



Editorial

European birth cohorts offer insights on environmental factors affecting human development and health

European countries, particularly the UK, have a long history of conducting birth cohort studies. Now a new birth cohort, the UK's Life Study, has ambitious plans to enroll tens of thousands of participants and a hope that it will succeed where its counterpart in the USA, the National Children's Study (NCS) has failed.¹ The NCS was dissolved in December 2014 by the Director of the National Institutes of Health (NIH) amid concerns over the study's feasibility and costs.^{2,3} Although the NIH remains committed to the overarching goals of the NCS,² to 'find alternative ways to study child development and environmental influences on health',⁴ it is unclear when and how this is likely to happen. However, ready options to address the goals of NCS are available among the European birth cohorts^{5,6} and are likely to have international relevance beyond Europe.

Authorized by the Children's Health Act of 2000, the NCS was a prospective birth cohort study developed to evaluate the effects of environmental exposures on child health and human development.^{2,7} The vision for the NCS was to enrol a probability sample of 100 000 children and examine a broad range of environmental and biological factors. The study was meant to be a 'complete assessment of the physical, chemical, biological and psychosocial environmental influences on children's well-being'² and to address socioeconomic and racial/ethnic disparities in environmental exposures and health outcomes.² Several Vanguard Centres were launched to test the feasibility, acceptability and costs of running the main study. But after years of struggling to get off the ground and numerous criticisms, a working group set up to review the fate of the study concluded that although the goals of the NCS were meritorious, the study was not feasible in its current form.²

The longitudinal birth cohort design was one of the strengths of the NCS when a panel of experts was convened to evaluate the study and recommend its future.² In its initial design, the NCS planned on enrolling women before conception, to account for antenatal exposures.

However, given the large costs, slow pace and inefficiencies involved with this recruitment strategy, the traditional recruitment at antenatal visits seemed appropriate and justified⁷ and was ultimately adapted.⁸

Collectively, European birth cohorts offer an excellent opportunity to investigate the types of questions that the NCS was intended to address. These cohorts bring together several key elements, in terms of sample size, sampling strategy, exposure measures and phenotypic richness, to fill the scientific gap left by the closure of the NCS. Some of the larger cohorts have been hailed as exemplars of efficiency in study development and implementation,^{7,8} but all of them are excellent resources to investigate the potential causal influences of many biological, social and environmental factors on human health. Most importantly, the scientific community does not have to wait over 20 years for the answers. Some of the cohorts already offer life-course and even inter-generational perspectives on human health and can contribute real, including mechanistic, insights into the picture of the health-disease continuum. In addition, many of these studies are working collaboratively to address a range of health issues.^{5,6,9}

The many European cohorts in existence—descriptions and links to individual study websites at [<http://birthcohorts.net/>][—]are varied in focus, each offering unique features and strengths. Many have taken the approach of enrolling women in pregnancy or the children shortly after birth. One of the exceptions is the Southampton Women's Survey (SWS) in the UK,¹⁰ which enrolled women pre-conception. These cohorts range in size from relatively small (SWS) to very large (for example, the Norwegian Mother and Child Cohort Study—MoBa,¹¹ the Danish National Birth Cohort—DNBC¹² and the UK's Life Study), in their geographical focus from local (SWS, the UK's Avon Longitudinal Study of Parents and Children, ALSPAC,^{13,14} The Netherlands' Generation R study¹⁵) to nationally representative (Life Study, the UK's

Millennium Cohort Study, MoBa, DNBC), in data collection methods and in the range and depth of their phenotypic characterization (ALSPAC, for example, is one of the most phenotypically rich studies in the world). Many of these studies have sufficiently detailed information to allow major contributions to both biomedical and social science research (for example, ALSPAC and Generation R, among others) and have the potential to contribute to more fundamental biological research. Some of these studies began soon after WWII (the UK's 1946 and 1958 Birth Cohort Surveys^{16,17} or as recently as February 2015 (Life Study). They represent a range of exposures to environmental factors, economic conditions and social phenomena. An additional unique feature of some of these cohorts is their linkage to participants' administrative records (medical, educational, criminal and economic), which not only provides additional outcome measures¹⁸ but also allows researchers to fill in gaps when missing data or non-response threaten to introduce bias.^{19,20}

