Chapter 4
Developmental Origins of Health and Disease (DOHaD) Cohorts and Interventions: Status and Perspective

Fumihiro Sata

Abstract The concept of Developmental Origins of Health and Disease (DOHaD), which has emerged over the past decades, links the state of health and disease in later life with environmental factors of the early life. It was the pioneer work of David J. Barker, Southampton University, United Kingdom, who proposed the fetal origins of adult disease hypothesis, also referred to as the "thrifty phenotype" hypothesis or Barker hypothesis, which states that an adverse fetal environmental, such as undernutrition, increases the risk of noncommunicable diseases (NCDs) in adulthood. At the beginning of this century, the DOHaD theory incorporated much broader concepts: not only were poor physical conditions in adulthood, such as disease suffering, strongly associated with the fetal and infant environment, but also the ability to maintain a healthy lifestyle. Currently, the belief that adverse fetal-childhood environments, such as undernutrition, stress, smoking, and chemical exposure due to growth restriction, increases the risk of NCDs in adulthood, such as cardiovascular disease, stroke, hypertension, type 2 diabetes, chronic kidney disease, osteoporosis, cancer, and psychiatric disorders, is widely accepted. In Europe and America, birth cohort studies are very popular because they enable the integration of data sharing and meta-analyses for genome-wide association studies, epigenome-wide association studies, exposome, Mendelian randomization, and early intervention studies. Recently, in Japan, the concept of preemptive medicine, which is a novel medical paradigm that advocates for presymptomatic diagnosis, prediction, or intervention at an early stage to prevent or delay disease onset, has been proposed. Therefore, interdisciplinary studies that focus on fetal and childhood developmental periods are highly recommended as a political strategy. In this chapter, I will introduce DOHaD cohort studies and interventions and discuss their statuses and perspectives.

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Keywords DOHaD · Cohort studies · Interventions · Noncommunicable diseases (NCDs)

Abbreviations

BMI	Body mass index
BW	Birth weight
DOHaD	Developmental Origins of Health and Disease
EWAS	Epigenome-wide association study
GWAS	Genome-wide association study
NCDs	Non-communicable diseases
SNP	Single nucleotide polymorphism

4.1 Introduction

The Developmental Origins of Health and Disease (DOHaD) is a concept that has emerged over the past decades. It links the state of health and disease in later childhood and adult life with environmental factors of the early life, specifically the preconceptional, prenatal, and/or early postnatal periods. It was the pioneer work of David J. Barker, an epidemiologist at Southampton University in the United Kingdom, who conducted a series of descriptive epidemiological studies in England and Wales in the 1980s and found that mortality associated with cardiovascular disease appeared higher in the areas with higher infant mortality rates several decades before. By obtaining data from the Hertfordshire Cohort Study, a prospective survey that recorded all births in Hertfordshire from 1911 until 1948, Barker et al. showed that mortality rates for cardiovascular disease increased in individuals who had lower birth weights and with hypertension and impaired glucose tolerance displaying similar trends [1–4]. Based on these findings, Barker et al. proposed the hypothesis of the fetal origins of adult disease, also referred to as the "thrifty phenotype" hypothesis or the Barker hypothesis, which states that an adverse fetal environmental, such as undernutrition, increases the risk of noncommunicable diseases (NCDs) in adulthood [5–8].

At the beginning of this century, the DOHaD theory incorporated much broader concepts: not only were poor physical conditions in adulthood, such as disease suffering, strongly associated with the fetal environment, but also the ability to maintain a healthy lifestyle [9, 10]. Thus, this theory is a subset of the biological phenomenon of developmental plasticity, which encompasses those processes that generate alternative phenotypes from gene expression through the actions of environmental clues acting during developmental periods. Through the epigenetic control mechanism, also known as developmental programming, the most desirable phenotype is produced in response to the fetal environment to increase the likelihood of postnatal survival [11, 12]. Therefore, if the postnatal environment matches the fetal environment, such as the maintenance of similar nutritional and physical

conditions, then the individual will most likely sustain a healthy lifestyle after birth. Conversely, if the postnatal environment does not match the fetal environment, such as poor dietary and physical habits, then the individual will most likely succumb to an unhealthy lifestyle and have a higher risk for NCDs later in life. The DOHaD theory correlates fetal-childhood environmental factors with the incidence of NCDs in adulthood, and this concept has been supported by numerous epidemiological, birth cohort, and experimental studies.

Currently, the belief that adverse fetal-childhood environments, such as undernutrition, stress, smoking, and chemical exposure due to growth restriction, increases the risk of adulthood NCDs, such as cardiovascular disease, stroke, hypertension, type 2 diabetes, chronic kidney disease, osteoporosis, cancer, and psychiatric disorders, is widely accepted.

