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Alexander Vaiserman *Editor*

Early Life Origins of Ageing and Longevity

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Healthy Ageing and Longevity

Volume 9

Series Editor

Suresh I. S. Rattan, Department of Molecular Biology and Genetics, Aarhus University, Aarhus, Denmark

Rapidly changing demographics worldwide towards increased proportion of the elderly in the population and increased life-expectancy have brought the issues, such as "why we grow old", "how we grow old", "how long can we live", "how to maintain health", "how to prevent and treat diseases in old age", "what are the future perspectives for healthy ageing and longevity" and so on, in the centre stage of scientific, social, political, and economic arena. Although the descriptive aspects of ageing are now well established at the level of species, populations, individuals, and within an individual at the tissue, cell and molecular levels, the implications of such detailed understanding with respect to the aim of achieving healthy ageing and longevity are ever-changing and challenging issues. This continuing success of gerontology, and especially of biogerontology, is attracting the attention of both the well established academicians and the younger generation of students and researchers in biology, medicine, bioinformatics, bioeconomy, sports science, and nutritional sciences, along with sociologists, psychologists, politicians, public health experts, and health-care industry including cosmeceutical-, food-, and lifestyle-industry. Books in this series will cover the topics related to the issues of healthy ageing and longevity. This series will provide not only the exhaustive reviews of the established body of knowledge, but also will give a critical evaluation of the ongoing research and development with respect to theoretical and evidence-based practical and ethical aspects of interventions towards maintaining, recovering and enhancing health and longevity.

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Alexander Vaiserman
Editor

Early Life Origins of Ageing and Longevity

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Editor
Alexander Vaiserman
Laboratory of Epigenetics
Institute of Gerontology
Kiev, Ukraine

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Preface

Traditionally, gerontological research is focused on later stages of life cycle. Accumulating evidence, however, indicates that the rate of aging-associated functional decline (senescence) as well as the risk for chronic pathological conditions can originate early in life. It is already well established in numerous studies that all living things are highly plastic during their early development. Through particular developmental stages ("critical windows"), the organism is extremely sensitive to various environmental cues with the outcomes impacting subsequent stages of life cycle and later-life health status. Such kind of developmental plasticity has adaptive value because it attempts to match an individual's responses to particular environmental conditions that are likely to prevail in subsequent life; inadequate prediction, however, leads to an increase of the risk for chronic disease in later life. These processes are commonly referred to as "developmental programming." The mechanistic basis for the link between early and late stages of the life cycle is not entirely clear, but modulation of epigenetic regulation of gene expression likely plays a critical role in linking the adverse environmental conditions early in life to the risk of various aging-related pathological conditions in adulthood. Currently, these mechanisms are the subject of active debate and investigation.

Initially, these ideas were articulated by David Barker in the "fetal origins of adult disease" hypothesis on the basis of his early observation that small size at birth is linked to an elevated risk of hypertension, abnormalities in lipid metabolism, insulin resistance, and cardiovascular disease in adulthood. Subsequently, Barker's hypothesis has been confirmed by numerous observations and is currently accepted by most of the scientific community. Over the last few decades, it has evolved into the Developmental Origins of Adult Health and Disease (DOHaD) hypothesis that postulates that adverse environmental exposures during critical *in-utero* and early postnatal stages of development may permanently change physiological responses and cause functional impairments and disorders in adult life. Among the determining factors affecting these processes, developmental malnutrition seems to be the most important, although other factors such as stress or hypoxia may also be crucially involved. Collectively, these factors may to a great

extent determine not only the risk for subsequent adult-onset disorders but also the aging rate *per se* and, ultimately, longevity.

The possibility of developmental origins of aging-associated processes draws attention to factors contributing to developmental programming phenomenon that largely affect modern human societies. Among them, there are factors related to present-day lifestyle trends, such as Westernized dietary habits, low physical activity, high level of social stress, drug and substance abuse, and exposure to xenobiotics. All these factors may affect pregnant and lactating women, and they were shown to be able to adversely modulate epigenetic and other pathways that contribute to developmental programming of aging-related pathological conditions. It can be certainly assumed that these factors will substantially influence future trends in incidence of aging-associated disorders and in life expectancy. Therefore, further translational research is required to improve the understanding of early etiological mechanisms of age-related pathology. One of the most promising outcomes of such translational studies is development of epigenetic approaches aimed to predict which early life exposures would put exposed subjects at risk for a particular disease and which individuals will be more susceptible to develop particular pathological conditions later in life.

The elaboration of interventional strategies targeted at restoration of developmentally disrupted epigenetic patterns is increasingly considered as a promising treatment option to alleviate adverse effects of early life malprogramming and to reduce the risk of adverse age-related conditions in later life. Indeed, since developmentally induced epigenetic disturbances are potentially reversible, they can likely be corrected by specific epigenome-targeted pharmacological and/or nutritional interventions. Further development of such approaches will, of course, require the use of highly sensitive methods to detect potentially disadvantageous epigenetic alterations long before the clinical diagnosis of disease. After appropriate clinical trials, the implementation of such treatment strategies in clinical practice may hold great promise in preventing and treating a wide variety of chronic diseases and human healthspan extension.

This book brings together current research evidence and knowledge on the early life origin of aging and longevity in chapters written by leading experts in this area from around the world. It can likely be a relevant and useful resource not only for professional scientists and clinicians but also for scientifically interested amateurs wishing to know more about the current research in this rapidly evolving field.

Kiev, Ukraine Alexander Vaiserman

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Contributors

Vanda Aronsson CHESS, Centre for Health Equity Studies, Department of Public Health Sciences, Stockholm University/Karolinska Institutet, Stockholm, Sweden

Michael D. Barnes Department of Public Health, Brigham Young University, Provo, UT, USA

Barbara Barth Integrated Program in Neuroscience, McGill University, Montreal, QC, Canada;
Department of Psychiatry, Faculty of Medicine and Ludmer Center for Neuroinformatics and Mental Health, McGill University, Montreal, QC, Canada

Andrzej Bartke Department of Internal Medicine, Southern Illinois University School of Medicine, Springfield, IL, USA

Alessandro Bigoni Department of Epidemiology, University of São Paulo School of Public Health, São Paulo, Brazil

Adriana Carrieri Department of Nutritional Sciences, Program in International Nutrition, Center for Childhood Nutrition Education and Research, New Jersey Institute for Food, Nutrition, and Health; Rutgers, The State University of New Jersey, New Brunswick, NJ, USA

Cyrus Cooper MRC Epidemiology Lifecourse Epidemiology Unit, Southampton General Hospital, University of Southampton, Southampton, UK

Elisabetta Damiani Department of Life and Environmental Sciences, Polytechnic University of the Marche, Ancona, Italy

Susanne R. de Rooij Department of Clinical Epidemiology, Biostatistics & Bio Informatics, Amsterdam University Medical Centers, Location AMC, Amsterdam, The Netherlands

Elaine M. Dennison MRC Epidemiology Lifecourse Epidemiology Unit, Southampton General Hospital, University of Southampton, Southampton, UK

Laurette Dubé Desautels Faculty of Management, McGill Center for the Convergence of Health and Economics, McGill University, Montreal, QC, Canada

Rosita Gabbianelli Unit of Molecular Biology, School of Pharmacy, University of Camerino, Camerino, Italy

Michael C. Goates Harold B. Lee Library, Brigham Young University, Provo, UT, USA

Thea N. Golden Center for Research on Reproduction and Women's Health, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Daniel J. Hoffman Department of Nutritional Sciences, Program in International Nutrition, Center for Childhood Nutrition Education and Research, New Jersey Institute for Food, Nutrition, and Health; Rutgers, The State University of New Jersey, New Brunswick, NJ, USA

Emma C. Johns MRC Centre for Reproductive Health, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK

Michelle Lampl Center for the Study of Human Health, Emory University, Atlanta, GA, USA

Simon C. Langley-Evans School of Biosciences, University of Nottingham, Sutton Bonington, Loughborough, UK

Oleh Lushchak Department of Biochemistry and Biotechnology, Vasyl Stefanyk Precarpathian National University, Ivano-Frankivsk, Ukraine

Michael J. Meaney Integrated Program in Neuroscience, McGill University, Montreal, QC, Canada;
Douglas Hospital Research Centre, 6875 Boulevard LaSalle, Montreal, QC, Canada;
Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research (A*STAR), Singapore, Singapore

Bitte Modin CHESS, Centre for Health Equity Studies, Department of Public Health Sciences, Stockholm University/Karolinska Institutet, Stockholm, Sweden

Beverly Muhlhausler Food and Nutrition Research Group, Department of Food and Wine Sciences, School of Agriculture, Food and Wine, University of Adelaide, Glen Osmond, SA, Australia

M. Lelinneth B. Novilla Department of Public Health, Brigham Young University, Provo, UT, USA

Justin M. Packer Department of Public Health, Brigham Young University, Provo, UT, USA

André K. Portella Desautels Faculty of Management, McGill Center for the Convergence of Health and Economics, McGill University, Montreal, QC, Canada

Clare M. Reynolds Liggins Institute, University of Auckland, Auckland, New Zealand

Rebecca M. Reynolds MRC Centre for Reproductive Health, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK;
BHF/University Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK

Tessa J. Roseboom Department of Obstetrics and Gynaecology, University of Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands;
Department of Clinical Epidemiology, Biostatistics and Bioinformatics, University of Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands;
Amsterdam Reproduction and Development, Amsterdam, The Netherlands;
Amsterdam Public Health Research Institute, Amsterdam, The Netherlands

Clare Shere MRC Epidemiology Lifecourse Epidemiology Unit, Southampton General Hospital, University of Southampton, Southampton, UK

Patricia Pelufo Silveira Integrated Program in Neuroscience, McGill University, Montreal, QC, Canada;
Department of Psychiatry, Faculty of Medicine and Ludmer Center for Neuroinformatics and Mental Health, McGill University, Montreal, QC, Canada;
Douglas Hospital Research Centre, 6875 Boulevard LaSalle, Montreal, QC, Canada

Rebecca A. Simmons Center for Research on Reproduction and Women's Health, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

David Q. Stoye MRC Centre for Reproductive Health, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK

Liou Sun Department of Biology, University of Alabama at Birmingham, Birmingham, AL, USA

Denny Vågerö CHESS, Centre for Health Equity Studies, Department of Public Health Sciences, Stockholm University/Karolinska Institutet, Stockholm, Sweden

Alexander Vaiserman Laboratory of Epigenetics, Chebotarev Institute of Gerontology, Kiev, Ukraine

Mark H. Vickers Liggins Institute, University of Auckland, Auckland, New Zealand

Liu Yang BHF/University Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK

Part I
Overview

Chapter 1
Epidemiology of Early Nutrition and Adult Health: Metabolic Adaptations and Body Composition

Daniel J. Hoffman, Alessandro Bigoni and Adriana Carrieri

Abstract The intrauterine period of growth is extremely important for lifelong health as growth and development of fetal tissues and organ systems occur at a very rapid pace. Any perturbation to this process, either through nutritional insufficiency or exposure to endocrine disruptors or toxins, not only interrupts or delays the growth process, but in some cases results in metabolic abnormalities that challenge adult health. In terms of early childhood nutrition and growth, a number of studies have reported that stunting is a risk factor for obesity and central adiposity. However, other studies have reported divergent findings. Regardless, it is well accepted that nutrition during early childhood through adolescence has a profound effect on healthy growth and deficits in energy or specific micronutrients have a negative impact of adult height and growth. More important, the growth pattern, such as slow or rapid growth, is now considered to be a primary factor in terms of body composition and health. This chapter will describe the relationship between poor growth in utero and early childhood as a risk factor for adult chronic diseases based on epidemiologic and clinical studies. As well, the influence of poor growth during childhood on metabolism and body composition will be explored as potential areas in which mechanisms may explain epidemiological studies.

Keywords Early nutrition · Metabolic adaptation · Body composition · Lifelong health · Adult disease · Obesity

D. J. Hoffman (✉) · A. Carrieri
Department of Nutritional Sciences, Program in International Nutrition, Center for Childhood Nutrition Education and Research, New Jersey Institute for Food, Nutrition, and Health; Rutgers, the State University of New Jersey, Dudley Road, New Brunswick, NJ 08901, USA
e-mail: dhoffman@aesop.rutgers.edu

A. Bigoni
Department of Epidemiology, University of São Paulo School of Public Health, São Paulo, Brazil

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1.1 Introduction to the Developmental Origins of Adult Health and Disease

Human health is often defined as the absence of disease. However, the absence of disease is not a simplistic definition, but a complex set of characteristics determined by a number of factors related to diet, environment and economics, as well as country of residence and educational status. All of those factors, contributing to a real state of health, highlight the interplay of both biological and socio-economic factors that allow a normal developmental process to occur, key to an optimal health during the lifetime. Yet, there is debate as to how specific factors, such as pre-conception health of the mother and father, maternal exposure to sufficient or insufficient calories, protein, and micronutrients, fetal exposure to environmental toxins or drugs, as well as nutrition during early childhood interact to influence fetal and offspring growth and development.

It should really come as no surprise that nutrition from conception through childhood contributes to the long-term health of any organism, including humans. There is substantive evidence that nutritional deficiencies either in utero or during early life has permanent effects on growth, development and later health. As well, the impact of maternal and child malnutrition on growth is a well-known public health issue and is most apparent when discussing the long-term effects of micronutrient deficiencies on a child's health and development. For example, vitamin D deficiency leads to poor differentiation of enterocytes that also impairs the intestinal absorption of calcium and phosphorus, limiting or halting bone mineralization, resulting in rickets (Sahay and Sahay 2012). Perhaps one of the most significant examples of how vitamin deficiencies can cause long-term disease is the effect of folate deficiency on fetal growth. Folate is critically important for fetal DNA synthesis and cell proliferation which is why a mother's daily requirement is 5–10 times greater than a non-pregnant woman (Antony 2007). A deficiency in maternal folate intake causes abnormal neural development resulting in lifelong cerebral and neurologic impairments, neural tube defects and even death. The importance of folate for lifelong health is clear when one considers that periconceptional supplementation with folate reduced the risk of delivering a child with neural tube defects by 60% compared to women who consumed a placebo (Mulinare et al. 1988). In addition to nutrient deficiencies, the excess of some nutrients, such as alcohol, can result in impaired growth and "fetal alcohol syndrome" (Astley et al. 2016; Carter et al. 2013). Thus, deficiencies of specific nutrients that support development are known to have permanent effects on a newborn or infant and has been known for several decades. However, what was less accepted among the scientific community was that general deficiencies, such as energy restriction, or weight gain or exposure to an excess concentration of hormones (e.g. cortisol), may have lasting metabolic and endocrine responses that increase the risk of chronic diseases for offspring of mother who experienced such problems.

Since the mid-1980s, there has been a steady increase in the number of scientific publications on the influence of nutrition in utero and during critical periods of growth on adult health. This should not be a novel idea considering the evidence

of "programming" in other species as well as human. For example, it is well documented that the sex of turtles, alligators, and lizards develop differently depending on the temperature at which eggs are incubated (Gilbert 2000) Similarly, profound disruptions to brain and neurological development in humans occurs when exposed to the Zika virus (Rasmussen et al. 2016). This nascent areas of research quickly became an important field due to its impact in the scientific and public health arenas, giving rise to what is now called "developmental origins of health and disease" (DOHaD).

Barker and Osmond first documented that chronic diseases normally associated with higher income were prevalent in lower income regions of England and Wales. Specifically, there was a high correlation between infant mortality and ischemic heart disease as well as cerebro-vascular disease (Barker et al. 1993). This initial study was complemented by an analysis of mortality and birth weight in the same region and it was found that among men, the standardized mortality rate declined as birth weight increased (Barker et al. 1993). The standardized mortality rate between low and normal birth weight men was no different when analyzed using body weight at age 1 year. A similar relationship was found for women, but for birth weight only. At the same time, it was reported that breastfeeding until 1 year of age was associated with CVD in men, but not women. There is no clear explanation for this finding, but it was suggested that breastfeeding may down-regulate thyroid function and increase low density lipoprotein (LDL) concentration. At the same time, there may be differential development of the liver during gestational growth retardation as Barker also reported that infants born with a small abdominal circumference, reflecting a small liver, were more likely to have higher serum total cholesterol and LDL concentrations, independent of gestational length, social class, and alcohol and smoking status (Barker et al. 1993). Nonetheless, it is apparent that the intrauterine experience programs health and risk for disease differently for men and women, but subsequent analyses were not able to test the interactions with environmental, hormonal, or dietary factors that exist during growth and adulthood and may mitigate existing associations.

Since Barker's early publications, a great number of studies were developed with the Hertfordshire cohort where over 15,000 babies had birth weight and early feeding practices documented in the early part of the 20th century. As there is a rich dataset with several important anthropometric and dietary measures, including breastfeeding, approximately 265 studies have been conducted to assess the impact of those early nutritional parameters on risk for chronic diseases in adulthood. A number of these studies are discussed below and form a very small percent of the number of studies that have been published using data from the Hertfordshire cohort. Still, the striking and consistent results of many of the studies from the Hertfordshire cohort inspired others to either investigate similar existing cohorts or use the lessons learned from Barker and others to form new and even more detailed longitudinal cohort studies.

1.2 Famine and DOHaD

Famines are an unfortunate part of civilization and have occurred for thousands of year and continue to occur even in modern time. As with many human disasters, famines are often associated with "natural events", such as drought or disease, but in reality are intimately related to socio-political events that are intended to exert control over others or used as a means to gain political power. While unfortunate, the existence of famines has allowed for a number of novel scientific questions related to DOHaD to be asked using retrospective designs. Aside from the large number of such studies, the vast number of publications that have been generated is well beyond the scope of this chapter. However, a brief critical summary of some of the more salient famine studies will be presented with an emphasis on those studies related to chronic diseases.