European birth cohorts have data and/or samples available for access by the wider scientific community, thereby acting as large repositories of information ready to be interrogated. Precisely because many of the European birth cohorts have collected and archived biological samples, they can be very responsive to the emergence of new technologies, such as sophisticated genetic analyses.¹ For example, ALSPAC and an increasing number of the other cohorts, are able to prospectively investigate the influences of environmental factors on patterns of DNA methylation in mothers and children^{21,22} and are currently building metabolomics profiles of their participants across the life cycle. Alternatively, cohorts can use these technological advances to understand how social factors (collected earlier) affect the underlying physiological processes.²³

Clear data access policies are in place in the European cohorts, available data are detailed on publicly accessible websites and decision-making is swift. When finite resources are requested, an independent arbitration process exists to decide whether the proposed study/measures fall within the cohort's research priorities, are likely to offer novel insights or will yield high-level impact. The studies are governed by small groups of cohort study experts who can respond fairly quickly to the changing scientific and infrastructural needs. Some studies hold public consultations on upcoming waves of surveys or assessments to gather input from the wider scientific community, and thereby keep abreast of trends in a given field of inquiry (the Millennium Cohort Study is one example of this). A real strength of some of the studies (for example, ALSPAC) is the deliberate involvement of cohort participants in research design and governance²⁴ and the emphasis on cohort engagement strategy and research.²⁵ Infrastructural elements allowing flexibility, responsiveness

and 'consensus-driven science' are critical to the success of a birth cohort.¹

Many European birth cohorts coordinate efforts with other longitudinal studies, at either the infrastructural or the scientific level, through joint governance, harmonized data collection or metadata or research consortia. For example, several EU-funded projects (CHICOS, ENRIECO, GA²LEN, MeDALL and others) brought together a large number of European birth cohorts to address a variety of health issues.^{5,6,9} In another example, the CLOSER network [<http://www.closer.ac.uk/>] brings together a number of the major UK birth cohorts as well as the UK Household Longitudinal Study (Understanding Society), to encourage interdisciplinary research, facilitate the use of longitudinal data and share resources and expertise.

Whereas existing European birth cohorts offer an excellent opportunity for research on early determinants of human development and health, two important issues need to be acknowledged. First, an argument has been made that new cohort studies are needed to account for the changing landscape of exposures.^{1,26} Children born today enter an increasingly digitized world, with economic uncertainty and greater income disparities. They are also likely to be more affected by climate change and the greater movement of people around the globe than previous cohorts. Second, studies conducted in any given region or country address specific socio-cultural contexts of the area they represent. For example, the NCS reflected the socio-cultural context of the American population^{8,26} with a very specific ethnic, racial, urban-rural mix and social experiences. Although exposure to some social phenomena is undeniably culture specific, European cohorts represent a wide range of exposures to a variety of common social, biological and chemical factors influential to health, and this range of exposures encompasses those likely to be experienced elsewhere in the world. In fact, epidemiologists already pool, integrate and quantify health effects through systematic reviews and meta-analyses. In the very least, findings from the existing cohorts can suggest specific hypotheses that can be tested in targeted samples in other contexts. However, studies do not need to be representative of the wider population to show valid relationships between exposure and disease.²⁷

The European birth cohorts have made important contributions to science and the public health agenda. It is impossible to summarize those here (but see references 28–34 for a few recent examples, showcasing some of the scientific contributions in the areas of prenatal exposures, obesity, respiratory health and social inequalities). Additionally, the cohorts keep the record of their publications and highlight their impact on public health and policy on their websites. Nevertheless, birth cohorts hold

considerable untapped potential. Through innovative approaches, such as cross-cohort comparisons, replication studies or large consortia,³⁵ European birth cohorts should be utilized to search for preventable causes of poor growth, development and health because they are likely to yield valid, generalizable ‘truths’ about the determinants or causes of health and disease. There is already overlap among exposure and phenotype measures across the European cohorts,^{5,6} but the issue of measurement standardization is non-trivial and likely to require a great deal of effort³⁶ with respect to existing information, and planning with respect to future data collection. To facilitate harmonization, the existing cohorts need to agree on the collection of key common variables, including their periods of reference and categories, without losing their unique attributes. There also needs to be sustained investment from funders to ensure long-term success for greatest health impact. Another important advantage of the existing European cohorts is that some of them, either through cross-generational (ALSPAC) or life-cycle perspectives (the 1946, 1958 and 1970 Birth cohorts in the UK), can provide important insights into early predictors of the disease process and/or outcome in later adulthood.³⁷ These findings could be translated now or in the near future into preventative measures for the betterment of society.

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