4.2 Status of Birth Cohort Studies

In Europe and America, birth cohort studies are very popular because they enable the integration of data sharing and meta-analyses (Tables 4.1 and 4.2). Birthcohorts.net, a database of birth cohort networks, has approximately 70 birth cohort studies registered predominantly in Europe that meets the following criteria: initiated in 1980 or later, have at least 300 mother-child pairs, have at least 1 year of follow-up, and provide well-documented data, including questionnaire data and biological samples with appropriate times of collection [13, 14]. The Environmental Health Risks in European Birth Cohorts (ENRIECO) is a project dedicated to environmental risk assessment of chemical substances based on Birthcohorts.net data [15]. The executive committee of the European Union (EU) developed the Child Cohort Research Strategy for Europe (CHICOS) under the 7th Framework Program (7FP) of the European Commission to integrate and evaluate data from existing cohort studies, registration systems, and related European databases to construct health data banks that can be used over the next 15 years [16]. In the United Kingdom, the Cohort and Longitudinal Studies Enhancement Resources (CLOSER) consolidated eight representative birth cohort studies with different starting times to evaluate socioeconomic and biological factors and apply them for health policy [17]. In Asia, the Birth Cohort Consortium of Asia (BiCCA) is a consortium specializing in children's environmental health and is composed of 27 birth cohorts in East Asia, mainly in Japan, China, Korea, and Taiwan [18]. Recently, two birth cohort consortia specializing in genome-wide association studies (GWAS), the Early Growth Genetics (EGG) Consortium and EArly Genetics and Lifecourse Epidemiology (EAGLE) Consortium, have been established [19, 20]. The International Fetal and Newborn Growth Consortium (Intergrowth-21st) is a collaborative research effort on behalf of eight countries, including the United Kingdom, the United States, and China, to evaluate infant growth from the fetal period to early childhood [21]. As more data are collected on the health and nutrition of participating mothers, Intergrowth-21st will use the findings to implement appropriate prenatal care.

Table 4.1 Overview of epidemiological studies associated with Developmental Origins of Health and Disease (DOHaD)

Year	Concept/theory	Descriptive epidemiology	Observational studies	Intervention/proposal
1980		**England and Wales** a strong geographical relation between ischemic heart disease mortality rates and infant mortality several decades ago (Lancet 1986)		
1990	**Barker hypothesis** **Fetal origins of adult disease** (BMJ 1990, Fetal Matern Med Rev 1994, Int J Epidemiol 2002) **Brenner Hypothesis** (Bull Mem Acad R Med Belg 1994)		**Hertfordshire Cohort Study** [***birth weight***] coronary heart disease, hypertension, impaired glucose tolerance (Lancet 1989, BMJ 1991) **Dutch Hunger Winter of 1944–1945** [***prenatal famine***] Schizophrenia (Arch Gen Psychiatry 1992, 1996) **Nurses' Health Study** [***birth weight***] cardiovascular disease (BMJ 1997)	
2000	**Developmental Origins of Health and Disease (DOHaD)** • Mismatch concept • Developmental plasticity (Science 2004; Nature 2004)	**Japan (1980–present)** Increasing prevalence of low birth weight (Lancet 2007, OECD Health Statistics 2016)	**Helsinki Birth Cohort** [***catch-up growth***] coronary heart disease (N Engl J Med 2005) **Chinese famine of 1959–1961** [***prenatal famine***] Schizophrenia (JAMA 2005) **Genome-wide association study (GWAS) – ALSPAC, NFBC1966** [***BMI, obesity***] ***FTO*** (Science 2007)	**Ministry of Health, Labour and Welfare** Dietary Guidelines for Pregnant and Lactating Women (2006) **Science Council of Japan** [Proposal] Prevention against lifestyle-related diseases from prenatal and childhood (2008)

2010			**– EGG/EAGLE Consortium** [***BMI, obesity***] ***OLFM4, HOXB5*** (Nat Genet 2012) [***birth weight***] ***CCNL1, ADCY5, CDKAL1, ADRB1, HMGA2, LCORL, et al.*** (Nat Genet 2010, 2013; Nature 2016) [***birth head circumference***] ***12q15, 12q24, 17q21*** (Nat Genet 2012) [***birth length***] ***DCST2, GDF6, TTC17-HSD17B12, LCORL, PTCH1, GPR126, HMGA2*** (Hum Mol Genet 2015) **Epigenome-wide association study (EWAS)** **– MoBa** [***maternal smoking***] ***AHRR, CYP1A1, GFI1*** (Environ Health Perspect 2012) [***birth weight***] ***ARID5B, XRCC3*** (Am J Epidemiol 2014) **– Dutch** Hunger Winter of 1944–1945 [***birth weight***] ***INSR, CPTA1*** (Nat Commun 2014) **– PACE** [***maternal smoking***] ***AHRR, MYO1G, CNTNAP2, GFI1, et al.*** (Am J Hum Genet 2016) **Mendelian Randomization** **– EGG Consortium** [***birth weight***] Maternal obesity-related traits (JAMA 2016) **Exposome** **– EXPOsOMICS project** (Int J Hyg Environ Health 2016)	**Southampton Women's Survey (SWS): Southampton Initiative for Health** Intervention for disadvantaged women (J Health Psychol 2011; J Dev Orig Health Dis 2016; Healthcare 2017) **EarlyNutrition Project** Randomized controlled trial, e-learning, EarlyNutrition Academy (Proc Nutr Soc 2012; Ann Nutr Metab 2014) **Liggins Education Network for Science (LENScience)** School-based intervention (J Dev Orig Health Dis 2012; Healthcare 2014; Health Promot Int 2017) **Japan Science and Technology Agency (JST)** [Strategic Proposal] Promoting Life Course Healthcare: Importance of Preemptive Medicine in pregnancy to childhood (2014) [Overlooking Report of Research and Development] Life Science and Clinical Research Fields (2015)

