

## Population-Based Studies are Necessary to Study the Effect of Intrauterine Life

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With 1 Figure

### *Abstract*

Epidemiological research is important to describe and explain the developmental origins of health and disease, including genetics, environment, behaviour and time. Systematic evidence underlines the importance and the interdependence of the determinants. However, the key challenge for public health is prevention. To achieve this goal the research agenda must identify (*i*) causal mechanisms, (*ii*) supporting or hindering factors of the environment and the individual, (*iii*) vulnerable/ sensitive phases of the individual and (*iv*) trajectories over time. In our view prospective population based cohort and intervention studies like the SNIp-study provide the most promising way to meet this complex challenge.

### *Zusammenfassung*

Die epidemiologische Forschung ist von großer Bedeutung für die Beschreibung und Analyse der Entstehung von Gesundheit und Krankheit in der kindlichen Entwicklung, einschließlich Genetik, Umwelt, Verhalten und Zeit. Die Herausforderung für das Gesundheitssystem ist aber letztlich die Prävention. Voraussetzung dafür ist die Erforschung kausaler Mechanismen, fördernder Bedingungen und Barrieren des Individuums als auch der Umwelt sowie von vulnerablen Phasen und Entwicklungspfaden über die Zeit. Prospektive, populationsbasierte Kohortenstudien, wie z. B. die SNIp-Studie, bieten dazu einen viel versprechenden Ansatz.

Epidemiological research is playing an important role in describing, analysing and ultimately understanding the life-long effects of intrauterine life. While G. DÖRNER had shown the effect of environmental changes during pregnancy on outcomes later in life based on experimental research with animals (DÖRNER 1976), it was BARKER who first introduced empirical data on humans (BARKER and OSMOND 1986). He proposed the fetal origins of adult disease hypothesis, which is sometimes referred to as “Barker’s hypothesis”, by stating that, “coronary heart disease, type 2 diabetes, stroke and hypertension originate(s) in developmental plasticity, in response to undernutrition during foetal life and infancy” (BARKER 2004). He started out with analysing the association between mortality from selected diseases with infant mortality and childhood nutrition data in England (BARKER et al. 1986). Initially this work was regarded as heretical which, however, only caused him to reinforce his research efforts. By personal involvement and down to earth epidemiological fieldwork, including copying handwritten documents and spending countless hours in registries, he generated a database for empirical research on prenatal risk factors for later disease (BARKER et al. 1989). This inspired a considerable array of epidemiological studies which provided convincing empirical evidence that turned many critics to supporters (GILLMAN and RICH-EDWARDS 2000).

Classical empirical evidence stems from the Dutch famine during WWII (RAVELLI et al. 1976) after which consistent associations between low birth weight and higher incidence of hy-

pertension and higher prevalence of adult-onset diabetes were observed. A higher birth weight is associated with decreased risk of coronary heart diseases and stroke (MORLEY 2006). Size at birth is considered a marker for fetal nutrition (BARKER 2004), and birth weight is considered a summary measure of fetal growth. Determinants include genetic growth potential, gestation length, maternal size, maternal factors (metabolic and nutritional status, utero-placental perfusion and placental function) (MORLEY 2006). Recently, associations between exposure to maternal smoking and preterm delivery or lower birth weight (THYRIAN et al. 2005), between the metabolic syndrome and preterm delivery (CHATZI et al. 2009), or maternal-fetal nutrition and intrauterine growth restriction were established (SANKARAN and KYLE 2009).

In general, the determinants of the development of diseases in later adulthood under research are: genetics, the environment, and individual factors like behaviour and time. There is systematic evidence for the importance of all of them, and Figure 1 illustrates their complex relation and influences on disease over the course of life.