1.2.1 Dutch Famine

Perhaps the most well known of famine studies is that of the "Dutch Winter Famine" that occurred between late 1944 and early 1945 in which a specific segment of Holland was under Nazi control and food rations allowed into the restricted zone contained an average of 800–1,200 calories per person, per day. Women who conceived or were already pregnant during famine gave birth to children who would then become part of the "Dutch Famine cohort". Roseboom et al were among the first to study the long-term impact of the exposure to the Dutch famine prenatally and in the first period of infancy on the survival of 2,254 people born in Amsterdam. They found that the no significant differences in mortality from 18 to 50 years of age, but a significant increase in mortality i in the first 18 years of life relative to birth weight, length and head size such that being born small increased the risk of early mortality (Roseboom et al. 2001). Similarly, Painter et al found no association between adult mortality and prenatal exposure to famine. The authors also report a positive relationship between birth weight and cancer mortality that is not mediated through famine (Painter et al. 2005). However, the authors argue that the trends indicate a positive association between famine exposure and mortality at later ages and propose that the lack of significance is due to follow-up time and overall cohort age. The argument by Painter et al was corroborated by a study published almost a decade later in which famine exposure in the first trimester increased the risk of mortality by 12% compared to those not exposed to the famine in utero (Ekamper et al. 2014). Additionally, an 8% increase in risk for mortality was reported in the cohort exposed to the famine during the first days of life after birth. The findings reported by Ekamper et al. were possible after enough follow-up had been reached for the necessary number of outcomes to reach statistical power, an improvement over previously conducted. These results are consistent with the concept that an early stimulus or insult, depending of the development stage, result in long-term consequences for function of the organism

(Hoffman et al. 2017). This programming effect is exemplified by the relationship between anthropometric measures reported by Roseboom, as well as the differences between first trimester and first days of life exposure to famine, where those exposed in the first trimester had a higher risk of mortality compared to those who were exposed at a later stage.

1.2.2 Chinese Famine

Previously termed the "Great Leap Forward Famine", the Chinese famine lasted longer than the Dutch famine and affected a mostly rural population. From data collected on the Chinese famine, it was found that the relationship between famine exposure and mortality was similar to those from the Dutch famine (Song 2009), but important methodological aspects of working with this type of cohorts are quite different. In the work of Song, mortality hazard related to famine exposure of those born right before and right after the famine are respectively, 1.2 and 1.09 ($p < 0.05$). However, this result was primarily confounded by a "period effect" caused by the unusually higher mortality risk of being born during a famine. Thus, Song concludes that the Chinese Famine had a limited effect on mortality, but that this effect did not continue after the famine was over.

In addition to mortality, another topic explored with the Chinese famine cohort was mental health and cognition at later ages. Huang and Zhou explored the influence of famine exposure in cognitive abilities among 2,685 of 45 years old and above exposed to the famine while in the uterus or in the first infancy (Huang and Zhou 2013). From this analysis, they reported an inverse association between famine exposure and cognitive abilities in later life and argue that this association is most likely to be due to socioeconomic disadvantages more than neuro-physiological pathways. However, the authors recognize that the sample size is small and that their results are not generalizable to all of China. Moreover, it was reported that women born during the famine had higher risks of developing mental disorders compared to those not exposed to the famine (Huang et al. 2013).

The physiological influences of famine exposure appear to not be limited to mental disorders or chronic diseases, but may influence even acute health disorders. In one such study, those exposed to the famine prenatally and in early life had higher prevalence of anemia in adulthood in comparison to those who were not exposed (Shi et al. 2013). As well, the authors reported a 37% increase risk of anemia in the prenatally exposed group, even after adjusting for socioeconomic indicators, hypertension, BMI and alcohol and tobacco consumption. Thus, a great deal of knowledge has been gained studies of the Chinese famine, especially important is the consideration that some of the studies have elegantly merged famine exposure relative to current diet, modeling the interaction between biological and environmental exposures.

China's Great Famine distinguishes itself from the others not only due the magnitude of its impact on the total number of deaths, but also the fact that most of the people affected were from rural areas. One leading hypothesis behind the effects of

in utero famine exposure on health in later life is that during the period of scarcity, potential epigenetic mechanisms act to prepare the offspring or newborn to the seemingly hostile environment (Bateson et al. 2004; Fleming et al. 2018). However, this mechanism has a threshold and if the environmental insult is too great the organism perishes. Nonetheless, such hypotheses explain the period effect that may have confounded the results of Shige Song. However, when looking to specific physiological differences, the influence of early mortality is reduced, corroborating the results reported by Cheng Huang et al. and Shi et al.

1.2.3 Finnish Famine

The Finnish Famine lasted from 1966 to 1968, during which 102,921 people were born and 36,022 survived to the age of 60. One study on the effect of famine exposure on mortality found no association between famine exposure and epigenetic profiles relative to mortality (Saxton et al. 2012). A similar conclusion was reported by Hayward et al in which the effects of the famine are most likely to influence mortality around the time of birth and not in later-life (Hayward et al. 2015). The discordance between the findings from the Finnish Famine cohorts and the other mentioned may be due the fact that after the Finnish Famine, the population returned to its previous levels of consumption and production. Some studies indicate that DOHaD is not only modulated by the severity of the insult during development, but also by the mismatch between the environment to which the organism adapted and the one that it was truly exposed (Jablonka and Raz 2009). The logic behind such explanations callback to the idea of "programming" in the sense that a program can only work properly in the settings in which it was built, otherwise problems, manifested as diseases, may begin to emerge.

1.3 Historical Birth Cohorts and DOHaD

As famines are unnatural occurrences, the ability of to collect data well during a famine is severely restricted due to ethical and practical constraints. Thus, research on DOHaD relies on historical cohorts that have often been initiated without the forethought that they would be used for research, but for which quality data on diet, size at birth, and infant health are available.

1.3.1 Poor Growth as a Risk Factor for Obesity

Nutritional deprivation, either as insufficient energy, micronutrient, or protein intake, during conception through early childhood, manifested in being born small for ges-

tational age (SGA) or growth retarded, is associated with adult obesity (Lucas et al. 1999). Based on existing studies, the link between poor growth and later risk for obesity appears to be related to the specific gestational exposure to famine. Among one of the first studies of in utero famine exposure and obesity found that men from the Dutch famine cohort who were exposed to famine during the first two trimesters of gestation had a higher risk of being classified as obese compared to those exposed during late gestation and early infancy (Ravelli et al. 1976). Similar to results from the Dutch famine studies, women who had been exposed to the Chinese famine in utero were more likely to be obese compared to those who were born after the famine (Meng et al. 2018). As well, a study from Sweden reported a U-shaped relationship for birth weight and BMI reporting that adults born weighing less than 2500 g or greater than 3500 g had a higher risk of obesity compared to those born weighing 3000 g (Eriksson et al. 2001). Furthermore, the pattern of disease risk varied according to gender and growth trajectory. Recently, it has been reported that exposure to famine as a fetus may have trans-generational effects on risk of poor health as offspring of women from the Dutch famine cohort were born with a higher ponderal index and were twice as likely to report "poor health" as adults (Eriksson et al. 2001). Additionally, offspring of fathers born during the Dutch famine had a higher BMI compared offspring from fathers who were not exposed to the famine (4.9 kg, CI 0.8–9.1), even after adjusting for sex and age (Veenendaal et al. 2013). Within these studies is an important caveat to consider as BMI was used as the index for adiposity and is an imperfect tool for assessing excess body fat mass. However, BMI is generally accepted as a screening tool for clinical studies and is useful for population studies. Still, there are a number of important limitations to BMI that lessen the impact of studies seeking to determine the relationship between early nutrition and later body composition or body fat distribution. Regardless, many recent studies have used advanced body composition techniques, such as stable isotope dilution and imaging, that support specific many results presented in this chapter.

The size of a newborn, be it birth weight, length, or ponderal index, is simply one dimension of growth and it has become increasingly recognized that growth during the post-natal period may play an equal, if not greater, role on adult health. Specifically, the rate of growth, using either change in BMI Z-score (BMIZ) or rate of weight gain, has been found to be predictive of adult BMI or body composition (Salgin et al. 2015). A very important cohort study that addresses growth patterns, along with social and biological factors that may influence growth and development is the Birth to 20 (Bt20) study in South Africa (Musa et al. 2016). In the Bt20 study, 3,200 newborns were recruited in Soweto, Johannesburg, South Africa in the early 1990s and underwent measures of body composition, growth, and socioeconomic indicators. The post-natal growth patterns were then used to determine how growth, relative to size at birth, acted as a risk factor for later health outcomes. It was reported that birth weight and weight gain were not associated with "unhealthy" lipid profiles, adjusted for linear growth from birth to 4 years (Musa et al. 2016). Yet, rapid gain of height and weight from birth were associated with being overweight in adolescence. Moreover, when rapid weight gain occurred early in life, children were found to have earlier menarche and increased adult adiposity, risk factors for

metabolic disorders and some forms of cancer (Charalampopoulos et al. 2014). On the other hand, a study of intrauterine growth retarded children in the U.S. found that they had a higher waist circumference and increased insulin resistance compared to children born with normal birth weight, even when controlling changes in BMIZ from birth to age 10 years (Crume et al. 2014). It was argued that the lack of statistical association between body composition may be related to the time of follow-up and is wholly consistent with a study from Brazil in which early rapid growth was positively associated with obesity in adulthood (Monteiro and Victora 2005). Yet one more study found that children who had greater weight gain, also had greater fat mass (FM), independent of birth weight, compared to children with a slower rate of weight gain (Leunissen et al. 2009). As well, results from the Project Viva study of U.S. children emphasized how interactions between birth weight and weight gain in early childhood was associated with greater adiposity, adjusted for birth size (Perng et al. 2016). In other words, children who experience a rapid change in BMIZ from six months to one year postnatal were more like to have insulin resistance, regardless of birth weight. Similarly, a rapid gain in BMIZ during the first six postnatal months was associated with higher systolic blood pressure in childhood (Crume et al. 2014). These results are consistent with the evidence that early nutritional programs and interventions that target weight gain may offer a great impact on obesity later in life (Ling et al. 2016).

It is important to note that excess body fat mass is not necessarily pathogenic, although it has been associated with an increased risk of metabolic disorders. Indeed, children born small who underwent more rapid growth than peers were more likely to be insulin resistant than children who experienced slower post-natal growth rate (Crowther et al. 2008). It has also been reported that birth size and post-natal growth have independent effects on skeletal development, depending on the timing of growth. In a study of South African children, Vidulich and colleagues found that born small and remaining small through the first year of life was associated with both smaller bones and bone with lower mineral content in the femoral neck (Vidulich et al. 2007). Finally, children from the Southampton Womens's Survey had a positive association between intrauterine growth, bone size and bone density, indicating that the effects of the DOHaD cannot disturb metabolic pathways only, but also have long term influences on skeletal development (Harvey et al. 2010).

In summary, clearly nutrition during gestation has profound and lasting effects on body size and body fat distribution, but also on other components of body composition that may promote osteoporosis and limit the development of metabolically active tissue, contributing to metabolic disorders. It is necessary to temper the impact of such studies as different methods to assess body composition were used, as well as different statistical analyses. Therefore, it is an important caveat that future studies attempt to normalize methods so that new results are more comparable with existing studies.

1.3.2 Poor Growth as a Risk Factor for Chronic Diseases

While obesity per se is not considered to be a chronic disease, it is associated with an increased risk for many metabolic disorders. Still, there are a number of studies from well documented famines that have shown that poor gestational and post-natal growth also increased the risk for certain metabolic diseases. One clinical study of the Dutch famine cohort found that lower glucose tolerance existed for adults who were exposed to the famine during gestation compared to those that were never exposed to the famine (Ravelli et al. 1998). In a separate study, the relationship between gestational famine exposure and hypertension found that adults who had been exposed to famine during any 10 week period of gestation were more likely to have hypertension compared to unexposed adults (Stein et al. 2006). In fact, a higher birth weight decreased the odds of hypertension by 33%, independent of gender. Yet, there is no clear association between specific periods of famine exposure and hypertension, most likely due to the smaller sample size when the complete cohort is split into sub-groups for more detailed analyses. Nonethelesss, one study of the Chinese famine found that adults who were exposed to the famine during middle childhood had a 50% increased risk for T2D compared to those not exposed to famine (Wang et al. 2016). More important, this relationship persisted even after adjustment for drinking and smoking status, and family history of diabetes. The risk, however, changed according to period of exposure, being higher in the middle childhood group, and according to sex, reporting a higher risk for women. A similar study of the Chinese famine also reported that adults exposed to the famine during the first years of childhood were almost three times more likely to have hypertension compared to those who had no being exposed to the famine (Chen et al. 2018). Consistent with these studies, adults who experienced gestational exposure to famine in Bangladesh and were underweight as adults were reported to be overweight as well as hyperglycemic compared to unexposed adults (Finer et al. 2016).

Finally, a study of Utah pioneers prenatally exposed to a severe food shortage during critical periods of in utero development within the winter months of 1855–1856 were more likely to die earlier compared to those who were not exposed. The effect of famine exposure on mortality was more significant for men compared to women, owing to a number of confounding factors such as activity, gender bias, or stress (Hanson and Smith 2013). It was concluded that in utero programming can have deleterious effects on future health, but the authors were cautious in their conclusions and added that catch-up growth of offspring during the first years of life could play a role in the outcome of interest. While there are certainly methodological differences between various studies of famine exposure and later health, the basic aspects of such studies are relatively consistent and allow for broad conclusions to be based on their findings.

1.3.3 Poor Growth as a Risk Factor for Mental Health Diseases

One less studied area of DOHaD focuses on the impact of poor nutrition in utero or early childhood on mental health. An accumulating number of studies, however, reported a link between poor nutrition early in life and cognitive development and later-life mental health. In the Dutch famine study prenatal exposure to the Dutch famine nearly tripled the risk for schizophrenia (Hoek et al. 1998). Strikingly similar results were published in which prenatal exposure to the Chinese famine from 1959 to 61 nearly doubled the risk of schizophrenia for adults in the famine exposed group compared to those born after the famine (St Clair et al. 2005). These studies provide significant evidence that nutrient deprivation appears to have a profound effect on later mental health due to acute exposure to famine. The relevance of finding similar results in the Dutch and Chinese cohorts is strengthened by the fact that they are two vastly different cultures, a factor well known as being a confounder in mental disorder studies, as well as having very different post-natal nutritional and social environments.

Aside from mental health, studies from different countries have reported that poor nutrition in childhood has a significant negative impact on cognition. In Peru, stunted children (defined as height-for-age Z-score or HAZ < -2.0) scored significantly lower on a series of cognitive tests compared to taller children (Crookston et al. 2010). Furthermore, children who experienced catch-up growth (indicating a positive change in HAZ) had cognitive scores similar to children who remained stunted. However, when a multi-country study was conducted on growth and cognitive performance with over 8,000 children from four developing countries, children who recovered height from age 1 to 8 years performed poorly compared to children who were never stunted but scored better than children who remained stunted (Crookston et al. 2013), suggesting that timing of nutritional interventions is vital to improving human capital. This point is made even more clear by a study of stunted children in Jamaica who received psychosocial stimulation and scored markedly higher on IQ, verbal, and reading tests compared to stunted children who did not receive such stimulation. Recently, as some of the children from this cohort are now parents, it was reported that offspring of stunted parents scored lower on a battery of cognition tests, independent of birth weight and height-for age but it is not clear if the effects are related to social or biological factors. Furthermore, stunted children in India who received nutritional supplementation for six months had cognitive test scores similar to children who remained stunted, as well as those who recovered height (Sokolovic et al. 2014). While the degree of stunting at age two years has shown consistent and long-term cognitive deficits, such deficits in a cohort from Cebu, Philippines, declined by age 11 years (Mendez and Adair 1999). Based on the studies reviewed, the timing of interventions is clearly critical to the overall impact of nutrition on brain development during gestation and childhood. This is an area of research that warrants much greater attention to improve human capital throughout the world, but especially in lower income countries.

In summary, a large number of studies provide evidence that supports the concept of DOHaD. As presented, most studies using data from famine and longitudinal cohorts have reported that poor nutrition or growth during the "first 1,000 days" are risk factors for a number of chronic diseases later in life. Exactly how and when different tissue and organ systems are influenced by nutrient deprivation remain major research questions, but new studies are providing intriguing insights into potential mechanisms behind DOHaD as discussed below. Still, it is important to consider how improving the understanding of nuances between conflicting studies can inform the research community in a way that shapes future research designs and agendas.

1.4 Growth Retadation and DOHaD

Regarding post-natal nutrition insults, while stunting is formally defined as children whose length or height is below the 10th percentile of healthy children of the same age, there is some discussion as to the appropriateness of using cutoffs outside of programmatic or epidemiologic research. Simply, using a categorical definition of poor growth restricts the population or sample under investigation to the "worst of the worst" in the sense that a child who is slightly above the cutoff is categorized as "healthy", but may actually be more anthropometrically or physiologically similar to an "unhealthy" child than a child well above the cutoff. Thus, research on growth needs to be clear as to the objective and determine a priori if poor growth should be defined using a categorical or a continuous measure.

1.4.1 Global Prevalence of Stunting

Globally, the percentage of stunted children decreased from 40 to 27% between 1990 and 2010, respectively, and is expected to reach 22% by 2020 (de Onis et al. 2011). Asia experienced an overall decrease in stunting from 1990 to 2010 (49–28%), however, in Africa, the prevalence of stunting has remained at 40% since 1990. It is predicted that this trend will continue and, in 2020, Africa and Asia will have the same number of stunted children (de Onis et al. 2011). There are a number of reasons some countries have seen an improvement in the nutritional status of their children while others have not. For example, civil strife disrupts a large number of sectors of civil society and is often accompanied by a deterioration in health care, food security, and sanitation, factors associated with a quality diet, health and optimal growth. For areas of the world that have been subject to civil unrest and economic challenges, the prevalence of stunting remains high, such as 50% in Eritrea and East Timor, 47% in Guatemala and Yemen, and 41% in Afghanistan and East Timor (United Nations 2018). Thus, while it is important to look at global and regional trends in the fight against undernutrition, it is necessary to focus on countries that are not doing as well

as others to best determine policies or practices that may be improved, even in the face of political or social challenges.