[Abbreviations] *ALSPAC* Avon Longitudinal Study of Parents and Children, *NFBC1966* Northern Finland Birth Cohort 1966, *EGG* Early Growth Genetics, *EAGLE* EArly Genetics and Lifecourse Epidemiology, *MoBa* Norwegian Mother and Child Cohort Study, *PACE* Pregnancy And Childhood Epigenetics Consortium

Table 4.2 Major consortia based on birth cohort studies in the world

Consortia	Objective	Participant birth cohorts
CHICOS	– Data sharing – Integrated healthcare database construction	[Belgium] FLEHS, [Czech] Czech Early Childhood Health, [Denmark] ABC, CCC2000, COPSAC-2010, DARC, DNBC, HHf2, IVAAQ, Lupercus, Odense Child Cohort, [Faroe Islands] CHEF, [Finland] LUKAS, NFBC 1986, [France] EDEN, ELFE, PARIS, PÉLAGIE, TIMOUN, [Germany] BabyCare cohort, CHOP, DONALD, Duisburg, GINIplus, LeuBiCo, Life Child, LISA-PLUS, MAS 5, MAS-90, SNiP, [Greece] RHEA, [Ireland] BASELINE, Growing up in Ireland, Lifeways Cross-Generation Cohort Study, [Italy] Co.N.ER, GASPII, MUBICOS, NINFEA, Piccolipiù, Trieste child development cohort, [Lithuania] KANC, [Netherlands] ABCD, GECKO Drenthe cohort, Generation R, KOALA, MEFAB, PIAMA, Predict Study, PRIDE Study, WHISTLER, [Norway] ArcRisk, HUMIS, MoBa, NorFlu, [Poland] Krakow cohort, REPRO_PL, [Portugal] G21, [Slovakia] PCB Cohort, [Spain] INMA Project, [Sweden] ABIS, BAMSE, INUENDO, [Switzerland] BILD, [Ukraine] FCOU, [United Kingdom] ALSPAC, BiB, Determination of maternal caffeine intakes associated with increased risk to the fetus, EHL, GMS, GUS, Isle of Wight Birth Cohort study, LRC, Merthyr Allergy Study, NCCGP, Newcastle Thousand Families Study, SEATON, SWS
CLOSER	– Data harmonization – Data linkage – CLOSER search platform – Research impact – Training and capacity building	HCS, NSHD/1946BC, NCDS, BCS70, ALSPAC, SWS, MCS, UKHLS
ENRIECO	– Environmental health risk assessment	ABC, ABCD, ALSPAC, BAMSE, BiB, CHEF, DBNC, EDEN, ELFE, FLEHS, Generation R, G21, GINIplus, INMA Project, INUENDO, KOALA, LRC, LISA-PLUS, NFBC 1966, NFBC 1986, NINFEA, PIAMA, RHEA, SNiP
BiCCA	– Environmental health risk assessment	[Bangladesh] HRBC, [China] LWBC, NJMUBC, SBC, [Japan] HBC study, Hokkaido Study, TSCD, [Korea] CHECK, COCOA, EDC study, MOCEH, PSKC, [Malaysia] USM pregnancy cohort, [Mongolia] Birth Cohort Study in Mongolia, UGAAR Study, [Nepal] Nepali, [Philippines] CLHNS, [Singapore] GUSTO, [Sri Lanka] KCHS, [Taiwan] TBPS, TEC, TMICS, [United Arab Emirates] MISC, [Vietnam] Bien Hoa study, DaDoCiV, DaNang

Table 4.2 (continued)

Consortia	Objective	Participant birth cohorts
EGG	– GWAS	ALSPAC, CHOP, CoLaus study, COPSAC, DNBC, EFSOCH, ERF, EPIC, Fenland Study, Generation R, GINI-plus, GOYA, HCS, HBCS, INMA Project, Inter99, Leipzig, LISA-plus, NCDS, NEO, NFBC1966, NFBC1986, NTR, ORCADES, PANIC, PIAMA, RAINE, Sorbs, STRIP, TEENAGE, TDCOB, YFS
EAGLE	– GWAS	NCDS, ALSPAC, CATSS, CHOP, COPSAC, DNBC, Exeter Family Study, Generation R, GINI-plus, HBCS, INMA, LISA-plus, MoBa, NTR, NFBC, Project Viva, TCHAD, TEDS, RAINE
Intergrowth-21st	– Scientifically robust clinical tools to assess fetal growth and the nutritional status of newborn infants	Research units in Brazil, China, India, Italy, Kenya, Oman, the United Kingdom, and United States
EpiGen	– EWAS	Liggins Institute, University of Auckland, represented in the consortium by Auckland UniServices Ltd Human Development and Health Academic Unit, University of Southampton MRC Lifecourse Epidemiology Unit, University of Southampton Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research National University of Singapore
PACE	– EWAS	ALSPAC, CHAMACOS, CHS, GECKO Drenthe Cohort, Generation R, IOW, MeDALL, which includes four component cohorts (INMA, EDEN, BAMSE, PIAMA), MoBa, NFCS, NEST, Project Viva, GALA II, SEED
EXPOsOMICS	– Exposome	RHEA, Piccoli+, INMA, ALSPAC

