long-term follow-up of a large randomized controlled trial of a breastfeeding promotion programme suggests that these associations are unlikely to be causal.[37] The majority of observational studies in which this association has been examined have been conducted in high-income countries where breastfeeding is strongly socially patterned, with rates being much higher in mothers from high socio-economic backgrounds. It would be interesting to examine these associations in populations where breastfeeding is either not socially patterned or is differently patterned (i.e. more common in women from lower socio-economic groups). If a similar association was found in these populations it would argue against socio-economic confounding as an explanation for the observation in high-income countries.

The future

To paraphrase the Danish philosopher, Søren Kierkegaard, life in the future will only be understood by looking back at how pregnant mothers, infants and children live their lives now. Thus, the birth cohorts that we establish now have to be thought of as a resource for the future as well as the present. This will involve some generosity by present-day epidemiologists who may not witness, nor gain credit for, the benefits of their foresight and labours in their own working life. Every new birth cohort study should include some measurements that are

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feasible to assess and that represent common behaviours in current cohorts of pregnant women, infants and children, but that we cannot necessarily say are going to affect health now or in the future (if someone had done that in the 1950s for cigarette smoking some of the historical birth cohorts without such data might be even more valuable now). Those involved in establishing new birth cohorts also need to think carefully about collecting detailed and well-measured data in other family members and not only focus on the index child. DNA should be collected in family members, for measuring genotype and DNA methylation and samples that can be used for metabolomic and proteomic studies should be collected so that they can be used for understanding causal mechanisms affecting disease, health and longevity. We believe that there are some pertinent reasons to correct the evident dearth of existing birth cohorts in LMIC, to continue to support the few birth cohorts in these populations that are in existence and to establish new ones. Finally, cross-cohort comparisons and replication of findings from birth cohorts requires systems that support data-sharing and knowledge of existing and planned birth cohort studies. Plans to expand the existing European Birth Cohorts Network could provide a useful start (www.birthcohorts.net).

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