1.4.2 Stunting in Latin America

In Latin America, much progress has been made in the past 20–30 years to decrease the prevalence of poor growth, but such efforts have been eclipsed by the "nutrition transition" and the emergence of the double burden of disease. Nonetheless, at present, 9.6% of children are severely to moderately stunted and 1.3% are moderately to severely wasted in Latin America and the Caribbean (World Health Organization 2018). In specific countries, such as Ecuador, there is a high prevalence of stunting that has been linked to household economic status and dietary diversity (Weigel et al. 2018). In Brazil, the prevalence of growth retardation has improved greatly in recent years, partly due to economic development that has reduced the number of families living in poverty and partly due to national nutrition programs that have promoted nutrition and education in lower income communities (Yokoo et al. 2018). It is imperative to highlight the differences regarding the prevalence of stunting among different countries in Latin America. For example, 48% of children under the age of 5 in Guatemala are stunted compared to 2% of children in Chile (World Health Organization 2018). Still, one cannot generalize as to why some children become stunted and others do not within specific countries, regions or continents, but rather evaluate the prevalence individually to better plan policies and other interventions for each country (Corvalán et al. 2017).

1.4.3 Stunting in Africa

Countries in Africa and Asia tend to have a high prevalence of both wasting and stunting resulting from poor maternal nutrition as well as ongoing food insecurity due to political unrest, economic disparities, and poverty. For example, while in 2015 there were 98.5 million fewer stunted children under 5 years of age than in 1990, the global prevalence is partly reflected by gains in some regions, but not others as the number of stunted children in sub-Saharan Africa increased by 12.4 million in the past 25 years (Campisi et al. 2017). In Kenya, approximately 30% of children under two years of age were stunted (Ndemwa et al. 2017) while in South Africa, 26% of boys and 19% of girls under two years were stunted (Hanson et al. 2018). In summary, great advances have been made in many countries to improve nutrition and lower the prevalence of growth retardation, but many countries still face serious challenges and an increasing prevalence of stunting that has the potential to limit educational attainment and economic advances for members of the lowest income groups or in marginalized communities.

1.4.4 First 1,000 Days Concept

Extending the concept of DOHaD to include growth after the "first 1,000" days, essentially considering nutritional insults that impact linear growth and results in chronic growth retardation, is an important consideration given the vast number of children worldwide who are classified as stunted (de Onis et al. 2018). Stunting, as well as more moderate growth retardation, affects upwards of 150 million children worldwide, with the majority residing in low- and middle-income countries (de Onis et al. 2011). For decades, stunting was associated with poverty and lack of access to adequate nutrition, generally thought to be a problem of insufficient calories and micronutrients. However, in the mid 1990s, a study of four countries found that stunting in adolescence was a risk factor for obesity in adulthood (Popkin et al. 1996), a new paradox given the conventional thinking that obesity was a problem of wealth and excess caloric intake. Subsequent clinical studies of stunting and obesity support this initial finding and offer potential biological explanations for the relationship between stunting and fat deposition. One study of adolescent girls in Senegal who were stunted before the age of 2 years, accumulated more subcutaneous fat on the trunk and arms compared to non-stunted girls, even when adjusted for BMI (Bénéfice et al. 2001). Likewise, a separate study of Guatemalan children who were stunted had a BMI above the median for US children of the same age, but low extremity fat assessed using skinfold measurements (Schroeder and Martorell 1999). When adults from the same cohort had anthropometric measures conducted, those who were severely stunted as children had greater central fat, even when adjusted for total FM and other confounding factors, compared to those who were moderately or never stunted (Schroeder et al. 1999).

To further explore and understand the relationship between stunting and obesity, a clinical study of stunted children in Brazil was conducted to assess metabolic adaptations that may promote excess adiposity. Briefly, stunted children were recruited from the same shantytowns as normal height control children, the gain of truncal fat mass was greater during a four-year period, independent of total fat mass (Hoffman et al. 2007). It should be noted that the method to assess adiposity in this study involved the use of imagining, a far more accurate methodology than anthropometrics alone. Nonetheless, there are other studies that have reported divergent results. For instance, longitudinal analyses of the Bt20 cohort found that stunting at age 2 years was not associated with a high BMI or central adiposity (Cameron et al. 2005). As well, one study of indigenous children in Bolivia reported that stunting was associated with a lower BMIZ and body fatness assessed using skinfold measurements (Tanner et al. 2014). Still, in a separate Brazilian cohort, there were no significant associations between indices of undernutrition (such as WHZ or HAZ) and adiposity (Gigante et al. 2009). One important caveat to this cohort from Brazil is that the proportion of children who were found to be undernourished was relatively low (less than 10%), but poor growth early in life was associated with shortness later in life, a significant predictor of poor health outcomes and other factors associated with poverty, but not with excess adiposity or obesity. Moreover, a recent study from Nepal found that

stunted children in a low-income and less developed region, have poor lean tissue accretion and less fat mass compared to normal height children (Wells et al. 2018). To best understand the complementary and conflicting results presented in these studies, despite the fact that subject characteristics or inclusion criteria may have bee similar, the differences in methods used to assess outcomes, sample size, and socio-economic environment of the study sample all contribute to potential differences in associations and conclusions. Certainly, investigators may make the best attempt to control for all possible confounding factors, but interactions between a any number of factors is bound to influence associations that do not allow for a consensus on the question being studied.

Based on the studies discussed above, there is clearly an abundance of research that has provided solid evidence that poor nutrition in the "first 1,000 days" has an impact on body composition and body fat distribution later in life, phenotypes that may increase the risk for metabolic disorders and other nutrition-related chronic diseases. Certainly, it is wise and prudent to consider that growth continues well after the first 1,000 days and future research needs to consider the dynamic events during later childhood and puberty that may either interact with or exacerbate, maybe even attenuate, the nutritional insults during early development. As well, as a child grows, their dietary and activity patterns, along with exposure to a number of environmental toxins, contribute to their life course and influence their initial risk of chronic diseases, along with their gestational and early life exposures. Still, the ability to greatly control and influence a child's exposure to unhealthful diet or environment are greatest during the first 1,000 days.

1.4.5 Stunting and Metabolic Adaptations

While most of the studies discussed in this chapter were epidemiological or clinical, one of the criteria for assessing causality in epidemiology is the existence of plausible biological mechanisms that support results from population studies. Yet, studies of humans complement other animal studies and appear to suggest specific metabolic mechanisms behind the association between in utero or post-natal under-nutrition and adult health. In fact, studies of human energy expenditure, including resting metabolic rate (RMR) and substrate oxidation, have reported that metabolic adaptations may increase the risk for greater adiposity later in life. Two such studies found no significant differences in RMR between stunted children and normal height children (Hoffman et al. 2000a; Wren et al. 1997). Yet, two studies reported a significantly lower RMR in growth retarded children compared to normal height children (Aidam et al. 2005; Said-Mohamed et al. 2012). Apparent differences in human studies of body composition or energy metabolism may easily be attributed to differences in methodologies used or the statistical analyses used. For example, for those studies that reported no significant finding related to RMR, investigators used ratios for energy metabolism per unit body composition and it is generally accepted that the more appropriate analysis would have use linear regression analyses where

body composition is entered as a confounding variable. Regardless, there is substantial data that either support the hypothesis that nutritional insults early in life program metabolic adaptations that may increase the risk for chronic diseases under obesogenic conditions, such as high dietary fat intake or low physical activity, but conflicting studies do not negate these results, rather they create an impetus for more refined research to be conducted.

Given these methodological differences, it is still important to address impact of poor growth on energy metabolism and body composition, but perhaps employing a more nuanced approach to studying specific elements of energy metabolism, such as substrate metabolism, a key metabolic risk factor for fat deposition. Studies on substrate oxidation in growth retarded children are generally more consistent compared to studies of energy expenditure. A number of clinical studies have reported specific metabolic adaptations associated with low birth weight or growth retardation. As discussed above, the study of stunted children in Brazil measured basal substrate oxidation and found that stunted children metabolized fat at a lower rate than normal height children, independent of fat mass and macronutrient intake (Hoffman et al. 2000b). Along those lines, a study of men from the Hertfordshire Cohort reported that men who were born small had a lower rate of 24-h fat oxidation compared to those men born with a higher birth weight (Kensara et al. 2006). In addition, a study of the Buryat in southern Siberia found that adults who were significantly shorter than their peers following the fall of the Soviet Union had a lower rate of fat oxidation (Leonard et al. 2009). Finally, North Korean children who were either stunted or short for age had a significantly lower rate of fat oxidation compared to North Korean children who were not growth retarded (Lee et al. 2015). It is important to consider that these similar results come from studies of adults and children with vastly different cultural and genetic differences. Thus, one could conclude that that poor growth, either in utero or during childhood, is associated with a metabolic adaptation that promotes fat storage and under the right environmental conditions. A challenge to understanding more intricate aspects of metabolism in growth retarded children is the ethical issues related to invasive methods. Obviously, studies on rodents are able to provide great insight into potential metabolic mechanisms that may develop following growth retardation and are discussed in detail in a number of review papers beyond the scope of this chapter (Goldstein et al. 2017; Tain and Hsu 2017; Tain et al. 2017a, b).

1.4.6 Social Determinants of Growth and Role in DOHaD

Poor growth associated with poor dietary intake or intrauterine exposure to stress hormones or other environmental factors is generally a reflection of poverty and other structural factors that may be difficult to modify. Yet, when one considers the biology of DOHaD and the implications for lifelong health, it is important to consider the number of social and economic factors that may interact with dietary intake and and environmental exposure. Such factors may range from maternal education, household

income, access to nutritious food, air quality and sanitation, all of which have great potential to adversely influence maternal and paternal health, nutrient availability, and fetal growth.

Perhaps the most insightful study to date that has the ability to address social and economic influence on the biology of DOHaD comes from the Bt20 cohort. One salient study from this cohort reported that socio-economic status was protective against risk for hypertension independent of size at birth (Hoek et al. 1998). It was also found that a high degree of social support and income were associated with greater bone mineral content, adjusted for body composition and pubertal development (Crookston et al. 2010). Returning to the study of the Chinese famine, adults who were born during the famine and live in high income areas had a greater risk of T2D, suggesting that prosperity may further increase the risk for specific chronic disease previously thought to be attributable to famine exposure only (Wang et al. 2015). In terms of interactions between social and biological factors, in utero famine exposure was found to increase the risk of T2D, yet those adults exposed to the famine who ate a "Western" diet were even more likely to have T2D compared to those who ate a "traditional" diet, illustrating the intricate interaction between in utero and environmental exposures on chronic disease development (Li et al. 2011).

Birth weight is often used to reflect the intrauterine growth experience, but studies of post-natal growth report that the impact of socio-economic status on risk and/or recovery from growth retardation play very significant roles in the biological outcomes studied. For example, a higher birth weight was associated with a lower risk of stunting, but higher maternal education was protective only in girls while a higher SES was protective for boys (Sokolovic et al. 2014). In terms of cognitive development, children who recover from stunting by 5 years of age experienced greater cognitive challenges compared to normal height children. In fact, the cognitive problems in children recovered from stunting were estimated to be as severe as those measured in stunted children who remained stunted (Sokolovic et al. 2014). While single country studies are subject to criticism given the number of social and cultural differences between various countries can impact the variables being studied, it is useful to consider multi-country studies. To that end, based on data from a large multi-country study of growth and human capital, children born with a higher birth weight or a rapid gain in height by age 2 years, had a higher level of education that was estimated to increase adult income by 5% (Sokolovic et al. 2014). Moreover, in terms of economic productivity, it was found that height at 2 years of age was the greatest predictor of overall human capital. Clearly, the negative effects of growth retardation are physiological and threaten the long-term health of an individual, but it is important and necessary to consider the impact of cognitive damage associated with poor nutrition as these outcomes may interact with general health to limit a person reaching their full human potential, in both biological and social terms.

1.5 Summary and Conclusions

In summary, while DOHaD began with a series of epidemiological studies, the exact mechanisms to explain and support the results presented were scarce. However, over the past 20–30 years, substantial evidence from additional cohort, small mammal, and even epigenetic studies have proposed plausible and consistent mechanisms linking poor nutrition in early life to risk of chronic diseases in adulthood. Given the studies reviewed, it is apparent that particular physiological and behavioral adaptations following acute and chronic undernutrition, either in utero or during early childhood, have significant impacts on adult health. However, it remains a challenge for future research to design cohort studies using new technologies in proteomics, metabolomics, and epigenetics to refine the knowledge of potential mechanisms of DOHaD. Perhaps even more important is that the research community remains cognizant of the social and economic conditions in which children are exposed to poor nutrition and incorporate interventions that not only lower the risk of chronic diseases in adulthood, but also actually improve education and nutrition of women in lower and middle income countries.

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Chapter 2
General Biology of the Developmental Origins of Health

Michelle Lampl

Abstract Health across the life span is predicted by cellular health as established in tissue and organ structure and function early in life. The cellular machinery of mitosis and the platforms for transcription-mediated cell differentiation give rise to phenotypic varieties of embodied experience through growth. Earliest cell fate decisions reflect stochastic processes. Competitive cell lineage commitments follow, encouraged by gene expression patterns influenced by the environment through hierarchical hub negotiations, and carried out by translational signaling. Cell-level negotiations emerge as the anlage for building multi-cellular bodies. Mechanistically linked to cell fate, metabolic strategies underlie early cell decisions and are core influences on variable phenotypic outcomes in changing environments. Fundamental biological processes, including oxidative stress, inflammation and stem cell regenerative potential mediate healthy aging at the cellular level. This chapter is an overview of fundamental biological platforms for developmental programming of life-course cell level dynamics involved in building the fetal body.

Keywords Stem cell · Embryo · Fetus · Developmental programming · ROS · Healthy aging

2.1 Introduction

One of the principle questions raised by the observations associating fetal development and healthy aging is "what is it about size at birth that predicts later health?" Predicated on theoretically-based adaptive associations (Godfrey et al. 2007; Bateson et al. 2014), interpretations of population-level epidemiologic data led to investigations largely focused on relationships between maternal nutrition and birth outcome to address the birth size/later health link. These studies have included descriptions of growth patterns and organ sizes as predictors of disease (Fall et al. 2008; Eriksson et al. 2018) by way of nutrition (Roseboom et al. 2000; Warner and Ozanne 2010;

M. Lampl (✉)
Center for the Study of Human Health, Emory University, Candler Library 107, 201 Dowman Drive, Atlanta, GA 30322, USA
e-mail: mlampl@emory.edu

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Fleming et al. 2017), stress (Fowden 2017), and various environmental exposure causal pathways (Velazquez et al. 2019).

A developmental cellular perspective identifies fundamental determinants of cell origins and function as important mechanistic sources influencing processes involved in building a fetal body and supporting healthy aging. Organisms are developmentally constructed according to biological principles that unfold on foundational cellular platforms. Selective gene transcriptional activation and inhibition are the biology underlying the differentiation of all developing tissues (Folmes and Terzic 2014a). By coupling real time metabolic flux to cell fate decisions, mammalian organisms grow and develop according to threshold effects, with hubs that integrate information from redundant systems-level signal systems (De Caluwé et al. 2019).

A brief overview of fundamental cellular strategies offers perspective on generic pathways that link development and early growth to healthy aging across a lifetime.

2.2 Growth: A Cellular Process

The developmental origins of health across the lifespan are initiated in the maternal environment of the pre-conception ova (Fleming et al. 2017; Velazquez et al. 2019). Here, energetic strategies become embodied in subsequent cell lineages as fundamental biological processes influence a sequence of cell proliferation, differentiation, and enlargement. Proliferation, or increase in the number of cells, relies on the mitotic machinery and cell cycle controls that permit or inhibit cell division based on molecular stop/start mechanisms (Soufi and Dalton 2016). In this way, size records the environment. Cell differentiation follows, reflecting serial changes in gene expression patterns, influenced by cross-talking pathways of hierarchically-arranged response molecules. These signal pathways reflect the translation of environmental circumstances to promote, inhibit or disinhibit gene transcription (Tahmasebi et al. 2018). Cell sizes reflect volumetric fluctuations due to hydrative expansions and diminutions, storage and secretion of biological molecules, and the incorporation of newly formed microstructures in response to dynamic physiological circumstances (Barrett-Jolley et al. 2010). Each of these fundamental biological processes operates at the behest of chemical signals, reading the environment and contributing to morphological changes in form and function of cells individually, tissues and organs collectively. Taken together, these three processes underlie growth in size and control growth tempo, while interfacing the environment and contributing to phenotypic variability. This is well-illustrated by skeletal growth (Lampl and Schoen 2017). An overview of platforms that are responsive to fundamental processes associated with metabolism is critical for understanding how earliest development sets parameters that subsequently unfold as health across a lifetime.

2.3 Cellular Dualities: Alternative Cell Fate Decisions

Mammalian development occurs as a sequence of decision points between alternative cell fates (Pfeffer 2018). The initial steps to building the body unfold as the ova and sperm membranes fuse to form the first zygotic cell, a totipotent cell, with the ability to give rise to all cell types in the developing organism as well as the extra-embryonic tissue. This totipotency is retained for approximately the first five cell divisions as the zygote becomes a blastocyst (Wigger et al. 2017). Thereafter, cell lineage fates are progressively restricted. This occurs as genes that are co-expressed in early stem cells become mutually exclusive with cell commitment to specific fates (Artus and Chazaud 2014). The mammalian preimplantation embryo harnesses this dichotomous gene expression option to balance the proportion of cells that will give rise to the fetus itself and the proportion that will give rise to the in utero support system. Empirical evidence suggests that the initial lineage choice is stochastic, with a feedback mechanism that balances proportions of two distinct cell fates through mutually repressive interactions (Lander et al. 2009; Lo et al. 2009).

The first major cell fate decision occurs in accord with spatial location and local milieu (Wigger et al. 2017). The cells that will become the fetus are located in the middle of the multiplying blastocyst cells, and will become known as the "inner cell mass" (ICM). The inner cell mass cells will become the pluripotent embryonic stem cells (ESC). These are clonal cells characterized by the capacity to differentiate into all embryo/fetal tissues only, with the ability to self-renew. The surrounding cells, known as the trophectoderm (TE) after the first differentiation event, will become the placenta. The signaling pathway underlying this first differentiation point is known as "Hippo": inactivation of Hippo signaling permits blastocyst cells to retain plasticity and totipotency, while Hippo activation promotes blastocyst cell divergence to TE cells (De Caluwé et al. 2019; Hilman and Gat 2011; Ardestani et al. 2018). ICM cells are then again confronted by dual destinies to either remain as pluripotent embryonic cells, or differentiate to cells of the primitive endoderm and yolk sac (Artus and Chazaud 2014). This follows relatively quickly as the yolk sac is essential to meet the nutritional needs of the developing embryo (Hermitte and Chazaud 2014). Once again, the embryo and future fetus derive primarily from the innermost cells. The precise cellular allotment reflects a balance between fibroblast growth factor (FGF) and mitogen-activated protein kinase (MAPK) signaling (Wigger et al. 2017; Schröter et al. 2015). In these two sequential steps, cells are committed to auxiliary roles (placental and yolk sac lineages) at the expense of the embryonic/fetal fate, balancing cellular contributions to the future body in exchange for nutritional potential. These early cellular commitments may prove to both over-build the body and under-deliver metabolic needs for fetal size, expressed as variability in fetal growth rates and neonatal morphologies (Young et al. 1998; Lampl et al. 2009; Fernández-Gonzalez et al. 2004; Buttitta and Edgar 2007), with potential postnatal health consequences.