Abbreviations: Appendix B

In addition, worldwide consortia have been developed that specifically address the underlying tenets of the DOHaD theory. Researchers in New Zealand, the United Kingdom, and Singapore are participating in an international consortium, the EpiGen Global Research Consortium, in an effort to use epigenetic techniques and tools for early intervention in at risk pregnant women and children [22, 23]. The Pregnancy And Childhood Epigenetics (PACE) consortium is comprised of researchers at the National Institute of Environmental Health Sciences (NIEHS) and around the world who are using epigenetics to investigate how early-life environmental factors impact human disease [24, 25]. Recently, a need arose for the development of methodology that analyzes an individual's environmental exposure with the same

precision of GWAS or whole genome sequencing methods. Christopher P. Wild, Chair of Molecular Epidemiology at the University of Leeds and Director of the International Agency for Research on Cancer (IARC), proposed the need for an "exposome" to match the "genome," to raise awareness for exposure assessment methodology [26]. An EU-funded project, EXPOsOMICS, aims to develop a novel approach for assessing exposure to high-priority environmental pollutants, such as air and water contaminants, during critical periods of life by characterizing the external and internal components of the exposome [27]. Yet, Mendelian randomization is a GWAS-based theoretical method for environmental risk assessment that uses genetic factors associated with environmental factors to assess the causal effect on internal biomarkers, such as body mass index (BMI), systolic blood pressure, and fasting glucose levels [28].

4.3 Genome-Wide Epidemiological Researches in Birth Cohorts

In adult cohort studies, GWAS have aided in the development of the DNA microarray technique and have been actively performed to elucidate associations between various outcomes such as traits and diseases and genetic factors, with numerous genome cohorts establishing specific consortia to perform data integration and meta-analysis for each outcome. In 2007, *Science* magazine named "human genetic variation" as the breakthrough of the year because of the tremendous advancement in the understanding of how genomes differ from one human to another [29]. Since then, GWAS reports have dramatically increased [30, 31], and several consortia specializing in GWAS meta-analyses of birth cohort studies, such as the EGG and EAGLE Consortia, have been established [19, 20]. These consortia have conducted risk evaluation of various outcomes from the viewpoint of life-course epidemiology, and in cooperation with consortia that have already been established in adult cohort studies, these consortia have contributed to the identification of associations between childhood factors and adulthood NCDs or traits that developed over time [32–36].

Since GWAS have been conducted in adult genome cohort studies, a small number of birth cohort studies have also participated in GWAS. Of particular prominence, in one of these studies, an association of a single nucleotide polymorphism (SNP) rs9939609 in the obesity-associated *FTO* gene with BMI, obesity risk, and type 2 diabetes was detected in multiple populations [32]. The association between BMI and this SNP has been confirmed in a total of 38,759 participants from 13 cohort studies, including two birth cohort studies: the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Northern Finland Birth Cohort 1966 (NFBC 1966), which participated in the EGG and EAGLE Consortia. The 16% of adults who were homozygous for the risk allele weighed approximately 3 kg more than adults who did not inherit the risk allele and had l.67-fold increase in odds for

obesity; this observation was seen in subjects over the age of 7 years and reflected a specific increase in fat mass [32]. Regarding early-onset obesity, meta-analysis was conducted for the 13,848 participants of European descent from 14 cohort studies in North America, Europe, and Australia, who were also included in the EGG Consortium (5530 obese people with a BMI greater than the 95th percentile and 8318 controls with a BMI less than the 50th percentile) [33]. According to this large-scale study, two genetic loci, rs9568856 near the *OLFM4* gene and rs9299 of the *HOXB5* gene, were detected at the genome-wide significance level. Meta-analysis also revealed a significant association between these loci and adult BMI.

