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EDITORIAL

Collaboration is needed to co-ordinate European birth cohort studies

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Epidemiological research shows that disease aetiology often has to be evaluated with a life-course perspective,[1] starting as close to the time of conception as possible[2] and, furthermore, that genetic predisposition, environmental exposures, and social context have to be considered simultaneously.

Several birth cohorts have been established in Europe in the last decades and more are being planned. In total, the established birth cohorts encompass approximately 300 000 children and their parents. There are at least three reasons why these cohorts should work closely together and facilitate the use of these data on a collaborative basis. The first and most obvious reason is to increase *statistical power*. The second is *efficient design* since a large study population in many countries will allow selective sampling by exposure or outcome. The third is *replication* of results which is a crucial aspect of epidemiology, especially in the area of genetic epidemiology. We now have the opportunity of building in the close future a mega birth cohort in Europe (probably designed as a virtual European Birth Cohort), that together with existing cohorts could cover more than half a million children.

Exposures during the prenatal and postnatal period have implications for children's health and may also have implications for morbidity occurring later in life, including asthma and allergy, cancer, mental illnesses, delayed neurodevelopment, cardiovascular diseases, and more. Exposures during early life are of concern since children are more susceptible than adults, partly because of their size and higher relative exposure levels, and probably also because critical periods of exposure may exist with respect to health later in life as a consequence of periods of rapid development. Long-term health effects may occur through various pathways including 'programming', pathophysiological changes beginning early in life, and lifestyle factors that track into adulthood. Historical observational studies have made important contributions to our understanding of the role of early exposures, but most of these studies lack actual exposure data and are based upon surrogate measures such as birth weight or other anthropometric measures. To advance our discipline we need more than surrogate measures for early exposures and nutritional factors.

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Birth cohorts in the EU: fait accompli

European researchers have accumulated a long experience in research using birth cohorts.[3–5] The recent launch of huge initiatives in Denmark[6] and Norway[7] will lead to the enrolment of 200 000 pregnant mothers and their offspring in these two countries. There are numerous smaller ongoing or planned birth cohorts in the Faeroe Islands, several in the UK, in Germany, Spain, France, The Netherlands, Sweden, Belgium, Finland, Italy and possibly other countries (see for example[5,8,9]). Altogether these cohorts will include information for approximately 300 000 newborns and most have plans to follow them for several years. All these cohorts have started enrolment before birth and have collected blood samples from mothers and children (and some from fathers too). Some are general pregnancy cohorts with multiple aims, while others are specialized in evaluating, for example, specific food and water contaminants or air pollution. In Europe we have the know-how, we have the numbers and we have the population and exposure diversity.

Why should we collaborate? Statistical power

Several of the important outcomes for public health in children are fortunately rare, for example childhood cancers, type 1 diabetes, and most congenital malformations. A study of 300 000 newborns would have enough power to identify a relative risk of around 1.5 for a rare outcome, such as a study of neural tube defects given a 20% population exposure. A study of 300 000 would have very high power to search for early causes of common diseases such as asthma. Having very high power for many fairly common diseases is particularly important for genetic association studies and for studies on gene–environment interactions. The very high proportion of false positive results in genetic association studies is a major problem[10] that can be avoided only with large studies and very low *P*-values. Another important aspect is the evaluation of exposure–response that is essential for risk assessment.

Why should we collaborate? Efficient design: sampling from the EU population

A close collaboration should handle the environmental, social, cultural, and genetic differences between the EU populations as an asset rather than a problem. Sampling for outcomes,

exposures and genetic traits using cohort or nested case-control designs could be done so as to maximize efficiency. Differences in contextual and environmental factors between populations are obvious and prominent, and these differences are valuable when biological pathways are to be distinguished from social pathways. Genetic distances between Caucasian populations are also documented.[11] In addition, in recent years there is considerable population admixture in many European societies through migration from Africa, South and Latin America, and Asia.

Examples of sampling on the basis of special exposure circumstances that could be done more efficiently within a diverse (international) and large sampling frame could be the evaluation of breastfeeding and cognitive function. Other scientific questions such as the hormone disruptor effects of oral contraceptive use after getting pregnant and congenital malformations in male infants; consequences of consumption of medical drugs during the first weeks of pregnancy and reproductive outcomes; evaluation of populations with well contrasted environmental exposures such as disinfection by-products in drinking water; evaluation of cohorts of women with specific diets such as Inuit or women from the Faeroes, or cohorts of women with Mediterranean diets; obese women who lost weight before getting pregnant and risk of gestational diabetes, are all examples of projects that would profit from large samples with a diversity in exposure.

Why should we collaborate? Replication of findings

Replication of findings in observational studies is needed to eliminate false positive or false negative findings. Replication is not a *sine qua non* condition for causal inference since lack of consistency could be due to differences in the distribution of other causal factors of importance for the endpoint under study. Lack of consistency in findings will, however, in most cases be caused by uncontrolled confounding, chance findings, or other errors.

How could we achieve collaboration: a virtual European mega birth cohort

A close co-ordination of existing studies should be the basis for further research. Existing studies share, to some extent, a core data structure and such a common element should be maintained. New studies could add specifically targeted protocols, should preferably be specialized rather than general, and study selected populations of special interest. These studies should certainly include populations in new EU countries.

A close co-ordination and joint evaluation of specific hypotheses would not necessarily require the physical pooling of cohorts. It would be sufficient to establish efficient routes of communication and co-ordination that allow a quick and detailed identification and promotion of areas of common research. This type of collaboration could be seen as a virtual European pregnancy mega-cohort. Such an effort would require commitment from researchers involved in setting up birth cohorts to a regulated, but open-access data policy for all researchers. Individual cohorts are funded mostly by national means and co-ordination can only succeed if substantive EU funds become available.

Combining existing and new birth cohorts would have enough power to evaluate new hypotheses, sufficient know-how, and a wide spectrum of exposures, diseases, and genetic backgrounds. The time has come to use the European scene to do more efficient and conclusive studies that could match some of the large US cohorts. This ambitious and invaluable project at the European level requires a much stronger commitment from the EU, especially concerning long-term support. The EU must make room for long-term health research as has been the case in physics for example. Beside the benefits of important scientific results within the near future or within the time limits set by any short-term funding, we also regard this as an investment in setting up this infrastructure in Europe to maintain Europe's leading position in this area of health research.

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