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Translational challenges for the developmental origins of health and disease: time to fulfill the promises for innovative prevention strategies

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Editorial

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Introduction

An overwhelming body of evidence has shown that various adverse exposures during the fetal and postnatal period may have persistent influences on growth, development and health and the subsequent risk of chronic diseases throughout the life course.[1] The important landmark studies by David Barker *et al.* were primarily based on observations linking low birth weight or preterm birth with non-communicable diseases, such as cardio-metabolic diseases, type 2 diabetes and chronic obstructive respiratory diseases in adulthood.[1,2] Birth weight and preterm birth are unlikely to be the causal factors per se leading to non-communicable diseases in later life. Birth weight and gestational age at birth are merely proxies of different fetal exposures and growth patterns and the starting point of childhood growth.[3] Results from observational prospective cohort studies have identified various lifestyle and nutrition-related adverse exposures during the fetal and postnatal period, which are independent of size at birth, associated with development of risk factors for non-communicable diseases. These findings are supported by experimental animal studies.[1] Currently, the concept has widely been accepted that the first 1000 days of life, including oocyte and sperm cell development in the preconception period, embryonic and fetal growth in pregnancy and the postnatal development up to infancy, are critical for health outcomes throughout the life course.

The theme of the 10th World Congress on Developmental Origins of Health and Disease (DOHaD) in Rotterdam, the Netherlands (DOHaD 2017), was "Life course Health and Disease: Observations, experiments and interventions". The meeting was a great success with over 1000 participants from different countries and a wide variety of plenary, parallel, poster and workshop sessions. As organizers, we aimed to organize a meeting that would bring the exciting field of DOHaD an important step forward and link observational and experimental studies closer to new strategies for interventions in early life.

This supplemental issue of *Journal of Developmental Origins of Health and Disease* provides excellent examples of sessions, discussions and presentations at DOHaD 2017.[4–11] In this Editorial, I will discuss some issues of major interest for translation of DOHaD. After almost three decades of DOHaD research, it is time to fulfill the expectations for prevention of non-communicable diseases by improving growth and development during the first 1000 days. Clearly, there is an important role for translating research findings into policy. Hanson *et al.* and Penkler *et al.* addressed some major conceptual and contextual challenges to translate research findings into policy.[4,5] Based on some exciting sessions at DOHaD 2017 and the contents of this supplementary volume, I will focus on optimal use of life course observational studies, combining environmental exposures with various "omics" approaches, and the potential for intervention studies.

Optimal use of life course observational studies

Life course observational studies are still the cornerstone for research on the DOHaD. The retrospective cohort studies during the early 1990s led to exciting results on size at birth and later life diseases, but had some major methodological limitations.[2] In the 1990s and 2000s, many new prospective cohort studies from pregnancy or early childhood were initiated.[12] These studies have been very successful in identification of various sociodemographic, environmental lifestyle and nutrition-related factors in pregnancy or early childhood in relation to development of risk factors for diseases in later life.[12] As example, Vehmeijer *et al.* and van Elten *et al.* gave an overview of evidence on maternal stress and physical activity in pregnancy on offspring outcomes.[6,7] Tong and Giussani discuss a gestational hypoxia model for assessing the long-term maternal and offspring outcomes.[11]

Life course observational studies assess the associations of exposures across the life course on later-life disease risk.[13] Large-scale birth cohort studies provide a unique opportunity to model early life exposures in relation to later life outcomes. However, due to their nature, life course observational studies are not able to provide conclusions regarding causal relationships between

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exposure and outcomes.[8] Bias due to confounding is a crucial limitation of observational studies. Next to general confounding, some types of confounding, such as confounding by indication, confounding by baseline selection, time-varying confounding and mediator–outcome confounding, are relevant for life course observational studies.[8] The paper by Santos *et al.* describes various approaches to address these types of confounding.[8]

Recent studies used different types of approaches in observational cohort studies to address confounding. These approaches include sibling comparison studies, maternal and paternal offspring comparisons analyses, Mendelian randomization studies and randomized controlled trial analyses.[14] Sibling comparison studies enable better control for potential confounding factors shared within families,[15] but are limited because next to the major exposure of interest, other related characteristics (confounders) may also change over time. Maternal and paternal offspring comparison analyses explore the differences in strength of associations of maternal and paternal exposures with offspring outcomes.[16] Stronger associations for maternal exposures suggest an important role for direct intrauterine mechanisms, whereas similar or stronger associations for paternal exposures suggest a role for shared family-based, lifestyle-related characteristics or genetic factors.[16] Mendelian randomization approaches use genetic variants, known to be robustly associated with the exposure of interest and not affected by confounding, as an instrumental variable for a specific exposure.[17] Associations of these genetic variants with the outcomes of interest support causality for these associations. Randomized controlled trials are considered as the gold standard for causality studies. Because randomized studies are difficult to perform when maternal lifestyle factors, such as dietary patterns, smoking and obesity, are the major exposures of interest, previous studies focused on influencing for example obesity, such as dietary factors and physical activity levels.[18,19]