In addition, the EGG Consortium conducted a GWAS of the 10,623 participants of European descent from 13 birth cohorts and found that two genetic loci, rs900400 near the *CCNL1* gene and rs9883204 in the *ADCY5* gene, were significantly associated with birth weight (BW) regarded as indicators of fetal growth [34]. Correlated SNPs in the *ADCY5* gene were implicated in the regulation of glucose levels and increased susceptibility to type 2 diabetes, providing evidence that the well-described association between lower birth weight and subsequent type 2 diabetes has a genetic component, which is distinct from the proposed role of programming by maternal nutrition [34]. However, since this SNP has not been detected in individuals of Japanese descent, the marker cannot be used to evaluate Japanese populations. Next, the EGG and EAGLE Consortia conducted an expanded genome-wide association meta-analysis and follow-up study of BW for 69,308 individuals of European descent from 43 studies [35]. This large-scale study increased the number of loci detected at the genome-wide significance level to seven (*CCNL1*, *ADCY5*, *HMGA2*, *CDKAL1*, *5q11.2*, *LCORL*, and *ADRB1*), accounting for a variance proportion similar to that of maternal smoking. Five of the loci are known to be associated with other phenotypes: *ADCY5* and *CDKAL1* with type 2 diabetes, *ADRB1* with adult blood pressure, and *HMGA2* and *LCORL* with adult height [35]. These findings highlight genetic links between fetal growth, postnatal growth, and metabolism. Recently, the EGG and EAGLE Consortia performed a multi-ancestry GWAS meta-analysis of BW in 153,781 individuals participating in the EGG Consortium or UK Biobank and identified 60 loci where the fetal genotype was associated with BW [36]. Genetic correlations between BW and other health-related traits were estimated using linkage-disequilibrium score regression, which showed that BW had a strong positive genetic correlation with anthropometric and obesity-related traits, including birth length and, in adults, height, waist circumference, and BMI, while BW had an inverse genetic correlation with indicators of adverse metabolic and cardiovascular health, including coronary artery disease, systolic blood pressure, and type 2 diabetes (Figs. 4.1 and 4.2). For example, BW-associated regions, such as *CDKAL1*, *HHEX-IDE*, *MTNR1B*, *PLEKHA1*, *ADCY5*, and *ANK1*, are associated with type 2 diabetes, while *NT5C2*, *FES*, *EBF1*, *NRIP1*, and *ADRB1* are associated with systolic blood pressure, and *NT5C2* and *LCORL* are associated with coronary artery disease. Thus, big data from large-scale genome cohort studies suggest that life-course associations between early growth phenotypes and adult NCDs and traits may be genetically linked.

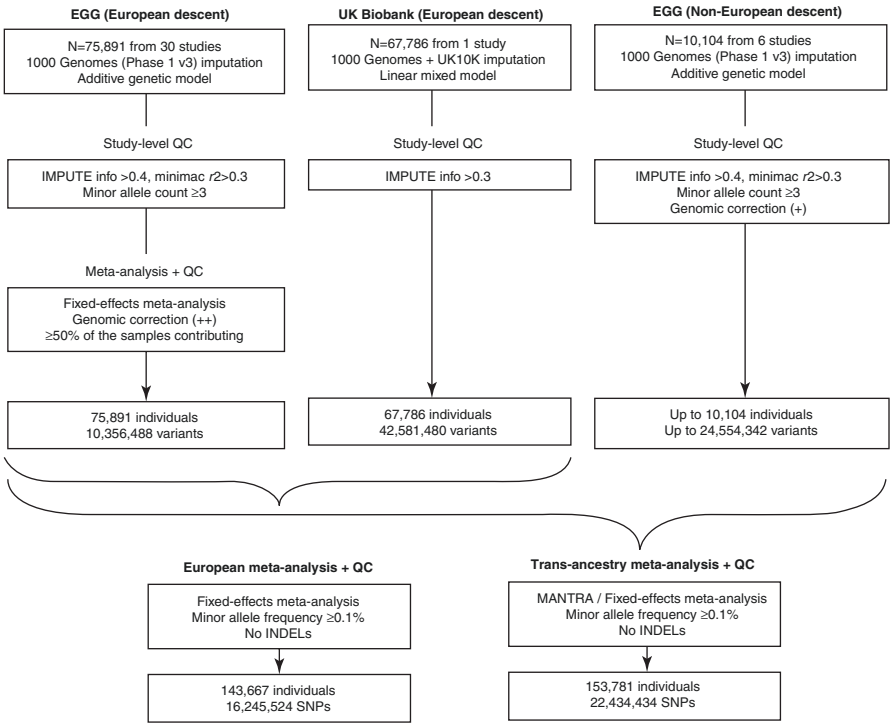

Fig. 4.1 Flow chart of the study design [36]

4.4 Birth Cohort-Based Evaluation of Epigenetic Changes and Exposome Reflecting Long-Term Environmental Exposures

Epigenetics refers to DNA modifications that do not alter the DNA sequence but instead reflect intergenerational environmental effects. In consideration of the DOHaD theory, epigenetic modifications, such as DNA methylation, caused by in utero exposures may play a critical role in early programming for the development of childhood and adult diseases. Epigenome-wide association studies (EWAS) have been employed to detect whole genome DNA methylation. Maternal smoking during pregnancy is a major risk factor for multiple adverse health outcomes in children, but the underlying mechanisms remain unclear. Norwegian researchers measured maternal plasma cotinine, an objective biomarker of smoking, during pregnancy in relation to DNA methylation at 473,844 CpG sites (CpGs) in 1062 newborn cord blood samples from the Norwegian Mother and Child Cohort Study (MoBa). Differential DNA methylation at epigenome-wide statistical significance was found for 26 CpGs mapped to 10 genes, and a US birth cohort study replicated the findings for CpGs in *AHRR*, *CYP1A1*, and *GFI1* at multiple comparison statistical significance [37]. Of the detected genes,