Similar sequential cell lineage assignments according to a chemically-induced decision tree pattern are the basis for constructing the body (De Caluwé et al. 2019; Pfeffer 2018; Turner et al. 2014). As genes are activated and inhibited, cellular pro-

tein expression patterns change, and common progenitors give rise to alternative cell fates (Lander et al. 2009; Lo et al. 2009). Both chronobiological elements (Hrushesky and Rich 2015) and environmental circumstances, ranging from oxygen and energy status to constituent availability, are communicated by molecular messengers across an array of pathways to promote and inhibit transcription until a point is reached where there can be no further shifting in cell destiny under the present conditions. Timing and chemical context are fundamental determinants of cellular destiny: similar proteins can have different effects conditioned on local environments and time-specific signal integration.

2.4 Oxygen

A fundamental influence on cell differentiation state is oxygen and change from anaerobic to aerobic metabolism is a hallmark of development. While mammalian cells evolved to be aerobic, relying on oxygen for cellular metabolism and energy (Nakazawa et al. 2016), energy production does not rely solely on oxygen itself. Glucose, the main source of energy for the body, can produce ATP anaerobically. Pluripotent stem cells thrive in hypoxic microniches. In oxygen concentrations below 1%, the maintenance of stemness is favored (Kwon et al. 2017; Mohyeldin et al. 2010) while both differentiation and senescence are inhibited (Kwon et al. 2017). Here, stem cells proliferate rarely and avoid oxidative stress by producing ATP through anaerobic glycolysis, thereby maintaining a low oxidative state and protecting DNA (Suda et al. 2011).

Increasing oxygen concentrations are associated with differentiation programs (Cipolleschi et al. 1993) in a concentration-dependent manner (Folmes and Terzic 2014b; Dunwoodie 2009; Mikkola and Orkin 2006; Papaioannou 2016; Cliff et al. 2017) based on threshold effects (Gu et al. 2016). For example, the first endoderm and mesoderm lineages-to-be have a lower threshold for a glycolytic to oxidative phosphorylation (OxPhos) shift by comparison with ectodermal lineage precursors (Cliff et al. 2017). In this way, sequential differentiation programs emerge from common source cells. In what has been described as a "race for fates" (Shen et al. 2019) mesodermal and endodermal derivatives separate (Kubo et al. 2004; Shen et al. 2019) from the same precursor under the influence of a cascade of transcription factors according to both threshold and timing effects. Overall, reactive oxygen species (ROS) influence multipotent stem cell derivatives (Atashi et al. 2015) in accord with unique concentrations and timing patterns of signaling molecules (Martin and Kimelman 2010; Diekmann et al. 2019) that reflect environmental conditions. With the caveat that much of our knowledge in this area is based on in vitro work, it appears that endo/mesodermal derivatives proceed by transcription-mediated gene expression in response to networks of signaling molecules. Central to this is the presence of a pathway that oversees energy availability and acts by modulating gene expression of oxygen-related response elements known as the hypoxia-inducible factor (HIF) pathway (Semenza 2017). HIF-mediated responses regulate the expression of hun-

dreds of mRNAs, to effect cell adaptation to changing levels of oxygen within tissues. One mechanism by which this works is modulating the HIF-1alpha protein to induce gene expression and thereby adjust cellular lifestyles to available oxygen, as well as fine-tuning a wide array of systems to up- and down-regulate energy delivery (Semenza et al. 1994). In this context, the broad functional effects of the HIF system are a biological statement that hypoxia is a metonym for energy, and a metabolic strategy.

Taken together, cell differentiation sequences express the activities of a wide spectrum of fundamental biological platforms that, in turn, contribute to developmental origins of health and disease across a lifetime. Hypoxia is a central orchestrator and is responsible for a dual outcome: it both contributes to proliferative potential in pluripotent stem cells (Lee et al. 2018) and arrests the cell cycle in differentiated mammalian cells (Goda et al. 2003).

2.5 Building and Reserving

Pluripotent stem cells are critical to building the organism de novo. They are also fundamental for the repair and replacement of cells needed to maintain tissue health with aging. For example, cardiovascular health relies on sufficient reserves of endothelial cells. Interfacing between the lumen and the vessel wall, endothelial cells contribute to the prevention of clot formation by inhibiting platelet aggregation and reduce the risk for atherosclerosis by impeding blockages secondary to inflammation and immune cell infiltration (Yau et al. 2015; Theodoru and Boon 2018). Endothelial cell demise occurs with oxidative stress and pro-inflammatory conditions, as well as chronic hyperglycemia. Vascular endothelial cells are particularly vulnerable to hyperglycemic damage as they are unable to downregulate glucose uptake when extracellular glucose concentrations are elevated, and high levels of intracellular glucose cause mitochondrial superoxide overproduction (Yao and Brownlee 2010), which in turn causes DNA damage (Mangialardi et al. 2014) by multiple paths. Endothelial cell turnover relies on sufficient numbers of Endothelial Progenitor Cells (EPCs), and EPC supplies require reserves of their lineage source, so-called CD34+ cells. CD34+ cells arise from the inner cell mass of the blastocyst and survive, dividing rarely, sequestered in microniches of the bone marrow. Circulating CD34+ levels have been found to correspond to levels in the bone marrow (Fadini et al. 2010), implicating the importance of both early developmental cell generation activities and the subsequent guardianship of healthy stem cell niches. Preserving stem cells at 1% oxygen requires their anatomical sequestration as exposure to the body's higher concentrations of oxygen, 21%, is an oxidative stress to stem cells that can be lethal.

The number of circulating CD34+ cells has been called a fundamental predictor of healthy aging and a biomarker of longevity (Mandraffino et al. 2012). Significantly fewer circulating CD34+ cells are found among patients with vascular-type cognitive impairment (Taguchi et al. 2008) and type 2 diabetes (Zafar et al. 2018), and bone

marrow CD34+ reserves decline with overweight, dyslipidemia and hypertension (Ross 2018). It is notable that birth weight is positively associated with CD34+ cell concentration (Chandra et al. 2012), independent of gestational age and traditional CV risk factors (Souza et al. 2019), offering a fundamental biological basis for epidemiological associations between birth weight and risk for CVD morbidity and mortality. These associations offer perspective on health disparities with a potential link between high rates of low birth rate (www.americashealthrankings.org), higher cardiovascular morbidity and mortality, and lower CD 34+ cell concentrations among African American adults (Samman et al. 2018) in the United States (Carnethon et al. 2017).

2.6 Building the Body: Cells Are Energy-Driven

Strategies for nutrient sensing and response are set in place among ova years before conception under influences from the maternal milieu. These include epigenetic methylation and ribosomal biogenesis (Fleming et al. 2017; Velazquez et al. 2019). Fertilized ova express these features and embryonic and fetal growth trajectories of somatic organs, such as the liver and kidney, embody them (Fleming et al. 2017). In this way, both postnatal growth and adult health reflect a cellular process set in motion prior to conception, when energetic mechanisms are initiated that will become refined and embodied during the assemblage of organs and their growth.

2.7 Phenotypic Outcomes Reflect Tissue Construction

In like manner, fetal tissues emerge as energetic calculations influence cell destinies: Lean tissue is more expensive to both construct and maintain than adipose tissue. Based on comparisons among tissue compartments (Heymsfield et al. 2018), energetics is a fundamental determinant of fetal organ construction and body composition. Under limited resources, growth of expensive organs is attenuated and fat is the default cellular destiny for mesodermal cells. These cellular negotiations may underlie phenotypic differences in body composition among populations living under challenging energetic circumstances whether derived from intergenerational maternal effects, ecological limitations, hyperglycemic/hypoxemic pregnancy challenges, maternal smoking, and fetal physiologies (Yajnik et al. 2003; Lampl and Jeanty 2004; Lampl et al. 2003) from the earliest ages (Lampl et al. 2012). Prenatal fat deposition is not occurring primarily as a preventive strategy to save the postnatal infant from harm, but because it is cheaper to build and maintain.

As important as tissue type is to postnatal life, developmental origins of health do not stop with cell lineage decisions manifest as body composition and organ development. Cell-level structural consequences embody physiological challenges of life in utero with the potential to influence a lifetime of functional resilience.

2.8 Fetal Challenges in Building the Body

Fetal functional anatomy is a conduit from fetal biology to healthy aging. This is well characterized by cellular responses to fetal hypoxia, a consequence of a wide range of influences including, but not limited to poor implantation, maternal vasculopathies, smoking, and diabetes. Hypoxia is a milieu that provokes fetal responses ranging from overall reduced growth, as hypoxia interferes with mitotic activity (Goda et al. 2003), to perturbed organ growth, altered vascular development and cellular structural alterations in response to molecular, cell and tissue level adjustments. A response sequence to hypoxia is exemplified by both the direct effects and side-effects of functional adjustments on behalf of the hypoxia-inducible factor (HIF) cascade (Semenza 2017).

Under hypoxia or energy shortage, fetal cardiac output increases to match body growth by increasing the work of the cardiac muscles and expanding ventricular dimensions in both wall thickness and overall size (Veille et al. 1990). Individuals with higher growth rates, or genetically-based growth potential, may be at higher risk for later disease as fetal organs respond by enhanced performance to keep up with metabolic demands. This may be exacerbated by fetal blood flow patterns that favor proximal oxygen delivery patterns, leaving the lower limb and body at the distal end of resources (Lampl et al. 2003). Specific organ strategies to upregulate fetal energy delivery include cellular perturbations that alter processes located in the liver and kidney in the first two fetal trimesters (Zanjani 1980). These are augmented by renal volume expansion and increased cardiac preload, which in turn promote cardiac growth via cell stretch-mediated growth factor effects (deAlmeida et al. 2007). Together, the kidneys and heart augment blood volume and distribution in an attempt to meet energetic demands, while changing their own morphology (Lampl et al. 2005) as they undergo hypoxia-driven hypertrophy. Animal models of similar compensatory or hypertrophic growth identify altered cellular growth patterns and associated increased risks for postnatal sequelae including arrhythmias (Sartiani et al. 2004), renal hyperplasia and cardiomegaly (Walter and Hamet 1986). The increased heart weight-to-body weight ratios expressed in the hypoxically-stressed fetus (Lampl et al. 2005) are found among spontaneously hypertensive rats during gestation, who go on to develop cardiac hypertrophy and hypertension in adulthood (Lewis et al. 1997).

2.9 Biological Fundamentals of Developmental Origins of Health and Disease

Data documenting what has been called fetal programming has been primarily undertaken from an adult clinical perspective. From a developmental biology viewpoint, adjusting cell type, proliferation rate and size according to metabolic signals is what embryos and fetuses do. Based on ancient multi-cellular organism metabolic prin-

ciples, energy signals determine fundamental processes that are harnessed in mammalian development. The process of normal fetal growth is a semi-facultative one by which growth occurs as cell level signals integrate mitotic activity, and differentiation decisions are made within available resources, according to a genetically-based and developmentally-timed schema.

It is likely that size at birth is but the proverbial canary in the coal mine. Size is a proxy for responses according to principles of energy-driven cell distribution, and is a signal, not the cause of lifetime health and potential lifespan attenuation. Size at birth is not a sine qua non for developmental origins of health and disease. Fetal body composition is determined as energy circumstances influence cell fates, which thereafter influence energy utilization and production through tissue composition. Compromised cell allocation during critical prenatal organ construction periods can further lead to lifelong compromises. Built according to time-sensitive cell destiny decisions, organs undergo construction and engage in activity patterns dictated by prenatal conditions. This can prompt micro-anatomical structural alterations, which then embody functional consequences.

Emerging with the structural and functional foundations constructed in utero, the fetal body meets the postnatal world where it will rely on the regenerative potential of stem cell reserves for healthy aging. The long term manifestation of developmental origins of health includes guardianship of safe havens for stem cells. Environmental influences that promote aerobic metabolic pathways, oxidative stress, and inflammation contribute to cellular wear and tear, and compromise healthy aging.

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Part II
Experimental Study of DOHaD

Chapter 3
Early Life Programming of Aging in Genetically Long-Lived Mice

Andrzej Bartke and Liou Sun

Abstract Mammalian aging and longevity are related to growth hormone (GH) actions and GH-dependent traits including growth, maturation and adult body size. In laboratory stocks of mice, genetic GH deficiency or resistance led to remarkable extension of healthspan and longevity. In GH-deficient Ames dwarf mice a brief period of GH replacement therapy normalizes ("rescues") many adult aging-related traits and shortens longevity. This indicates that absence of GH signals during the period of rapid pre- and early post-weaning growth importantly contributes to slow and healthy aging of these long-lived mutants. More work is needed to define the role of GH at different stages of life history in the control of aging.

Keywords Developmental programming · Trajectory of aging · Longevity · Growth hormone signaling · Healthspan

3.1 Introduction

There is considerable evidence that growth hormone (GH) actions have an important role in the control of mammalian aging and longevity. In laboratory stocks of mice, spontaneous or experimentally-induced genetic defects in GH signaling are associated with slower and healthy aging, and a very consistent, statistically significant extension of average and maximal longevity (Brown-Borg et al. 1996; Flurkey et al. 2001; Coschigano et al. 2003; Sun et al. 2013 reviewed in Brown-Borg 2015; Bartke et al. 2013; Basu et al. 2018). The increase of mean or median lifespan in these animals is remarkably large and can exceed 50% depending on the mutation, genetic background, sex, and diet (Brown-Borg 2015; Bartke et al. 2013; Basu et al.

A. Bartke (✉)
Department of Internal Medicine, Southern Illinois University School of Medicine, 801 N. Rutledge, P.O. Box 19628, Springfield, IL 62794-9628, USA
e-mail: abartke@siumed.edu

L. Sun
Department of Biology, University of Alabama at Birmingham, Birmingham, AL 35294-1170, USA

A. Vaiserman (ed.), *Early Life Origins of Ageing and Longevity*,
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2018; Bartke 2011). Survival of $Pit1^{dw}$ and $Prop1^{df}$ mice with hypopituitarism, including GH deficiency, GHRH-/-, and $GHRHR^{lit}$ mice with isolated GH deficiency, and GHR-/- mice with GH resistance in comparison to the normal (wild type) siblings of these animals is shown in Fig. 3.1. Corresponding human mutations that lead to hereditary GH deficiency or resistance provide considerable protection from age-related disease (cancer and diabetes) (Laron 2008; Costa et al. 2016; Guevara-Aguirre et al. 2011) and appear to promote healthy aging with retention of some youthful phenotypic characteristics (Aguiar-Oliveira et al. 2017, 2018), but, unexpectedly, have little or no impact on longevity in most examined cohorts (Aguiar-Oliveira et al. 2017; Guevara-Aguirre et al. 2015; Aguiar-Oliveira and Bartke 2018). However, studies of genetic polymorphism in exceptionally long-lived people (Dato et al. 2018; Flachsbart et al. 2009; Suh et al. 2008) and analysis of the pulsatile pattern of GH release in the offspring of long-lived families (van der Spoel et al. 2016) indicate that reduced somatotropic signaling is associated with healthy aging, reduced old age mortality, and extremes of survival also in our species.

Adult body size, a GH-dependent trait, is negatively associated with longevity not only in genetically altered but also in wild type mice (Miller et al. 2002; Rollo 2002; Wirth-Dzieciolowska and Czuminska 2000), as well as in other rodent species (Rollo 2002), dogs (Greer et al. 2007; Patronek et al. 1997), horses (Brosnahan and Paradis 2003), and, less consistently, in various human cohorts (Samaras 2007; He et al. 2014). The negative association of GH signaling and longevity implies that normal actions of GH include "pro-aging" effects, that is costs in terms of life expectancy and risks of adult disease. In support of this somewhat counterintuitive conclusion, major excess of GH release in transgenic mice and in humans with GH-secreting pituitary tumors is associated with reduced longevity along with increased risk for age-related disease (Pendergrass et al. 1993; Wolf et al. 1993; Colao et al. 2004; Holdaway et al. 2004), and, also in mice, various symptoms of accelerated aging (Bartke 2003).

Against this background, it was of interest to determine whether trajectory of aging depends on GH signaling throughout postnatal life or on GH action during the period of rapid postnatal growth which is a key determinant of adult body size. To address this question, we have examined the effects of six weeks of GH replacement therapy, started at the age of one or two weeks, on adult phenotypic characteristics related to aging and on longevity in long-lived GH-deficient Ames dwarf mice (Panici et al. 2010; Sun et al. 2017). In this article, we will review the findings from these studies and relate them to a broader question of developmental vs. adult role of endocrine signals in the control of mammalian aging. We will start with a brief review of endocrine defects and trajectory of aging in Ames dwarf mice and a discussion of mechanisms that are believed to be responsible for healthy aging and extended longevity of these animals.