Finally, the enormous wealth of high-quality prospective cohort studies enable collaboration on original data level.[12] The individual participant data meta-analyses have the advantages to examine smaller effect estimates, specific subgroups and mediator effects and maybe most importantly capitalize the available published and unpublished data. Individual participant data meta-analyses on environmental exposures and genetic associations have already been published as part of birth cohort collaborations, such as LifeCycle (www.lifecycle-project.eu) and EGG (http://egg-consortium.org/).[19–28]

Altogether, life course observational studies remain extremely important for research on DOHaD. The major issue of confounding can be addressed by analytical and design strategies. Collaboration between different cohorts leads to unique opportunities for better use of existing cohort data.

Combining environmental exposures with various omics approaches

Recent studies suggest that the associations of size at birth with diseases in later life is at least partly genetically determined. A multi-ancestry genome-wide association study (GWAS), meta-analysis of birth weight in more than 150,000 individuals identified 60 loci.[28] Approximately 15% of the variance in birth weight was captured by fetal genetic variation. Importantly, this study reported strong inverse genetic correlations between birth weight and cardiovascular and metabolic phenotypes, suggesting that the associations of early life growth with adult cardio-metabolic disease are in part the result of shared genetic effects.

Thus far, the number of studies using both variants for genetic predisposition and environmental factors for the additional risk are scarce. Future studies should combine genetic data from cohort studies with the detailed information about adverse exposures for identification of groups at risk and potential for more personalized prevention strategies.

Recent developments have enabled epigenome-wide studies in large cohorts, next to genome-wide studies.[29,30] Epigenetic modifications may be involved in mechanisms underlying associations of early life exposures with later life health outcomes. Life course studies starting in early life are excellent for studying the role of such modifications.[9] Thus far, DNA methylation is the most studied epigenetic mechanism in population research. Key challenges for genome-wide methylation studies include tissue specificity, cell type adjustment, issues of power and comparability of findings, genetic influences and exploring causality and functional consequences. In this issue, Felix and Cecil discussed these challenges in detail.[9]

Similar to epigenome studies, recent developments enable hypothesis-free approaches for metabolomics, proteomics and microbiome studies. These studies may lead to exciting new insights in yet unknown developmental adaptations in the earliest phases of life. Good collaboration between cohorts is a paramount for successful studies on these new areas.

Potential for intervention studies

Despite the limitations from observational studies, results from these studies strongly suggest that adverse maternal lifestyle factors during fetal life and infancy lead to increased risks of adverse health outcomes for mother and child throughout the life course.[1] These findings would suggest an enormous potential for translating findings into new preventive strategies. However, thus far, results from randomized controlled intervention trials targeting these lifestyle factors are inconsistent, and overall do not show a strong effect of lifestyle interventions on birth outcomes or maternal and offspring health outcomes. Currently, the lack of successful evidence-based interventions seems to be due to the periods for lifestyle interventions, the type of lifestyle interventions, the targeted populations, the collection of outcome data and the low power of the randomized controlled intervention trials. Gaillard *et al.* discussed these challenges in more detail.[10] Most importantly, it may be that previous intervention studies missed the most critical period.

Findings from observational and animal studies strongly suggest that the preconception period and early pregnancy appear to be major critical periods related to pregnancy complications and long-term adverse maternal and offspring health outcomes.[31] This period involves the embryonic phase and is essential for development of the placenta and fetal organs. Future randomized controlled intervention trials need to start lifestyle interventions from preconception onwards and assess the influence of these interventions on the course of maternal and offspring outcomes. These trials should also take father into account. Remarkably, the role of father in developmental programming is largely ignored in recent intervention studies.

Conclusions

The overwhelming amount of evidence that early life is important for health and disease in life course gives researchers on DOHaD the important responsibility to translate their findings into innovative population health strategies by several approaches: First, high-quality life course observations are crucial for exploring

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associations. There seems to be a yet unused potential for causal inference and multicenter collaboration in these studies. Second, the advances in genomic, epigenomic and other "omic" approaches are not only exciting from a biological perspective but should also be integrated with research on environmental exposures to identify groups at risk and develop prediction models. Finally, current evidence suggests that the preconception period or early pregnancy is the window of opportunity for new intervention strategies to improve health of parents and their offspring.

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