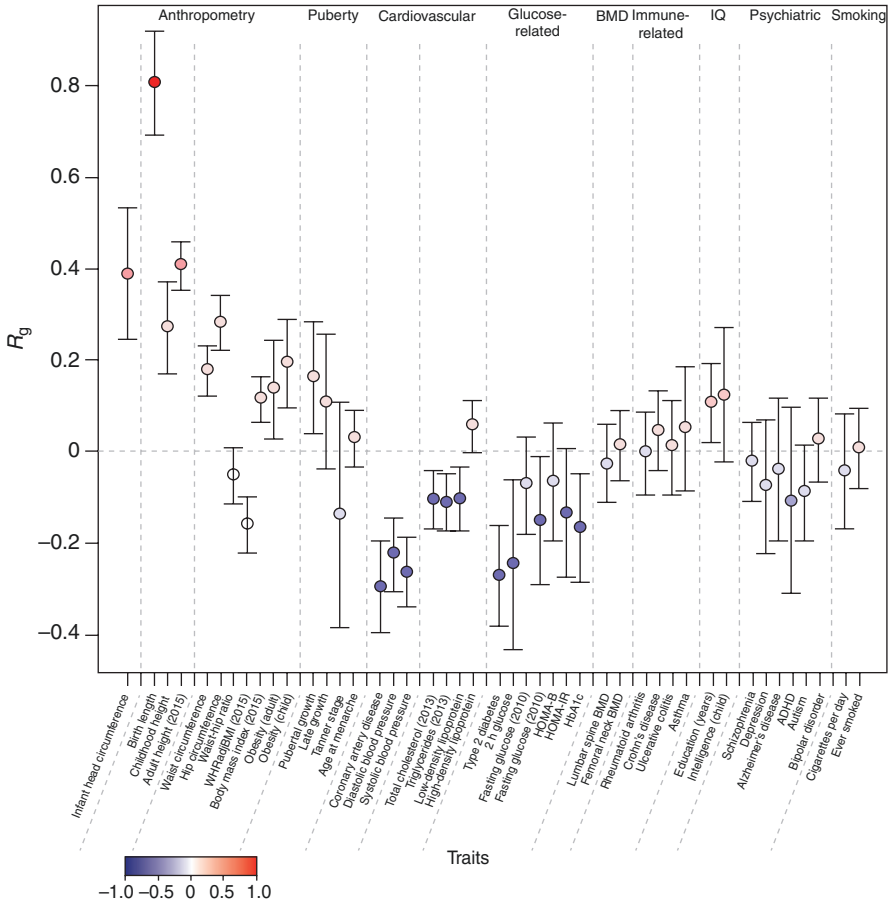

Fig. 4.2 Genome-wide genetic correlation between BW and a range of traits and diseases in later life [36]. Genetic correlation (R_g) and corresponding s.e. (error bars) between BW and the traits displayed on the *x* axis were estimated using linkage-disequilibrium score regression. The genetic correlation estimates (R_g) are color coded according to their intensity and direction (red for positive and blue for inverse correlation). *WHRadjBMI* waist-hip ratio adjusted for body mass index, *HOMA-B/IR* homeostasis model assessment of beta-cell function/insulin resistance, *HbA1c* hemoglobin A1c, *BMD* bone mineral density, *ADHD* attention deficit hyperactivity disorder

AHRR and *CYP1A1* play a key role in the aryl hydrocarbon receptor signaling pathway, which mediates the detoxification of smoking residuals. Recently, the PACE consortium completed a meta-analysis across 13 cohorts ($n = 6685$) and found cohort-specific associations between maternal smoking during pregnancy and DNA methylation in the offspring [25]. DNA methylation was detected at over 450,000 CpGs, and over 6000 of these CpGs, including CpGs in *AHRR*, *CYP1A1*, *GFI1*, *MYO1G*, and *CNTNAP2*, were differentially methylated in relation to maternal smoking at the genome-wide statistical significance level [25]. This large-scale meta-analysis of methylation data identified numerous loci involved in response to maternal smoking

during pregnancy that persisted into later childhood, thus providing insights into the underlying mechanisms of prenatal effects on later health statuses.

However, environmental exposures that disturb cellular and physiological processes and influence individual predisposition to diseases are likely to do so through active, or reactive, modulation of genome function, through changes in DNA methylation and transcription [38]. The exposome encompasses life-course environmental exposures, including lifestyle factors, from the prenatal period onward. Developing reliable measurement tools for such a complete exposure history is extremely challenging; yet, unlike the genome, the exposome is a highly variable and dynamic entity that evolves throughout an individual's life [26]. To develop a more cohesive view of environmental exposure, recognition must be given to toxic effects mediated through chemicals that alter critical molecules, cells, and physiological processes inside the body [39]. Thus, the environment can be reasonably considered to be the body's internal chemical environment, while exposures can be considered to be the amount of biologically active chemicals found in this internal environment [39]. Through this viewpoint, exposures are not restricted to chemicals entering the body via the air, water, or food but also include chemicals produced by inflammation, oxidative stress, lipid peroxidation, infections, gut flora, and other natural bodily processes. More than a decade has passed since the exposome concept was first proposed, and the subsequent years have been filled with discussions of definitions and challenges of the widespread implementation of the concept into research. However, it is time to move the concept from theory into practice, such as with the establishment of the EXPOsOMICS project, which aims to develop a novel approach for assessing exposure to high-priority environmental pollutants, such as air and water contaminants, during critical periods of life by characterizing the external and the internal components of the exposome [27]. Thus, the project focuses on the following two objectives: to assess exposure at the personal and population level within existing European short- and long-term population studies by exploiting available tools and methods for personal exposure monitoring and to employ multi-omics technologies for the analysis of biological samples, which serve as internal markers of external exposures (Fig. 4.3) [27].