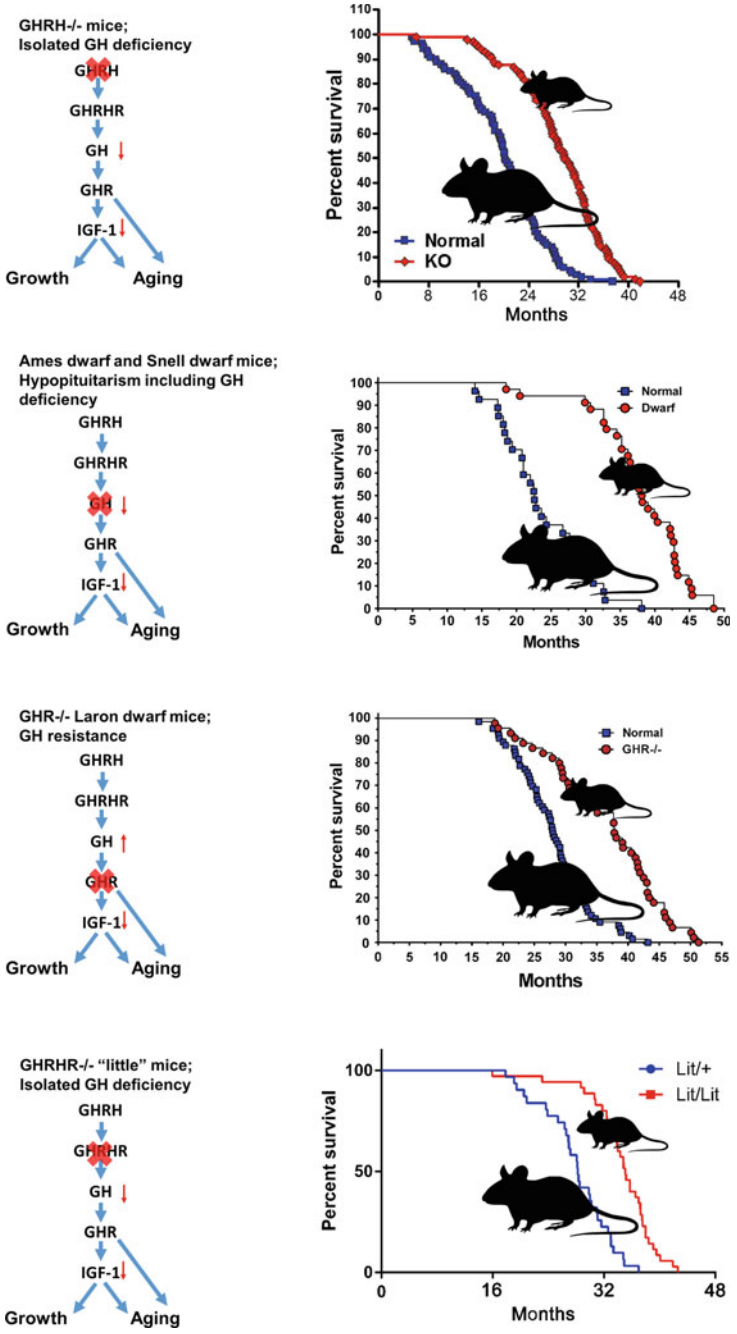

Fig. 3.1 Mutations interfering with GH synthesis or action result in reduced adult body size and extended longevity. Figure from Manuel H Aguiar-Oliveira and Andrzej Bartke. Growth Hormone Deficiency: Health and Longevity. Endocrine Reviews (2019) 40 (2): 575–601, https://doi.org/10.1210/er.2018-00216

3.2 Ames Dwarf Mouse, an Animal Genetically Predisposed to Extreme Longevity

A mutation discovered in a laboratory stock of mice (Mus musculus) at Iowa State University in Ames, Iowa, in the late '50s (Snell 1929a), produces hereditary dwarfism with homozygous mutants having apparently normal birth weight but soon falling behind their normal siblings in growth rate and reaching only half (or even slightly less) of normal adult body weight. The name originally proposed for these mutants, Ames dwarf mice, was intended to distinguish them from dwarf mice (now referred to as Snell dwarf mice) which were discovered much earlier (Snell 1929b) and remain widely used. Since these animals grew in response to injected GH, they were described as being GH deficient. Subsequent studies involving histological assessment of endocrine glands (Elftman and Wegelius 1959; Bartke 1964), hormone replacement therapy (Bartke 1965, 1968), and, eventually, cloning the gene involved and detailed characterization of its actions (Sornson et al. 1996) provided evidence that in addition to lacking GH, Ames and Snell dwarf mice also lack prolactin (PRL) and thyroid stimulating hormone (TSH). As expected from the absence of these three pituitary hormones, the Ames dwarf mice have drastically reduced circulating levels of insulin-like growth factor 1 (IGF-1) (Chandrashekar and Bartke 1993), and thyroid hormones (Borg et al. 1995; Brown-Borg 2007), are diminutive in size and hypothyroid with delayed maturation and retention of somewhat "juvenile" appearance including shorter snout and smaller, rounded ears. Apparently, adequate secretion of then other key adenohypophyseal hormones, adrenotropic hormone (ACTH), lutenizing hormone (LH), and follicle-stimulating hormone (FSH) (Bartke et al. 2013; Sornson et al. 1996) accounts for normal corticosterone levels (Borg et al. 1995), complete spermatogenesis and fertility in males (Brown-Borg 2015; Bartke et al. 2013) and ovarian cyclicity with production of fertile ova in females (Brown-Borg 2015; Bartke et al. 2013; Bartke 1966). Since activation of corpora lutea and adequate production of luteal progesterone in rodents are critically dependent on PRL, female dwarf mice fail to implant fertilized eggs and are sterile, but can produce live pups and raise them to weaning if given PRL replacement during the first half of pregnancy and during lactation (Bartke et al. 2013; Bartke 1966, 1973).

In 1996, Brown Borg and her colleagues reported that Ames dwarf mice live much longer than their normal siblings (Brown-Borg et al. 1996). Average, as well as maximal, longevity is increased in both sexes, although life extension is numerically larger in females. Subsequent work provided evidence for the delayed and initially slower aging of these animals (Brown-Borg 2015; Bartke et al. 2013) along with numerous indications of extended healthspan (Brown-Borg 2015; Bartke et al. 2013; Bartke 2011). This included a delay in cognitive aging (Kinney et al. 2001).

3.3 Multiple Mechanisms Link Reduced GH Signaling with Extended Longevity of Ames Dwarf Mice

Following demonstration of extended longevity in Ames dwarf mice and other mutants with suppressed GH signaling (Brown-Borg et al. 1996; Flurkey et al. 2001; Coschigano et al. 2003; Sun et al. 2013), we and others devoted much effort to identifying the underlying mechanisms. It quickly become apparent that long-lived GH-related mutants have numerous characteristics which contribute to their remarkable longevity (Brown-Borg 2015; Bartke et al. 2013; Basu et al. 2018; Bartke 2011). Prominent among them are features related to reduced fecundity (Bartke et al. 2013). The combined effects of reduced levels of anabolic hormones: GH, IGF-1, and thyroid hormones, and reduced activation of complex 1 of mTOR signaling (Brown-Borg 2015; Bartke et al. 2013) account for their diminutive body size. Lower levels of GH an IGF-1 undoubtedly contribute, and perhaps account for, delayed puberty, reduced litter size, and other reproductive characteristics. Within a species, smaller body size tends to predict extended longevity (Miller et al. 2002; Rollo 2002; Wirth-Dzieciolowska and Czuminska 2000; Greer et al. 2007; Patronek et al. 1997; Brosnahan and Paradis 2003; Samaras 2007; He et al. 2014; Bartke 2003; Bartke et al. 2001), although in comparisons between different species this relationship is generally opposite.

Early puberty and rapid production of large numbers of offspring characterizes many short-lived species, such as mice, voles, hamsters, and other small rodents, while a longer period of pre-pubertal development and having a single, and rarely more than two, offspring at a time, combined with a prolonged period of prenatal care, characterizes many long-lived species, including humans and other primates (Ricklefs and Wikelski 2002; Salzman et al. 2018). Reduced levels or action of IGF-1 and GH also provide a significant degree of protection from neoplastic disease, but extended longevity of Ames dwarfs and other GH-related mutants cannot be explained solely by reduced incidence or delayed onset of cancer (Ikeno et al. 2003, 2009). Other characteristics linking recued somatotropic signaling with the role of aging include profound alterations in carbohydrate and lipid metabolism. In Ames dwarf mice, circulating levels of both insulin and glucose are reduced and major enhancement or sensitivity of insulin was confirmed by testing for insulin tolerance (Dominici et al. 2002) and by hyperinsulinemic euglycemic clamp studies (Wiesenborn et al. 2014). Studies in Ames dwarfs and in Snell dwarfs, which have the same endocrine defects, provided evidence for major differences between these long-lived mutants and their normal siblings in hepatic lipogenesis, including cholesterol production, in the expression of genes related to lipogenesis and lipolysis (Boylston et al. 2004), in serum lipid levels (Wang et al. 2006), and in the amount and distribution of adipose tissue (Berryman et al. 2004; Masternak et al. 2012). Adipose tissue and expression and circulating levels of adiponectin are elevated in Ames dwarf mice (Menon et al. 2014; Louis et al. 2010), while the levels of interleukin 6 (IL-6) and tumor necrosis factor alpha (TNFα) are reduced (Wang et al. 2006; Hill et al. 2016). These changes in the profile of adipokines secreted by the

adipose tissue likely explain the paradox of coexistence of increased adiposity and improved insulin sensitivity in these animals (Hill et al. 2016). Metabolic characteristics of Ames dwarf mice include alternations in mitochondrial function leading to reduced production of reactive oxygen species (ROS) (Brown-Borg et al. 2012) likely related to improved beta oxidation of fatty acids and increased reliance on lipids as metabolic fuel (Westbrook et al. 2009). Reduced ROS production combined with improved anti-oxidant defenses (Brown-Borg 2015) in these animals account for reduced oxidative damage to DNA and other cellular components (Brown-Borg et al. 2012; Sanz et al. 2002). Although the role of oxidative stress and ROS-induced damage in the control of longevity continues to be debated (Perez et al. 2009), there is considerable evidence that they represent important mechanisms of aging. It has been shown that resistance to different types of stress is associated with extended longevity in worms, flies, and yeast (Finkel and Holbrook 2000). Intriguingly, dermal fibroblast cell lines derived from adult Ames dwarf mice are also resistant to the several cytotoxic stressors including heat, H_2O_2, cadmium, ultraviolet light, paraquat, and heat (Salmon et al. 2005). Further, Ames dwarf mice are also resistant to the toxic effects of the oxidative stressors such as diquat and paraquat in vivo (Bokov et al. 2009). Other characteristics of Ames dwarf mice representing likely mechanisms of their extended longevity include reduced mutation rate (Garcia et al. 2008), reduced burden of senescent cells (Stout et al. 2014), increased hepatic expression of genes coding for detoxifying enzymes (Brown-Borg et al. 2002). Additional mechanism linking reduced GH signaling with delayed and healthy aging are listed in Table 3.1.

Available evidence suggests that the remarkable extension of healthspan and longevity in Ames dwarf mice and other GH-related mutants results not only from the summation of the effects of the endocrine, metabolic, and stress resistance characteristics listed above, but also from complex interactions between them. For example, the major and very consistent enhancement of insulin sensitivity of these animals can be traced back to the absence of anti-insulinemic effects of GH, increased levels of adiponectin, reduced levels of pro-inflammatory cytokines, alterations in GH/IGF-1-dependent development of pancreatic beta cells, and reduced insulin release (Bartke et al. 2013).

3.4 Effects of GH Replacement Therapy in Juvenile Ames Dwarf Mice

Treatment of Ames dwarf mice with GH, started at one or two weeks of age, produced the expected stimulation of growth (Panici et al. 2010; Sun et al. 2017). While vehicle injected dwarfs grew very slowly, the increase of body weight in GH-injected dwarfs was comparable to the rate of weight gain in their normal (wild type) siblings (Fig. 3.2). Six weeks later, when the treatment was completed, there was prompt decline in the rate of weight gain of GH-injected dwarfs, but adult body weight and length of these animals continued to be greater than those of the vehicle-injected

Table 3.1 Key mechanisms linking reduced GH signaling with extension of healthspan and lifespan

Reduced growth stimulatory, mitogenic, and anti-apoptotic pathways
• Reduced hepatic expression and circulating levels of IGF-1 (Coschigano et al. 2003; Brown-Borg 2015; Bartke et al. 2013) • Reduced mTORC1 signaling (Sharp and Strong 2010; Fang et al. 2018)
Improved genome maintenance
• Reduced oxidative DNA damage related to reduced ROS production and improved antioxidant defenses (Brown-Borg et al. 2012; Sanz et al. 2002) • Improved DNA repair capacity (Podlutsky et al. 2017) • Reduced mutation rate (Garcia et al. 2008)
Metabolic adjustments
• Reduced insulin and glucose levels; enhanced insulin sensitivity (Dominici et al. 2002; Wiesenborn et al. 2014) • Increased amount and activity of brown adipose tissue; browning of white adipose tissue; increased thermogenesis (Darcy et al. 2016b) • Preferential utilization of fatty acids over carbohydrate as energy substrate (Westbrook et al. 2009) • Reduced hepatic lipogenesis and serum lipids (Boylston et al. 2004; Wang et al. 2006)
Reduced inflammation
• Reduced burden of senescent cells (Stout et al. 2014) • Reduced expression and levels of proinflammatory cytokines (Wang et al. 2006; Berryman et al. 2004; Masternak et al. 2012; Menon et al. 2014; Sadagurski et al. 2015; Hascup et al. 2016) • Increased plasma adiponectin levels (Masternak et al. 2012; Menon et al. 2014) • Suppressed macrophage-driven, age-related activation of inflammasome (Spadaro et al. 2016)
Other
• Improved maintenance of bone marrow stem cells (Kucia et al. 2011) • Increased hepatic production of hydrogen sulfide (Hine et al. 2017)

dwarfs. The increase in adult body weight of Ames dwarf mice treated with GH in early life was associated with increases in the absolute weights of the heart, liver, and kidneys, and a marked decrease in the weight of the inguinal (subcutaneous) fat pad, consistent with the well-established effect of GH on visceral organs and its lipolytic activity (Sun et al. 2017). Brain weight was not altered. Energy metabolism, glucose homeostasis, and expression of genes previously related to aging and longevity were examined at the age of 18–20 months; that is more than one year after the mice received their last injection of GH or saline. The results revealed partial normalization ("rescue") of the measured characteristics by early life GH treatment (Sun et al. 2017). Strikingly, some of the examined parameters were completely normalized, that is they became indistinguishable from values measured in normal (wild type) siblings of dwarfs (Sun et al. 2017; Sadagurski et al. 2015).

Effects of early life GH treatment in Ames dwarf mice included increases of serum levels of glucose and insulin and decreases in serum levels of adiponectin, ketone bodies, and LDL. In contrast, reduction of triglycerides in the serum of Ames dwarfs was not reversed by GH treatment (Fig. 3.3). These changes were associated

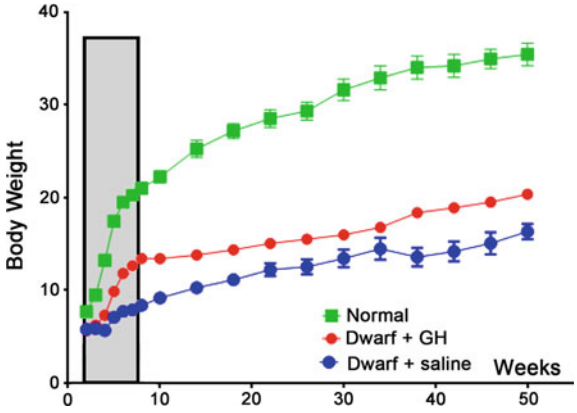

Fig. 3.2 Early GH treatment accelerates growth and increases adult body weight. Figure from Manuel H Aguiar-Oliveira and Andrzej Bartke. Growth Hormone Deficiency: Health and Longevity. eLife (2017) 6: e24059, https://doi.org/10.7554/eLife.24059

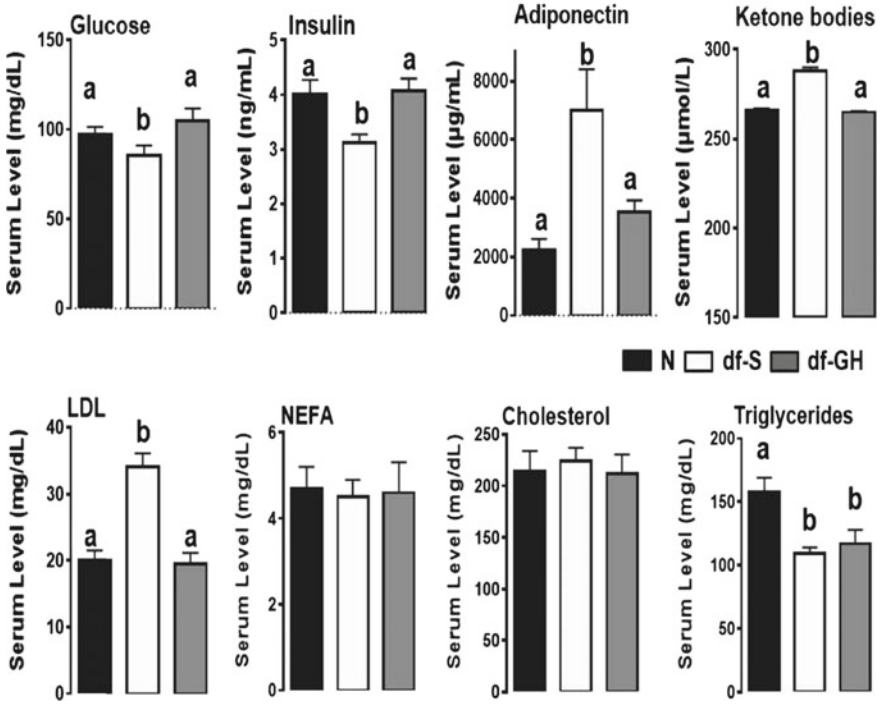

Fig. 3.3 Treatment of juvenile Ames dwarf mice with GH normalizes adult levels of various blood analytes. Figure from Manuel H Aguiar-Oliveira and Andrzej Bartke. Growth Hormone Deficiency: Health and Longevity. eLife (2017) 6: e24059, https://doi.org/10.7554/eLife.24059

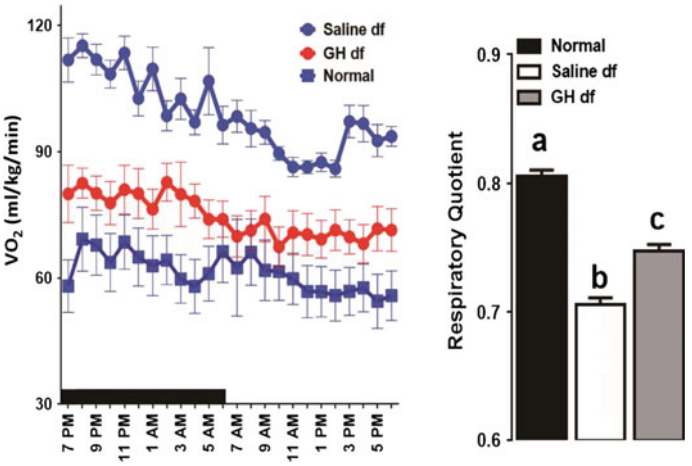

Fig. 3.4 Treatment of juvenile Ames dwarf mice with GH partially normalizes adult energy metabolism. Figure from Manuel H Aguiar-Oliveira and Andrzej Bartke. Growth Hormone Deficiency: Health and Longevity. eLife (2017) 6: e24059, https://doi.org/10.7554/eLife.24059

with a reduction of oxygen consumption per gram of body weight and an increase of respiratory quotient, implying reduced reliance on lipids (as opposed to carbohydrates) as metabolic fuel (Fig. 3.4). At the molecular level, dwarfs treated with GH in early life had normalized (or "supranormal") activation of hepatic cell signaling pathways such as MAPK and Akt signaling (Fig. 3.5). The similar patterns were found in transcriptional regulation of immediate early genes. Expression of various inflammatory markers is reduced in Ames dwarf versus WT mice, and early life GH replacement reversed many of these changes in the liver and in the epididymal fat pad, but not in the cortex indicating the tissue-specific effects of early life GH (Sun et al. 2017).