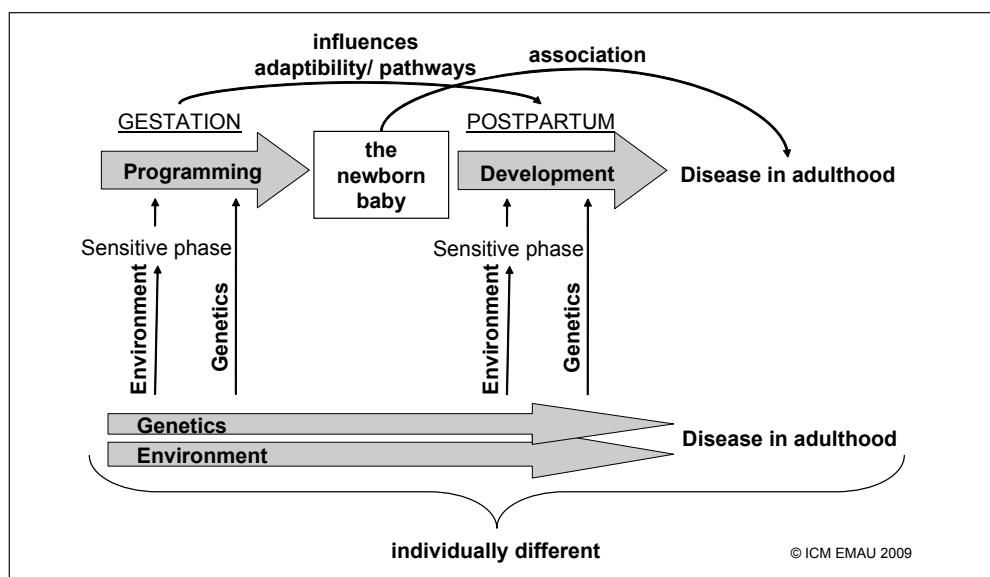


Fig. 1 The interaction of genetics, the environment, the individual and time on the development of diseases

The current model has been explained as, “when foetal environment is poor, there is an adaptive response, which optimizes the growth of the key organs to the detriment of others and leads to an altered postnatal metabolism, which is designed to enhance postnatal survival of intermittent or poor nutrition” (HALES and BARKER 2001). Genetic epidemiology has shown associations between genes and obesity, asthma, allergies, blood pressure, bone mineralization, anxiety, depression etc. (FRAYLING et al. 2007, GOLDING et al. 2009), and there is extensive experimental support from animal research for the epidemiological observations in humans (MORLEY 2006).

The impact of the environment, however, does not stop at the time of birth. The WHO estimates the burden of disease from preventable, environmental exposures at a minimum of

13 million deaths per year (PRUSS-USTUN et al. 2008). Environmental factors include environmental tobacco smoke (ETS) (COOK and STRACHAN 1999), contaminants in water and food (SUK et al. 2003), but also poverty, inadequate education, poor housing, and physical as well as mental health (EVANS 2004). There are gene-environment interactions conditional on the presence of particular exposures (EDER et al. 2004) as well as specific genes (CHOUDHRY et al. 2005).

These effects are not static over time since the susceptibility to an environmental factor may vary at sensitive phases during a child's development. Children are especially sensitive at different stages of gestation (SILBERGELD and PATRICK 2005), during infancy and in early childhood (MAKRI et al. 2004). ETS exposure before and after birth differs and Epstein-Barr virus infections differ with age at the time of infection (MACSWEEN and CRAWFORD 2003).

Epidemiologic research has provided interesting clues to possible mechanisms. There is evidence that the association between low birth weight and the increased incidence of hypertension is mediated by social class. Being born in the working class or lower middle class emphasizes this association (BARKER 2004). The association between birth weight and type 2 diabetes later in life is mediated by the adiposity rebound (AR). The AR indicates the point in time when the normal decrease in body mass index (BMI) in early childhood turns into an increase (ROLLAND-CACHERA et al. 1984). The earlier the AR in children with low birth weight, the higher the chance to be diagnosed with type 2 diabetes later in life (BARKER 2004).