4.5 Prevention of NCDs Through Effective Early Intervention

The first 1000 days of life, spanning from the fetus to the age of 2 years, represents a vulnerable period for programming NCD risk and is an important target for NCD prevention [40, 41]. Successful intervention during this period seems to greatly reduce the risk of NCD development later in life (Fig. 4.4) [42]. In Europe and the United States, a large-scale international collaborative research group has launched a project entitled, "Long-term effects of early nutrition on later health (EarlyNutrition)," to determine the most effective time and method of intervention with the assumption that nutritional intervention during the developmental period reduces the risk of NCDs in both pregnant women and their offspring [43, 44].

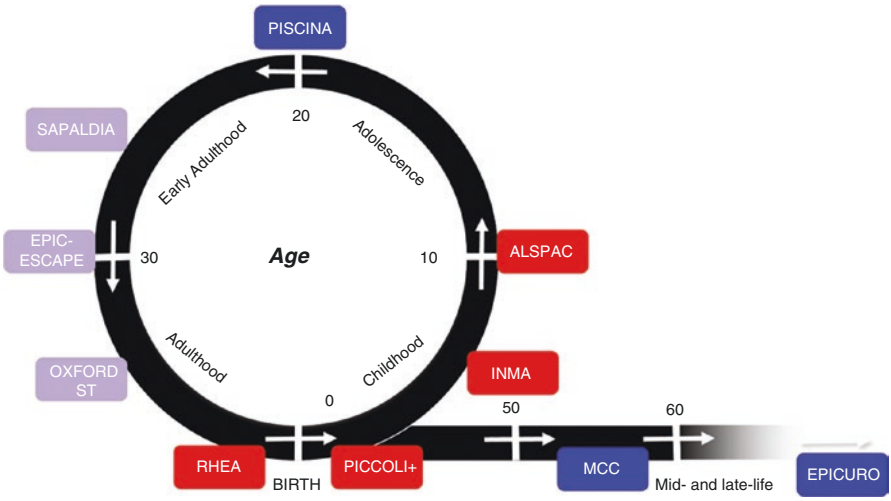

Fig. 4.3 The conceptual framework of EXPOsOMICS (life-long integration of cohorts) [27]

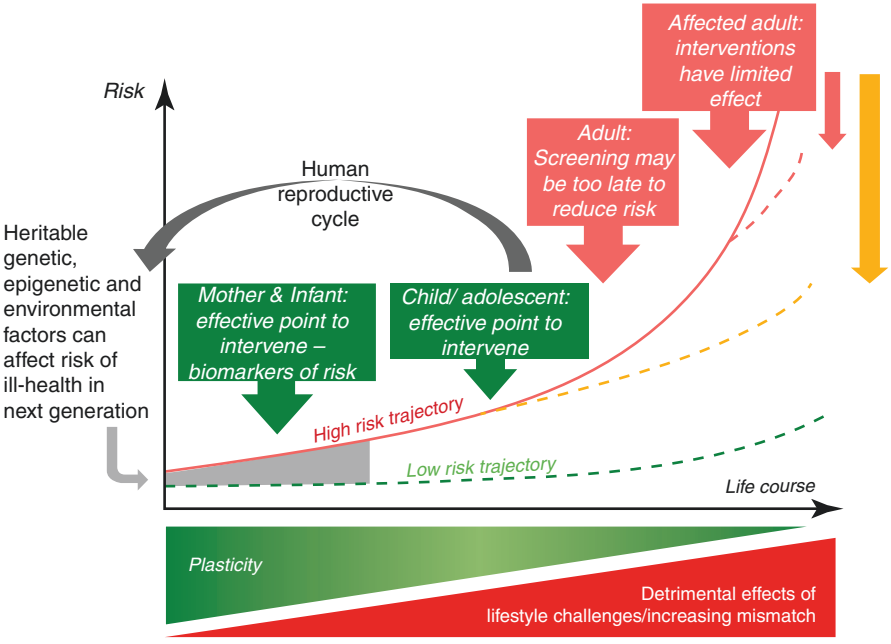

Fig. 4.4 Life-course view of noncommunicable disease (NCD) risk [42]. Risk increases in a nonlinear way as a result of declining plasticity and accumulative damage from lifestyle-imposed or other challenges. The effect of mismatch between developmentally and evolutionarily influenced phenotype and adult environment also increases through the lifecourse. Interventions in adults, especially those at high risk, can be beneficial but only to a degree. Screening in middle-aged adults may also be too late to reduce risk substantially. Interventions in adolescents and young adults are likely to be more effective and, importantly, can reduce the risk of NCDs in the next generation. The prenatal period establishes risk through interaction between genetic, epigenetic, and environmental factors