Xenobiotic metabolism enzymes, primarily active in the liver, play a major role in detoxification of a diverse range of damaging agents. Genetics studies in nematode Caenorhabditis elegans have identified a connection between the increases in xenobiotic activity and extended lifespan (Shore and Ruvkun 2013). This connection has been further validated in long-lived Ames dwarf mice (Sun et al. 2017; Amador-Noguez et al. 2004). Expression of genes involved in hepatic xenobiotic metabolism such as Cyp2b9, Cyp2b13, Hou3, Fmo3, and Sth2 are strikingly elevated in the liver of Ames dwarf mice and these changes were significantly (although not completely) reversed by early life treatment with GH (Sun et al. 2017). Intriguingly, farnesoid X receptor (FXR), the crucial protein in the regulation of xenobiotic detoxification process, was found upregulated in dwarf mice but completely suppressed by early GH treatment (Fig. 3.6).

In addition to the effects on metabolism, stress-related pathways and inflammation, early life GH treatment of Ames dwarf mice normalized (reduced) the capacity of their liver to produce hydrogen sulfide (H_2S) (Hine et al. 2017). This effect may

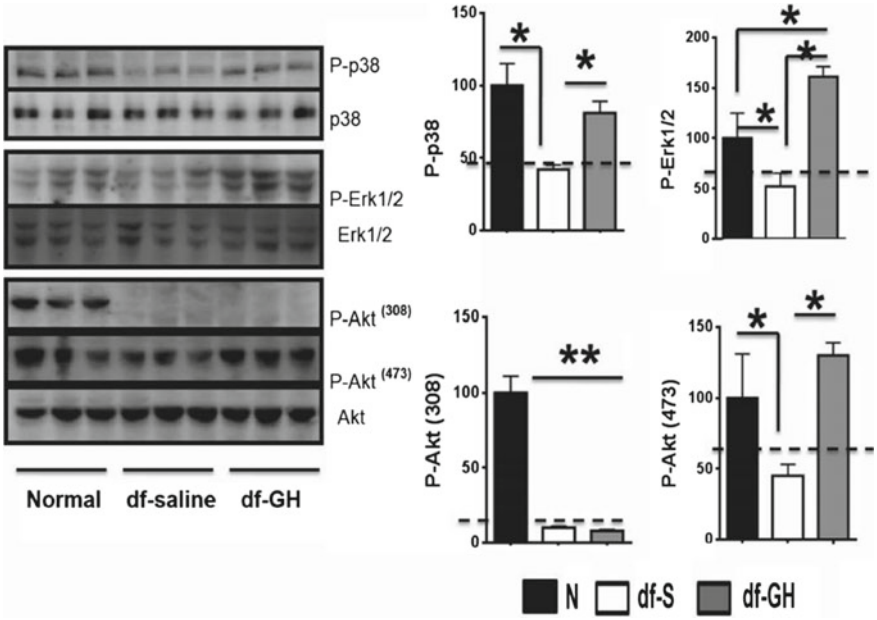

Fig. 3.5 Treatment of juvenile Ames dwarf mice with GH alters activation of hepatic cellular stress responsive pathways. Figure from Manuel H Aguiar-Oliveira and Andrzej Bartke. Growth Hormone Deficiency: Health and Longevity. eLife (2017) 6: e24059, https://doi.org/10.7554/eLife.24059

represent a mechanism of reduced (partially normalized) longevity of GH-treated dwarfs. H_2S can exert various beneficial and protective effects, and increase in hepatic H_2S production is involved in mediating some of the anti-aging effects of calorie restriction, GH deficiency, and hypothyroidism (Hine et al. 2017).

Chronic low-grade inflammation, termed as "inflammaging" has been shown to play an important role in the development of age-related diseases and pathology during aging (Franceschi and Campisi 2014). Ames dwarf mice were found to have lower levels of systemic and central (hypothalamic) inflammation during aging when compared with control mice at the same age (Sadagurski et al. 2015). Interestingly, early life GH exposure significantly reversed this low hypothalamic inflammation status in the Ames dwarf mice (Sadagurski et al. 2015) (Fig. 3.7) in late life. Preliminary data from ongoing studies indicate that physical endurance of middle-aged male dwarfs (measured by Rotarod) is also partially normalized (reduced) by early life treatment with GH. Surprisingly, identical GH treatment of female dwarfs appears to have no effect on their endurance measured when they reach middle age (McFadden and Bartke, unpublished).

Longevity of GH-treated dwarfs was significantly reduced, but remained longer than longevity of WT mice from the same strain (Sun et al. 2017) (Fig. 3.8). Treatment of WT mice with identical doses of GH per gram body weight had no impact on their longevity when the treatment was started at one week of age, but reduced

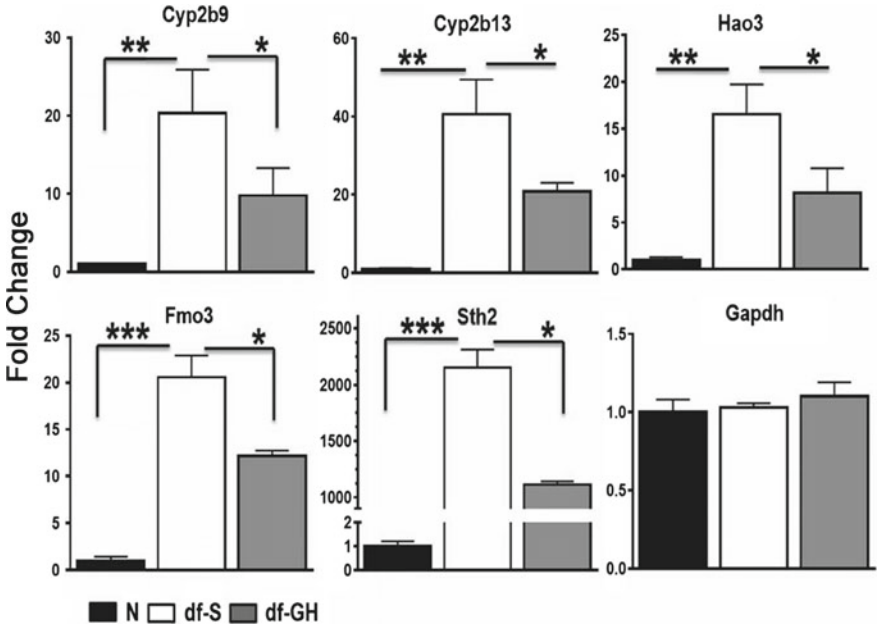

Fig. 3.6 Treatment of juvenile Ames dwarf mice with GH reduces adult hepatic expression of xenobiotic detoxification genes. Figure from Manuel H Aguiar-Oliveira and Andrzej Bartke. Growth Hormone Deficiency: Health and Longevity. eLife (2017) 6: e24059, https://doi.org/10.7554/eLife.24059

when it was started one week later (Sun et al. 2017). This unexpected effect was statistically significant in males but not in females. The interpretation of the impact of GH on longevity of WT mice is complicated because we did not evaluate the interactions of injected GH with the function of the somatotropic axis and endogenous GH release. The observed changes presumably represent combined impact of the suppression of GH release from the pituitary by exogenous GH via IGF-1 mediated negative feedback, the additive effects of endogenous and injected GH and GH-induced alterations in the diurnal pattern of pulsatile GH release.

3.5 Discussion

Our findings provide evidence that GH replacement therapy started before weaning and limited to a period of six weeks can profoundly influence adult phenotype and longevity of hypopituitary Ames dwarf mice. Supporting negative relationship of early life somatotropic signaling and longevity, knockdown of IGF-1 in normal (wild type) mice at 10 days of age increased female longevity (Ashpole et al. 2017). These results imply that GH and IGF-1 signals during the early life period normally

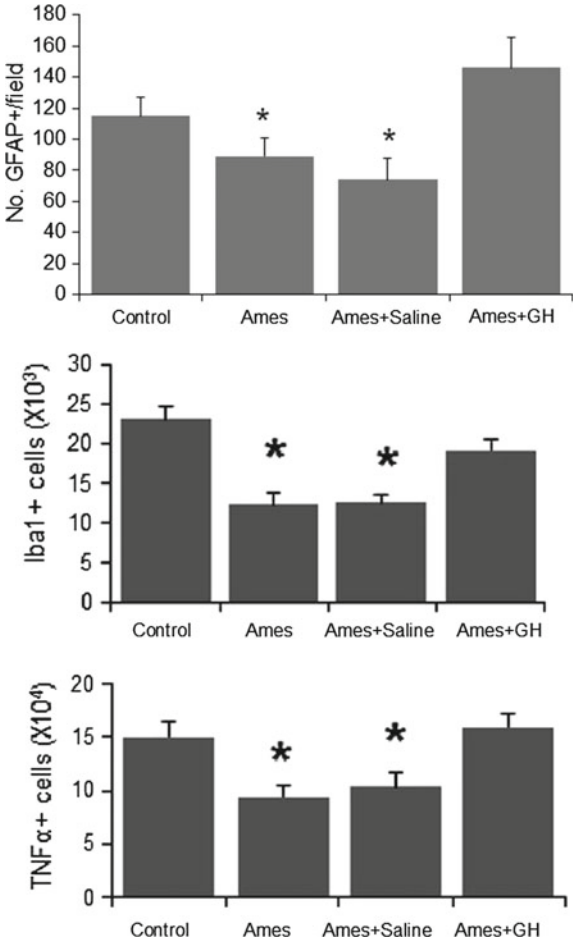

Fig. 3.7 Treatment of juvenile Ames dwarf mice with GH treatment normalizes hypothalamic TNFα and astrogliosis. $*P < 0.05$. Figure from Manuel H Aguiar-Oliveira and Andrzej Bartke. Growth Hormone Deficiency: Health and Longevity. eLife (2017) 6: e24059, https://doi.org/10.7554/eLife.24059

characterized by rapid somatic growth shape adult functioning and trajectory of aging and life expectancy. Recent studies in free-living female spotted hyenas (Lewin et al. 2017) indicate that IGF-1 levels in juvenile animals can predict life history traits, also including longevity in wild mammals living in their natural habitat.

Intriguingly, evidence available to date suggests that the effects of somatotropic signaling during development on the trajectory of aging may be specific to early postnatal life and not shared with other interventions affecting growth and metabolism. Preliminary results of studies ongoing in our laboratory indicate that identical regimen of GH replacement therapy (six weeks with the same doses per gram of body

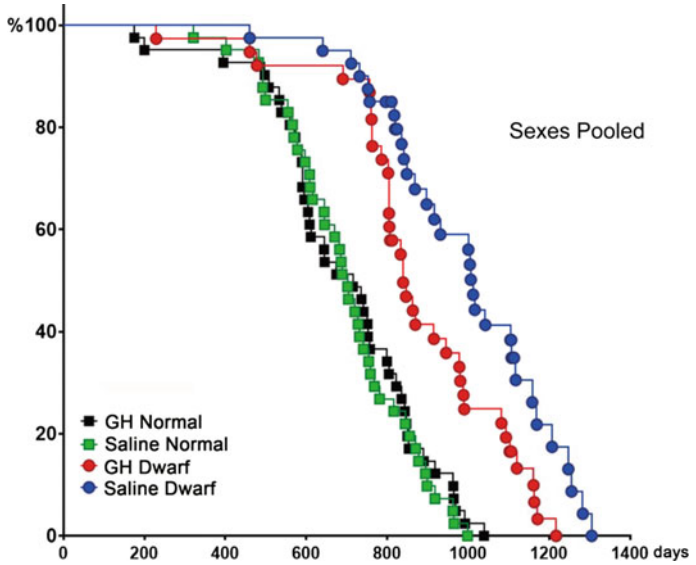

Fig. 3.8 Early life treatment with GH during shortens longevity of Ames dwarf (df) but not wild type (WT) mice. Figure from Manuel H Aguiar-Oliveira and Andrzej Bartke. Growth Hormone Deficiency: Health and Longevity. eLife (2017) 6: e24059, https://doi.org/10.7554/eLife.24059

weight) administered to middle aged or old Ames dwarf mice does not affect their longevity. Vergara and her colleagues reported that GH treatment of Snell dwarf mice started a few weeks later than in our studies failed to shorten their lifespan (Vergara et al. 2004). Treatment of juvenile Ames dwarfs with thyroxine stimulates their growth and sexual maturation, but it does not influence longevity (Panici et al. 2010) and does not produce persistent changes in energy metabolism or glucose homeostasis (Darcy et al. 2016a). Our ongoing studies also suggest that improvement in insulin signaling and glucose homeostasis induced by early life treatment of these animals with metformin or MSI-1436, a novel drug which acts as a calorie restriction mimetic, do not persist after the treatments are stopped. It remains to be determined whether difference in the responses to early life treatment with thyroid hormones, metformin, or MSI-1436, as compared to GH, may reflect different developmental "time windows" for their effects. Anisimov's laboratory reported alteration in lifespan of wild type mice after neonatal (days 3, 5, and 7) treatment with metformin (Anisimov et al. 2015).

The key conclusion form our studies is that hormonal signals during early life shape adult phenotypic characteristics that have been mechanistically related to aging (glucose homeostasis, energy metabolism, xenobiotic detoxification, stress responses) and influence longevity. Impact of hormonal signals during development on the trajectory of aging fits broadly with the concept of developmental origins of adult health and disease (DOHaD) discussed in other chapters and has important translational and public health implications. On the basis of our findings, we can

hypothesize that nutrition, exercise, environmental temperature, and other lifestyle factors affecting hormonal signaling during development can influence the trajectory of aging and life expectancy.

Our findings on the role of GH signaling during early life in the control of aging should not be taken as evidence that GH actions during adult life have little or no role. The Kopchick laboratory recently reported that targeted conditional disruption of GH receptor in adult mice significantly extended longevity of females (Junnila et al. 2016). Longevity of female mice was also increased by knockdown of IGF-1 at five months of age (Ashpole et al. 2017). Previously, Sonntag's group documented the important role of adult GH levels in the risk of cancer in laboratory rats (Sonntag et al. 2005). In GH-deficient Lewis dwarf rats, longevity is normal but it can be extended by limiting the period of GH deficiency to adult life (Sonntag et al. 2005). Results obtained in dwarf rats identify the negative impact of early life somatotropic (GH/IGF1) signaling on DNA repair capacity in adult life (Podlutsky et al. 2017). In addition to the potential impact of this effect on the susceptibility to cancer (Podlutsky et al. 2017), it is likely to impact aging and longevity. Impaired genome maintenance and defects in various DNA repair mechanisms emerge as some of the key mechanism of aging (MacRae et al. 2015; Milholland et al. 2017).

More work will be needed to decipher the relationships between GH levels at different stages of the life history and the trajectory of aging. The picture that might emerge could include early life promotion of growth, development, and sexual maturation at the expense of maintenance, repair, and life expectancy; quantitatively weaker "pro-aging" effects thereafter, and perhaps some protective (anti-aging?) role of the very low amounts of GH that continue to be secreted during senescence.

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Chapter 4
Immunological Basis of In Utero Programming of Adult Disease

Thea N. Golden and Rebecca A. Simmons

Abstract The in utero environment is critically important to fetal development and perturbations have been linked to adult diseases. Landmark studies from the Dutch famine showed that babies with low birth weights had significantly higher obesity rates as adults. In several other studies, low birth weight has been correlated with development of type 2 diabetes (T2D), cardiovascular disease and obesity. Maternal diseases, such as hypertension and gestational diabetes, also increase the risk of developing metabolic diseases as an adult. The immune system is implicated in the development of metabolic diseases. The fetal immune system is tolerant of its environment so as to prevent mounting an attack against maternal antigens. At birth, immune cells shift towards a pro-inflammatory phenotype. Disturbances to this delicate balance have been linked to metabolic diseases. In animal models of high maternal corticosteroids and intrauterine growth restriction (IUGR), pups are born with low birth weights and develop type 2 diabetes (T2D) as adults. In the IUGR model, development of T2D is dependent on interleukin 4 in the neonatal period. Development of the fetal immune system has the potential to effect offspring metabolic health.