These results have been summarised into principles (NATHANIELSZ 2006) that can guide future research:

- Critical periods of vulnerability to suboptimal conditions occur at different times for different systems → research needs to address different time periods, the complexity requires assessment of more different variables.
- The placenta plays a key role → asservation of bio-materials is mandatory.
- Compensation carries a price. In suboptimal conditions the developing baby attempts to compensate, which might cause problems later on → effects may show up a considerable time distance from their origins requiring prospective cohort designs.
- Programming may cross generations → intergenerational, longitudinal, and epidemiologic research is needed.
- Males and females may be affected differently → research into fetal programming must be gender sensitive.

Various research methods have been applied, but all show serious limitations. Twin studies and adoption studies are restricted in their generalisability (MORLEY 2005). Twins show a general constraint of fetal growth, the biology of fetal growth is different, on average the gestation is shorter etc. Cross-sectional studies have yielded many associations, but do not allow individual or even causal pathways. Retrospective research is limited by hindsight bias and memory effects causing over- or underestimation of various associations. Studies using birth cohorts can control for many of these problems, but they may have a selection bias, for example with respect to socio-economic status (KRAMER et al. 2009) or race/ethnicity (SAVITZ et al. 2005). Participants recruited in hospital settings were more likely to be black, younger, less educated, and unmarried compared to residents in the surrounding area (SAVITZ et al. 2005). Lower neighbourhood income was associated with preterm birth in the population, but not in the study cohort (KRAMER et al. 2009). Hence the methodological 'gold standard' to control for most of these problems are population-based prospective cohort studies.

The Danish National Birth Cohort comprises 101,042 pregnant women between 1996 and 2002 (OLSEN et al. 2001), and the Norwegian Mother and Child Cohort Study (MOBA) recruited 110,000 pregnant women from 1999 to 2008 (MAGNUS et al. 2006). More recently the USA National Children's Study has stated that its recruitment goal is 100,000 parents and children with prospective follow-up from birth to age 21 (KNOX and ECHEVERIA 2009). These cohorts include child, mother and father and collect biospecimen. They allow the analysis of complex associations. However, they are expensive (US > \$400 million), face considerable loss due to follow-up and are restricted to an a priori set of hypotheses that may not cover aspects that are relevant in other regions or future time periods.

Some regional studies control for some of these problems. The Avon Longitudinal Study of Parents and Children (ALSPAC) was established in the 1990s with 14,541 pregnant women covering 85 % of the population in the study area (GOLDING 2004). The Generation R Study in Rotterdam started in 2002–2006 with a 61 % participation rate of 3,787 pregnant women (HOFMAN et al. 2004).

Just recently a prospective birth cohort was initiated with the Survey of Neonates in Pomerania (SNiP) by the University of Greifswald, which has so far enrolled 6,747 child-bearing women between 2003 and 2008 (EBNER et al. 2010). The population coverage was 95 % with 75 % of the participants providing informed consent to participate in a detailed assessment (EBNER et al. 2010), including maternal records of the pregnancy, hospital records of mother and child, face-to-face interviews, questionnaires and biological samples from the blood cord, the placenta and maternal mouth swabs. It has been shown that the SNiP region could serve as model region for future research (THYRIAN et al. 2010).

The key challenge for future research into fetal programming is prevention. Based on the determinants illustrated in Figure 1 options are (*i*) to interfere on the genetic level, which is currently not – and probably never will be – feasible, (*ii*) to address maternal behaviour, which has been successful for example in supplemental food programs (RUSH et al. 1988), (*iii*) to change the fetal environment, e.g. banning of smoking in public places or supporting folate supplements in pregnancy (BADOVINAC et al. 2007), and (*iv*) intervene into developmental pathways postpartum by behavioural and environmental interventions (HANNÖVER et al. 2009). Research priorities for evidence based prevention include: identification of (*i*) causal mechanisms, (*ii*) risk or protective factors of the environment and the individual, (*iii*) vulnerable/ sensitive phases of the individual, and (*iv*) trajectories over time (in individuals as well as the environment). Results need to be translated into well designed preventive interventions with population impact (THYRIAN and JOHN 2007). In our view the most promising way to meet the challenge is to conduct prospective population based cohort and intervention studies.

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