Using existing cohort studies, ongoing and novel intervention studies, and a basic science program to investigate those key hypotheses, EarlyNutrition will provide the scientific foundations for evidence-based recommendations for optimal nutrition that considers long-term health outcomes, specifically obesity and related disorders. Already, EarlyNutrition has conducted randomized controlled trials for children and has provided educational training for researchers and healthcare professionals. Infant nutrition has a major impact on immediate outcomes, long-term health, and later disease risks, such as obesity and related disorders, and this phenomenon is referred to as "metabolic programming." Rapid weight gain in the first 2 years of life, most notably mediated by dairy protein, affects the insulin-like growth factor metabolic pathways, where epigenetic processes seem to play a role [45]. In addition, the Southampton Women's Survey (SWS), a prospective cohort study targeting women before pregnancy who reside in disadvantaged communities, found that developing sustainable, workable interventions and effective community partnerships requires commitment beginning long before intervention delivery and is key to the translation of developmental research into improved health outcomes [46–48]. On the other hand, Liggins Laboratories in New Zealand launched nutrition educational programs for school children that deploys texts, such as the Liggins Education Network for Science (LENScience), e-learning platforms, and original school-based edible education [49–51]. These programs should be multidisciplinary, utilizing both educational and health expertise, because even though health outcomes may not be evident in the short term, they may occur with learning-related behavior modifications, which are highly effective when sustained over a lifetime [51].

In 2006, the Japanese Ministry of Health, Labor, and Welfare published the "Dietary Guidelines for Pregnant and Lactating Women" [52]. The guideline offered evidence-based information on how pregnant women should consume foods on a daily basis and steadily increase their body weight during pregnancy. However, in 2008, the Science Council of Japan proposed the "prevention of lifestyle-related diseases from prenatal and childhood," which recognized the importance of early intervention [53]. Recently, the concept of preemptive medicine, which is a novel medical paradigm that advocates for presymptomatic diagnosis or prevention intervention at an early stage to prevent disease onset, has been proposed [12]. Traditionally, epidemiological studies often target middle-aged and elderly people, producing an abundance of epidemiological data for subjects over the age of 55 years; however, epidemiological data for subjects under the age of 40 years are extremely limited [54]. Further, biological samples taken from middle-aged or elderly subjects will inherently be affected by the processes of aging, even if the individual is healthy. Therefore, this data source is not suitable for detecting early biomarkers. Thus, current research efforts are recognizing the importance of interdisciplinary research that focuses on the fetal period through childhood, conducts science and technology workshops, and proposes strategic policies that address these issues [55–57]. Research themes that need to be addressed and promoted in the future are classified into three categories (Table 4.3) [56]. Among them, specification of core institutions and organizations that supervise the whole project from a mid- to long-term viewpoint and acquisition of human resources and development of the next generation are important and fundamental items common to all three themes.

Table 4.3 Important themes that should be promoted in the future

Important items common to all three themes
1. Specification of core institutions and organizations that supervise the whole project from a mid- to long-term viewpoint 2. Acquisition of human resources and development of the next generation 3. Appropriate activities in the perspective of ethical, legal, and social implications (ELSI)
Theme 1: Establishment, operation, and utilization of epidemiological bases
1. Integration of existing birth cohorts and biobanks together with formation of consortia 2. Establishment of an environment that facilitates access to the data by researchers 3. Initiation of a new epidemiological foundation that cannot be obtained by existing epidemiological research infrastructure 4. Establishment of new epidemiological bases shall be planned based on thorough discussions including measures to ensure mid- to long-term funding
Theme 2: Promotion of basic and fundamental life science studies
1. Promotion of researches in genome, epigenome, nutrition, disease, and behavioral sciences 2. Promotion of measurement techniques
Theme 3: Promotion of research and development toward social implementation and impact assessment involved with implementation
1. Collecting, managing, and analyzing in detail the big data obtained through promotion of epidemiological studies and life science studies 2. Quantitative assessment of impact on health, economy, and society

4.6 Conclusion

At the beginning of this century, the DOHaD theory incorporated much broader concepts: not only were poor physical conditions in adulthood, such as disease suffering, strongly associated with the fetal environment but also the ability to maintain a healthy lifestyle. Today, adverse fetal-childhood environments, such as undernutrition, stress, smoking, and chemical exposure due to growth restriction, are known to increase the risk of NCDs, such as cardiovascular disease, stroke, hypertension, type 2 diabetes, chronic kidney disease, osteoporosis, cancer, and psychiatric disorders, later in life. Currently, birth cohort studies are establishing consortia together to promote integrated data sharing and meta-analyses for GWAS, EWAS, exposome, Mendelian randomization, and early intervention studies. Recently, in Japan, a new medical paradigm of preemptive medicine was proposed, and policies have been created that emphasize the importance of fetal-childhood research. In particular, I hope Japan as a nation plans and initiates interdisciplinary national-scale, preemptive medicine projects based on the DOHaD theory, establishes a central research institution, and engages in international consortia focused on improving life-course healthcare. I have great expectations for this nation, and I look forward to the future implementation of these initiatives.

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