Keywords In utero programming · Intrauterine growth restriction · Fetal immune system · Pro-inflammatory phenotype · Adult disease · Metabolic health

4.1 Developmental Origin of Metabolic Diseases

It is becoming increasingly apparent that the in utero environment in which a fetus grows and develops may have long-term effects on subsequent health and survival (Hales and Barker 1992; Kermack et al. 1934). The landmark cohort study of 300,000 men by Ravelli and colleagues showed that exposure to the Dutch famine of 1944–45

T. N. Golden · R. A. Simmons (✉)
Center for Research on Reproduction and Women's Health, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
e-mail: rsimmons@pennmedicine.upenn.edu

T. N. Golden
e-mail: goldent@pennmedicine.upenn.edu

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during the first half of pregnancy resulted in significantly higher obesity rates at age 19 (Ravelli et al. 1976). Subsequent studies demonstrated a relationship between low birth weight and the later development of cardiovascular disease (Barker et al. 1989) and impaired glucose tolerance (Fall et al. 1995; Hales et al. 1991; Phipps et al. 1993) in men in England. Those men who were smallest at birth (2.5 kg) were nearly seven times more likely to have impaired glucose tolerance or type 2 diabetes than were those who were heaviest at birth. In addition, the investigators found a similar relationship between lower birth weight and higher systolic blood pressure and triglyceride levels (Barker et al. 1993). Subsequent studies in diverse populations through the world have demonstrated a significant correlation between low birth weight and the later development of type 2 diabetes (Curhan et al. 1996; Egeland et al. 2000; Forsen et al. 2000; Hales and Barker 2001; Jaquet et al. 2000; Leger et al. 1997; Lithell et al. 1996; McKeigue et al. 1998; Rich-Edwards et al. 2005; Valdez et al. 1994). More recent studies controlling for the confounding factors of socioeconomic status and lifestyle factors have further strengthened the association with low birth weight and increased risk of coronary heart disease, stroke, and type 2 diabetes (Curhan et al. 1996; Rich-Edwards et al. 1997). In 1976 the Nurses' Health Study was initiated and a large cohort of U.S. women born from 1921 to 1946 was established. The associations with low birth weight and increased risk of coronary heart disease, stroke, and type 2 diabetes remain strong even after adjusting for lifestyle factors such as smoking, physical activity, occupation, income, dietary habits, and childhood socio-economic status and occur independently of the current level of obesity or exercise (Rich-Edwards et al. 1997). In a study of 22,000 American men, those born lighter than 5.5 lb had a significantly higher incidence of adult hypertension and type 2 diabetes compared with average birth weight adults (Curhan et al. 1996). Similar to the Nurses Health Study, the association between birth weight and later disease is largely independent of the lifestyle risk factors (Curhan et al. 1996).

The long-term effects of uteroplacental insufficiency are dependent on the timing of the insult during gestation. For instance, undernourishment during early gestation increases risk of coronary heart disease and atherogenic lipid profiles (de Rooij et al. 2010; Roseboom et al. 2006). However, undernourishment during late gestation leads to abnormal glucose tolerance in the offspring (Ravelli et al. 1998). Micronutrients in the maternal diet also play a significant role in the healthy development of the fetus. For example, vitamin B12 deficiency is correlated with hypomethylation of the insulin like growth factor and is associated with low birth weight (McKay et al. 2012). Zinc deficiency during pregnancy is associated with immune dysregulation leading to chronic inflammation and increased cardiovascular risk in the offspring.

Maternal disease also effects offspring metabolic health. Gestational diabetes and pregnancy induced hypertension have a significant effect on development of adult disease. Elevated maternal glucose is correlated with increased offspring body mass index (BMI) (Crume et al. 2011; Deierlein et al. 2011; Pettitt et al. 2010; Boney et al. 2005; Malcolm et al. 2006), dysfunctional glucose homeostasis (Ford et al. 2009; Oben et al. 2010), and increased offspring diastolic blood pressure (Tsadok et al. 2011). Offspring born to mothers with hypertension during gestation experience

elevated blood pressure as adults (Geelhoed et al. 2010; Palmsten et al. 2010; Sproul et al. 2005).

In vitro fertilization (IVF) has recently been shown to alter offspring metabolic health. This work is ongoing, but several large studies show an association with IVF and other methods of assisted reproduction and low birth weight. In a study of children, ages 8–18 years old, peripheral body fat and peripheral body mass were elevated in children born from IVF compared to control (Ceelen et al. 2007). Other studies found higher blood pressure and fasting glucose in children born via IVF (Ceelen et al. 2008; Law et al. 1993). The effect of IVF on offspring metabolic health is not conclusive and the age of measurement in offspring may account for some disparities (Miles et al. 2007).

Offspring adaptation to intrauterine milieu has the potential to affect the next generation. Offspring born to diabetic rats are shown to have offspring of their own with reduced beta cell mass and fewer insulin producing cells (Holemans et al. 1991). Offspring born to rats on a low protein diet during pregnancy have hypertension that is seen in the F2 generation as well (Harrison and Langley-Evans 2009; Langley-Evans et al. 1999).

4.2 Fetal Immune Development

Careful development of the fetal immune system must account for the need to be tolerant of the maternal environment while preparing for a future pathogen rich environment post birth. Previously, it was thought the fetal immune system was immature thereby not mounting an immune response to maternal antigen. However, more recent work has discovered the fetal immune system is unique, not immature.

As early as 3–4 weeks human gestation, or embryologic day 7 in the mouse, myelopoiesis begins in the yolk sac. These early monocytes derive from the ectoderm even before there are hematopoietic stem cells (HSCs). At 5 weeks gestation, the fetal liver first forms and HSCs give rise to erythroid, lymphoid and myeloid cells (Kumaravelu et al. 2002; Medvinsky et al. 1996). The liver remains the dominant source of HSCs through 20–24 weeks gestation in the human and until birth in the mouse. The bone marrow is colonized just before birth in the mouse and in the second trimester of the human (Godin and Cumano 2005). Resident macrophages colonize tissues throughout fetal development. Depending on the specific tissue, resident macrophage origin can be from the yolk sac, fetal liver or bone marrow.

The fetal immune system is in a unique position in that about half of its polymorphic major histocompatibility complex (MHC) molecules arise from the father. Therefore, maternal proteins could present as foreign antigen, but the fetus must not mount an immune response (Mold et al. 2008). In fact, microchimerism has been verified as maternal hematopoietic cells are found in the fetus (Gammill and Nelson 2010; Lo et al. 2000; Loubiere et al. 2006; Maloney et al. 1999). Regulatory T cells (Tregs) have been shown to promote tolerance in the fetus. Tregs are higher in proportion in the fetus and decrease in number post birth (Cupedo et al. 2005;

Michaelsson et al. 2006). Other lymphocytes also experience a change in population post birth. T cells predominately express gamma/delta T cell receptor (TCR) in the fetus but alpha/beta TCR in the newborn and adult (Havran and Allison 1988, 1990). B lymphocytes also shift from B-1, a more primitive B cell, to B-2 post birth (Hardy et al. 1982; Hayakawa et al. 1986). Along with a replacement of cell populations, the gene expression of T cells (Mold et al. 2010) and function of macrophages (Krow-Lucal et al. 2014) change from a tolerant to pro-inflammatory phenotype post birth. This shift in immune populations was first proposed by Lee and Len Herzenberg as the layered model of immune development (Herzenberg et al. 1992).

4.3 Fetal Immune Perturbation Results in Adult Metabolic Disease

The development of the fetal immune system is a delicate balance. The placenta has protective measures to prevent maternal immune responses from crossing to the fetus. For example, 11 beta-hydroxysteroid dehydrogenases are in the placenta and convert active corticosteroids to inactive forms. In the presence of enzyme saturation or certain forms of prescription steroids, corticosteroids cross the placenta and can lead to intrauterine growth restriction and immune dysfunction in the fetus (McTernan et al. 2001). A study in Denmark, found an association between oral corticosteroid use during pregnancy and offspring development of diabetes (Greene et al. 2013). This study, conducted from 1997 to 2004, identified babies born to mothers who used either a topical, inhaled or oral steroid during pregnancy. They followed children through 2008 recording the incidence of type 1 or 2 diabetes diagnosis. Those fetuses exposed to oral corticosteroids, but not topical or inhaled, had a slightly higher risk of developing diabetes. Using an animal model of intraperitoneal injection of dexamethasone, glucose homeostasis abnormalities have been identified. Pups are born smaller to dams injected with dexamethasone and beta cell mass and insulin secretion is reduced (Chen et al. 2017). Whether or not altered immune function plays a role in the later development of type 2 diabetes is not clear. However, in the Chen study, at postnatal day 7 (D7), spleen weights were increased and stimulated splenocytes favored Th2 cytokine production in pups born to dexamethasone injected dams (Chou et al. 2017; Dietert et al. 2003; Kuo et al. 2014; Yu et al. 2014). Splenocytes isolated from PD7 dexamethasone exposed pups had decreased mRNA levels of MMP9, TNFα and GMCSF (Yu et al. 2014) and when stimulated with ConA had increased IL4 production (Chou et al. 2017). By 4 months of age, altered immune pathways were normalized (Chou et al. 2017; Kuo et al. 2014).

The IUGR model also implicates the immune system in the development of type 2 diabetes in the IUGR model. Using the bilateral uterine artery ligation model of IUGR, we identified aberrant inflammatory pathways in the neonatal rat that are causal to the development of type 2 diabetes in the adult (Jaeckle Santos 2014). Dams undergo surgery at embryologic day 18 [e18] and pups are born with low birth

weight and develop impaired glucose stimulated insulin secretion, reduced beta cell mass, reduced islet vascularity and adiposity. Abnormal immune pathways were identified in the islets of IUGR rats by microarray. At e19, IUGR pups had elevated Th2 and M2 signaling gene expression compared to adults which was associated with increased levels of interleukin 4 (IL4) , interleukin 2 (IL2), interleukin 10 (IL10), RANTES and eotaxin, and MCP1 in islet lysates of IUGR pups. By two weeks of age, much of the inflammatory signal was attenuated despite persistent immune cells in the islets and persistent loss of islet vascularity.

In order to test the causal role of the immune system in the development of type 2 diabetes in the IUGR rat, we used an antibody to interleukin 4 (IL4) (Jaeckle Santos 2014). IL4 neutralizing antibody was administered during the neonatal period; postnatal days 1–6 to IUGR pups. At two weeks of age, islet vascularity was normal in IUGR rats administered IL4 neutralizing antibody but reduced in those IUGR rats not administered IL4 neutralizing antibody. Glucose homeostasis at 15 weeks was also restored; glucose stimulated insulin secretion normalized, basal insulin secretion attenuated, and maximum insulin secretion restored. These effects persisted through adulthood as evidenced by normal fasting blood glucose, fasting c-peptide and islet mass in 6–10 month-old IUGR rats who had received IL4 neutralizing antibody but abnormal in IUGR rats who received vehicle. The early administration of IL4 neutralizing antibody, before signs of glucose intolerance or islet decreased vascularity, and the prevention of the development of the IUGR phenotype suggests increased IL4 in the fetal stage following IUGR is causal to the development of type 2 diabetes in the IUGR rat model.

4.4 Immunologic Basis of Metabolic Health

Immune modulation of metabolic health has recently gained widespread attention. Both innate (natural killer cells, mast cells, eosinophils, basophils, and phagocytic cells like macrophages, dendritic cells and neutrophils) and adaptive ($CD8^+$ and $CD4^+$ T lymphocytes, and B lymphocytes) immune systems play a critical role in metabolic disease progression. The predominant cell types that have been implicated are effector $CD8^+$ cytotoxic T cells (Tc; recognizes major histocompatibility class I antigen presentation), and $CD4^+$ T helper cells (Th1 and Th2; recognizes major histocompatibility class II antigen presentation), T helper 17 cells (Th17), T regulatory cells (Treg), and natural killer T cells (possess both innate and adaptive properties).

The cross-talk between the innate and adaptive immune systems has been explored in greater detail in adipose tissue (Brestoff and Artis 2015). Briefly, in obesity the enlarged adipocytes produce chemotactic adipokines and chemokines such as monocyte chemotactic protein-1 (MCP1) and leukotriene B4 (LTB4) which attract monocytes to adipocytes where they become adipose tissue macrophages (Osborn and Olefsky 2012). Additionally, adipocytes also secrete chemokines like C-C motif chemokine ligand 5 (CCL5; a.k.a. RANTES), C-C motif chemokine ligand 20 (CCL20), and C-X-C motif chemokine ligand 12 (CXC12) that contribute to the

recruitment of pro-inflammatory invariant natural killer T cells (iNKT), Tc, and Th17 cells of the adaptive immune system to adipose tissue (Ouchi et al. 2011; Sell et al. 2012). These cells release pro-inflammatory cytokines like tumor necrosis factor alpha (TNF-α; from iNKT cells), interferon gamma (IFN-γ; from cytotoxic T cells) and interleukin 17 (IL-17; from Th17 cells) that promote polarization of adipose tissue macrophages to pro-inflammatory M1 macrophages (Brestoff and Artis 2015; Sell et al. 2012). M1 macrophages with major histocompatibility complex class II [MHC II] antigen presentation polarize naïve $CD4^+$ cells to Th1 cells. Th1 cell polarization is also activated by leptin that is secreted by adipocytes (Ouchi et al. 2011). Th1 cells in turn, produce TNF-α and IFN-γ and further activate M1 macrophages establishing a vicious cycle (Brestoff and Artis 2015; Sell et al. 2012). In obese mice, the number of anti-inflammatory Th2 and Treg cells, which produce IL-4, IL-10 or IL-13 to promote an anti-inflammatory M2 macrophage polarization, is reduced compared to Th1 cells i.e. there is a shift towards an increased Th1:Th2 and Th1:Treg response in adipocytes (Brestoff and Artis 2015; Sell et al. 2012). The cross-talk between adipocytes, adaptive and innate immune cells progressively creates a pro-inflammatory environment in adipose tissue. The pro-inflammatory cytokines inhibit insulin signaling by direct serine phosphorylation of insulin receptor substrate-1/2 thereby inducing insulin resistance (Osborn and Olefsky 2012). Similarly, in insulin resistance and type 2 diabetes, a cross-talk between different innate and adaptive immune cells is triggered in metabolically sensitive tissues like pancreas, liver, skeletal muscle, gut, and blood vessels. This disrupts the pro- and anti-inflammatory balance eventually contributing to perturbed metabolic health.

Remarkable advances have been made in understanding how the host immune system senses metabolic stress at a cellular level. A distinct property of innate immune cells is the presence of receptors that recognize pathogen [e.g. lipopolysaccharide (LPS) and peptidoglycan of bacterial cells, or microbial nucleic acids], and host derived damage (e.g. increased glucose, free fatty acids, minimally modified low density lipoprotein, or endogenous stress induced ATP) associated molecular patterns (Li et al. 2014; Strowig et al. 2012). Once the receptors are triggered by either pathogens or cellular stress, a downstream signaling cascade is activated, which initiates the production of cytokines and chemokines. This amplifies the immune response and induces recruitment of antigen-presenting cells that activates the adaptive immune cell population to promote inflammation in order to resolve and restore normal tissue function (Li et al. 2014; Strowig et al. 2012).

There are three key interconnected, often overlapping, intracellular pro-inflammatory signaling pathways associated with metabolic disorders: Nuclear factor-κB (NFκB)-inhibitor of κB kinase (IKκB), c–Jun N–terminal kinase (JNK) and activator protein-1 (AP1), and inflammasomes (Osborn and Olefsky 2012; Lackey and Olefsky 2016). These signaling pathways can be activated by different receptors like membrane bound Toll-like receptors (TLRs), TNF-α receptor (TNFR), or cytoplasmic NOD-like receptors (NLRs) (Osborn and Olefsky 2012; Lackey and Olefsky 2016). In addition, mitochondrial dysfunction leading to production of reactive oxygen species, and increased endoplasmic reticulum stress leading to protein misfolding can also trigger these pro-inflammatory pathways (Osborn and Olefsky 2012;

Lackey and Olefsky 2016). Once activated, the pro-inflammatory pathways increase serine kinase phosphorylation of insulin receptor substrate 1 or 2 (prevents the downstream insulin signaling), and transcription of inflammatory genes (cytokines, chemokines and components of the inflammasome) (Osborn and Olefsky 2012; Lackey and Olefsky 2016). A combination of IRS1/2 phosphorylation and increased inflammatory gene transcription increases insulin resistance (Osborn and Olefsky 2012; Lackey and Olefsky 2016). Additionally, the inflammasome, a multi-protein complex comprised of scaffold, adaptor and caspase proteins, upon assembly activates caspase-1, which subsequently cleaves the pro-inflammatory IL-1 family of cytokines into their bioactive forms like IL-1β and IL-18, leading to inflammatory cell death [e.g. pancreatic β-cell death associated with reduced insulin secretion] (Li et al. 2014; Lackey and Olefsky 2016; Guo et al. 2015; Henao-Mejia et al. 2012). These interleukins, IL-1β and IL-18, also further contribute to increased insulin resistance (Osborn and Olefsky 2012; Lackey and Olefsky 2016). As inflammasomes can sense various signals of disrupted homeostatic cellular processes, they serve as a cytoplasmic surveillance system (Strowig et al. 2012).

In addition to the pro-inflammatory signaling pathways, anti-inflammatory signaling is triggered by G-protein coupled receptor 120 (GPR120), estrogen receptor alpha (Erα), and interleukin receptor 10 (IL-10), which attenuates insulin resistance (Osborn and Olefsky 2012; Lackey and Olefsky 2016; Brown and Simpson 2015). Although pro-inflammatory signaling usually triggers insulin resistance and glucose intolerance, a fine balance between pro- and anti-inflammatory cytokine levels determines the magnitude of inflammation and is essential in maintaining metabolic homeostasis.

4.5 Concluding Remarks

The intrauterine environment has long term effects on offspring health and disease. Epidemiological data identifies a fetal origin of metabolic diseases. Recently, the immune system has been implicated in the pathology of metabolic diseases in the adult. Interestingly, alteration of the fetal immune system is capable of resulting in development of metabolic disease in the adult.

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Chapter 5
Early Life Developmental Programming of the GH/IGF Axis and Long-Term Health

Clare M. Reynolds and Mark H. Vickers

Abstract It has now well established that alterations in the environment during early life development can have effects on the health of the offspring across the lifecourse and evidence for transmission of these adverse disease traits to future generations. A key component underpinning this early life developmental programming is that of dysregulation of the growth hormone-insulin-like growth factor (GH-IGF) axis. Phenotypic outcomes in programmed offspring closely resemble those associated with GH deficiency (GHD), including increased fat mass, altered insulin sensitivity and cardiovascular disorders. The GH-IGF axis plays a key developmental role in essentially all tissues and organs and work across a wide range of animal models has suggested that manipulation of this axis in the early life period can ameliorate the effects of adverse developmental programming, albeit in a sex-specific manner. Further understanding of how different exposures in the early life period, including altered nutrition, impact upon this axis is essential to define translatable strategies to reverse the consequences of early life adversity and improve health outcomes across the lifecourse.

Keywords Developmental programming · Growth hormone · Growth factors · Early life nutrition · Obesity · Energy balance · Metabolic syndrome · Epigenetics

5.1 Introduction

Alterations in the pre-conception and early life environment are now well established to increase the risk for the development of a broad range of cardiometabolic and neurobehavioural disorders in later life. This process, preferentially termed "developmental programming", falls under the "developmental origins of health and disease" or DOHaD framework. In particular, alterations in the maternal nutritional environment, including maternal undernutrition, excess caloric intake and specific macro/micronutrient deficiencies, have been shown to lead to programmed disorders in offspring including obesity, insulin resistance and hypertension. Moreover,

C. M. Reynolds · M. H. Vickers (✉)
Liggins Institute, University of Auckland, Auckland 1142, New Zealand
e-mail: m.vickers@auckland.ac.nz

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there are data suggesting that these effects may be transgenerational in nature thus perpetuating a cycle of disease across generations (Aiken and Ozanne 2014).

A characteristic feature of the available human epidemiological and clinical data and that derived from a wide array of animal models of developmental programming across a range of species is that of dysregulation of the growth hormone (GH)—insulin-like growth factor (IGF) axis (Setia and Sridhar 2009; Oberbauer 2015; Reynolds et al. 2017). Of note, phenotypes that typically arise as a consequence of early life developmental programming closely resemble that of GH-deficiency (GHD) including increased adipose tissue deposition, insulin resistance, sarcopenia and a range of cardiometabolic disorders. This is not unexpected—GH is a key regulatory hormone with a developmental role in most tissues and organs and, given that the GH axis highly dynamic during the early life developmental period, is particularly sensitive to environment influences including altered nutritional supply (Kappeler et al. 2009). Given the commonality around dysregulation of the GH-IGF axis in programming models, there has been increasing attention around this axis as a strategy for intervention to rescue the programmed phenotype and also investigations around the epigenetic regulation of this key axis. The effects of GH on growth promotion are largely determined by hormone-induced mediation of IGF-1 gene expression since IGF-1 is a primary, but not only, regulator of GH action on linear body growth (Lupu et al. 2001). Studies utilising components of the GH-IGF axis as intervention strategies in experimental models have suggested efficacy of these factors in reversing or ameliorating both the short and longer-term effects associated with developmental programming. However, the mechanisms of action remain poorly defined and data from such models, in conjunction with data derived from studies using GH in the clinical setting, also suggest that GH-related treatment modalities can also be linked to unwanted side effects including altered insulin sensitivity and oedema although these may relate to dosing and timing/duration of exposure. As such, further work is still required to understand the mechanistic role of the GH-IGF axis in developmental programming of later health outcomes before translation as an effective intervention modality in the context of DOHaD-related disorders can be undertaken.

5.2 Developmental Programming of the GH-IGF Axis—Evidence from Epidemiological Cohorts and Human Clinical Studies

In humans, GH itself plays virtually no role in the regulation of fetal growth with growth controlled directly via the IGFs with placental GH (GH2/GHV) being the primary regulator of circulating maternal IGFs during pregnancy (Setia and Sridhar 2009; Randhawa and Cohen 2005; Caufriez et al. 1993). Circulating fetal IGF-1 concentrations appear to be largely independent of fetal GH secretion and remain stable until approximately 34 weeks gestation at which point there is a significant increase until term. Similarly, fetal IGF-2 concentrations appear relatively stable from

mid pregnancy until a marked increase around 34 weeks of gestation (Reece et al. 1994). Fetal growth disorders including intrauterine growth restriction (IUGR) are commonly characterised by low systemic concentrations of IGF-1, -2 and IGFBP-3 and elevated concentrations of GH and IGFBP-1 (Setia and Sridhar 2009; Martin-Estal et al. 2016).

Programming of the GH-IGF axis arising due to alterations in the nutritional environment have been shown via epidemiological observations including that of the Dutch Famine Cohort of 1944–45. In particular, given the highly responsive nature of IGF-1 to altered nutrition, it has been shown that early exposure to famine was associated with increased IGF-1 and IGFBP-3 and decreased in IGFBP-1 and -2 in famine-exposed females in later life (Elias et al. 2004a). Given these responses are opposite to the immediate responses typically observed under famine conditions, it was hypothesised that this may represent long term reprogramming effects manifest upon improvement of nutritional status following the period of famine. It has also been shown in this cohort that breast cancer incidence in famine exposed women was significantly increased in later life compared to non-exposed women and was paralleled by increased circulating IGF-1 and IGFBP-3 concentrations (Elias et al. 2004b; van Noord 2004). However, these data remain observational in nature and no direct causality has been shown between changes observed in the GH-IGF axis and later disease—given that famine exposure likely leads to dysregulation across a number of key hormone systems, the observed changes in circulating IGF-IGFBPs in adulthood may simply represent a proxy measure of early famine exposure and later life outcomes (van Abeelen et al. 2012).

Poor maternal nutritional can often manifest in offspring being born small for gestation age (SGA) and is well known to be associated with an increased risk for a number of metabolic and cardiovascular disorders in later life including obesity, hypertension, type 2 diabetes (T2DM) and lipid disorders (Gluckman et al. 2008). Short children born SGA are at an elevated risk for GHD and/or IGF-1 resistance and GH treatment in these children has recognised beneficial, growth-promoting effect in both the short-and long-term (Jung et al. 2008). Less work has been done on alterations to the GH-IGF axis in the setting of maternal overweight/obesity. Maternal obesity can lead to either macrosomia (Ferraro et al. 2012a) or, in obese pregnancies characterised by placental dysfunction, fetal growth restriction (Radulescu et al. 2013a). Maternal obesity has been shown to attenuate cord blood expression of IGFBP-4 with IGBP-3 concentrations inversely related to markers of maternal insulin sensitivity (Ferraro et al. 2012b). Obesity in the pre-pregnancy period confers symmetrically larger infant body size and increased circulating concentrations of many hormones related to growth and appetite/energy balance but reduced IGF-1 concentrations, suggesting potential growth-promoting effects in the infant through other factors including insulin (Larnkjaer et al. 2018). With caesarean section, pre-existing maternal obesity and GDM are associated with lower IGFBP concentrations in maternal and cord plasma including an inverse relationship between cord plasma IGFBP-1 and birthweight (Lappas 2015).

It has been suggested, particularly in the case of IUGR, that programming of the GH-IGF axis may represent one of a number of potential (mal)adaptations that

are made in order to cope with an expected postnatal environment of suboptimal nutrition, thus acting to constrain the anabolic actions of GH (Donzeau et al. 2015). These changes in the GH-IGF axis thus fit with the concept of the "thrifty phenotype" or "predictive adaptive response" hypothesis that proposes that cues received by the fetus are thought to impact upon the development of a phenotype via making adaptations that are "matched" to the expected postnatal environment (Bateson et al. 2014; Hales and Barker 2001). When a developmental "mismatch" occurs [e.g. fetal undernutrition] followed by an environment of postnatal nutritional excess, then this can potentiate the disease risk and lead to adverse health outcomes in late life (Bateson et al. 2014).

5.3 Altered Programming of the GH-IGF Axis—Evidence from Animal Models

Most data to date on developmental programming of the GH-IGF axis has been derived from experimental animal models, primarily using rodent models. Studies across a range of mammalian species have highlighted the role of early life nutrition on long-term regulation of the GH-IGF axis in addition to studies examining non-nutritional approaches including increased stress exposure and uterine ligation. An early focus in the DOHaD research was around that of maternal undernutrition and outcomes that were largely focused around the impact of fetal growth restriction but there are now also increasing reports in experimental models on the impact of maternal overweight/obesity in altering regulation of the GH-IGF system. Moreover, programming needs to be seen as a continuum and not just impacting on those at either end of the birth weight spectrum as programming can occur at any birthweight.

5.3.1 Rodents

A number of rodent models have reported perturbations in the GH-IGF axis manifest due to a range of programming modalities in early life with a primary focus being that of altered maternal nutrition. Global maternal undernutrition throughout pregnancy results in a significant reduction in circulating IGF-1 concentrations concomitant with a reduction in placental weights (Woodall et al. 1996). Plasma IGF-1 concentrations are significantly reduced in the pups of undernourished mothers from day 22 of gestation until postnatal day 9 but were not significantly different at the later time-points. Using this experimental paradigm, it has been shown that these offspring develop obesity, appetite dysregulation, sedentary behaviour and hypertension in adulthood, all of which are amplified by exposure to a postnatal hypercaloric diet (Vickers et al. 2000, 2001a, 2003).

Glucocorticoids are widely viewed as key modulators of GH regulation in the rodent, particularly around the area of hypothalamic and pituitary regulation of GH secretion, development of somatotropes and tissue-specific responsivity (including decreased production of IGF-1) (Oberbauer 2015; Mazziotti and Giustina 2013). Increased exposure to glucocorticoids can lead to GH deficiency, a reduced growth rate and long term cardiometabolic complications. Studies in vivo suggest that glucocorticoids can both stimulate and inhibit the secretion of GH with the overall biological effects related to hormonal levels and the timing and duration of exposure (Mazziotti and Giustina 2013). In a rat model of maternal dioxin administration, fetal growth restriction was due to an impairment in GH expression and secretion arising, at least in part, to a reduction in circulating fetal and maternal glucocorticoid concentrations (Hattori et al. 2014). Given the reported long-term effects of increased corticosteroid exposure on limiting growth potential in neonates, GH treatment has been suggested in those born with glucocorticoid-induced GHD (Mazziotti and Giustina 2013).

It is well established that obesity results in a marked reduction in the secretion of GH and, in the non-pregnant state, obese individuals are characterised by a reduced half-life, daily production rate and frequency of GH secretory episodes (Scacchi et al. 1999). In the mouse, there is also some evidence that maternal obesity-induced changes in the GH axis may be responsible, at least in part, for transgenerational effects observed on body growth and glucose homeostasis in offspring. In this model, heritability of adverse metabolic traits was associated with changes in the GH secretagogue receptor (GHSR), circulating IGF-1 and IGFBP-3 in a maternal diet and sex-specific manner (Dunn and Bale 2009). Maternal obesity in the mouse induced via a high fat diet has also been associated with decreased embryonic IGF-1 receptor (IGF-1R) staining, reduced fetal size, increased placental *Igf2r* mRNA, and smaller offspring that go on to develop adiposity, glucose intolerance and lipid dysregulation (Jungheim et al. 2010).

Of note, it has been shown that two disparate models of altered maternal nutrition i.e. undernutrition and diet-induced obesity, result in similar adverse metabolic outcomes observed in offspring that are characterised by similar alterations in the IGF-IGFBP pathway (Smith et al. 2013). Specifically, both maternal undernutrition and a maternal obesogenic diet resulted in similar significant reductions in circulating IGF-1 and IGFBP-3 concentrations and reduced hepatic mRNA expression of IGFBP-1 and IGFBP-2 in both dietary models compared to controls.

5.3.2 Sheep

In singleton sheep pregnancies, it has been shown that nutrient restriction of the mother in the period from early to mid-gestation followed by re-feeding results in changes in fetal skeletal muscle and hepatic expression of IGF-1, -2 and/or GHR which may impact upon organ and tissue function in the postnatal period (Brameld et al. 2000). In this model it has also been shown that nutrient restriction of the

mother from early to mid-gestation can alter the association between IGF-1 and birth outcomes at term with the correlation between cord IGF-1 and fetal bodyweight and lean body mass lost in those exposed to maternal nutrient restriction (Heasman et al. 2000).

Early work in the sheep using an acute (72 h) model of maternal undernutrition demonstrated a decrease in fetal plasma IGF-1 concentrations that could be reversed following maternal glucose infusion and therefore indicated that nutrient availability, in particular availability of glucose, was a key determinant of fetal IGF-1 secretion (Bassett et al. 1990). Further work using a model of 48 h maternal starvation showed a significant reduction in fetal IGF-1 and -2. Fetal glucose replacement increased fetal IGF-1 and IGF-2 to near control levels whereas fetal insulin replacement raised fetal IGF-1 but had no effect on IGF-2. These data therefore suggested that IGF-1 and -2 were regulated independently in the fetal circulation with the influence of glucose on fetal IGF-1 likely to be mediated by insulin, whereas for IGF-2 glucose effects were insulin-independent (Oliver et al. 1996). In a sheep model of global nutrient restriction, altered skeletal muscle expression of IGF-2 has been reported with higher expression in nutrient restricted fetuses at gestational day 80 (Brameld et al. 2000). In this study, IGF-1 and GHR was not altered in muscle but hepatic production was reduced. It was hypothesised that the increase in IGF-2 may result in earlier and enhanced muscle differentiation during gestation and thus result in a disruption in myofibre number.

Periconceptional undernutrition in the sheep results in increased hepatic IGFBP-2 expression accompanied with lower maternal body weights and body condition (de Brun et al. 2015). In terms of defined critical windows of early development that can programme for altered adipose tissue deposition, nutrient restriction in the mother over the period of maximal growth of the placenta results in increased adiposity at term concomitant with enhanced abundance of IGF-1R and IGF-2R receptors. Conversely, nutrient restriction during the late gestation period, that coincides with the maximal fetal growth period, has no significant effect on adiposity (Symonds et al. 2004). In twin sheep pregnancies, the duration of maternal undernutrition can have differential effects on fetal growth and IGF-1 concentrations with umbilical vein and artery IGF-1 lower in those fetuses exposed to an extended period of undernutrition. This work also suggested that in twin ovine pregnancies, undernutrition of the mother followed by realimentation could induce a different change in fetal IGF-1 as compared to continuous nutritional restriction, with both differing physiologically from that of control pregnancies (Field et al. 2015).

In sheep models of maternal obesity, it has been shown that, in addition to a reduction in leptin signalling, there are programmed alterations in the GH axis that predispose towards adiposity in adult offspring (Tuersunjiang et al. 2017). This includes decreased circulating IGF-1 and a strong trend towards decreased GH in male offspring concomitant with reduced hepatic GH mRNA and IGF-1 mRNA and protein expression.

5.3.3 Primates

There is relatively little data on the impact of an altered early environment on programming of the GH-IGF axis in the non-human primate (NHP), particularly as regards long term outcomes. In the macaque, fetal concentrations of IGF-1, -2, and IGFBP-3 in normal pregnancies increase during the second and third trimester in a developmental profile similar to that of the human fetus (Tarantal and Gargosky 1995). Early work by Coulter and Han in the rhesus monkey suggested IGF-2 may play a role in the regulation of nutrient transport or placental hormone production and/or secretion in the syncytiotrophoblasts, and a potential role for IGF-2 and IGFBPs (particularly IGFBP-3) in cell to cell communication and interaction at the feto-maternal interface (Coulter and Han 1996a, b).

Direct administration of IGF-1 to the fetal rhesus monkey results in transient increases in circulating fetal [but not maternal] IGF-1 paralleled by an increase in select fetal organ weights and thus did provide some support for IGF-1 as a potential candidate for *in utero* therapeutic treatment of growth-compromised human fetuses (Tarantal et al. 1997). In a baboon model of maternal nutrient restriction, significant reductions in fetal weights were associated with alterations in the placental mTOR and IGF signalling pathways leading to a downregulation of placental nutrient transporters (Kavitha et al. 2014).

5.3.4 Other Models

Work in the guinea pig has shown that maternal undernutrition [40% global reduction] results in a 35% reduction in fetal and placental weights with a reduction in circulating fetal IGF-1 throughout gestation compared to controls (Dwyer and Stickland 1992). In this model, maternal IGF-2 was not affected by gestational age whereas fetal IGF-2 reached a peak at mid-gestation and was significantly reduced following maternal undernutrition. In both maternal and fetal serum, cortisol was inversely related with IGF-1. In this work, and in work by Jones et al. using a guinea pig model of uterine artery ligation to induce fetal growth restriction, it appears that fetal IGF-2 is strongly associated with hepatic glycogen deposition whereas fetal IGF-1 may have effects on mediating muscle growth (Dwyer and Stickland 1992; Jones et al. 1990). It has also been shown that chronic prenatal ethanol exposure in the guinea pig leads to marked sex-specific effects on the IGF axis with decreased central expression of IGF-1, -2, IGF-1R in male, but not female adult offspring and thus may be an early mechanism underpinning later life ethanol-related neurobehavioral teratogenicity (Dobson et al. 2014). In the neonatal piglet there is tight nutritional regulation of IGF-1 and, as with human infants and other experimental models, birth weight and plasma IGF-1 are positively correlated, with SGA piglets having significantly reduced circulating concentrations of IGF-1 compared to their appropriate for gestation age (AGA) littermates (Dauncey et al. 1994). Further work in the piglet

has suggested that changes in fetal thyroid hormones may, in part, modulate the ontogeny of GHR gene expression in the perinatal period and that this modulation is tissue-specific with differential regulation of the GHR observed in liver and skeletal muscle (Duchamp et al. 1996; Schnoebelen-Combes et al. 1996).

5.4 Epigenetic Regulation of the GH-IGF Axis

Epigenetic modifications arise due to one of four mechanisms; DNA methylation of CpG sites, histone modifications, chromatin reorganisation or regulation by small non-coding RNAs (miRNAs). Epigenetic processes play a key role in GH-IGF axis regulation, particularly in the processes around bone growth and development and lipid and carbohydrate metabolism (Alvarez-Nava and Lanes 2017). GH regulation of IGF-1 gene expression is mediated via signal transducer and activator of transcription 5b (STAT5b) and STAT5a (Wang and Jiang 2005). GH mediates a developmental epigenetic regulation of circulating of IGF-1 via a number of GH response elements (GHREs) (Fu et al. 2015). These GHREs interact with a number of tandem binding sites that vary in transcriptional potency within the IGF1 locus that are conserved across species (Alvarez-Nava and Lanes 2017; Eleswarapu et al. 2008).

There remains limited mechanistic data around epigenetic processes and developmental programming of the GH-IGF axis with most studies to date being associative in nature with cause-effect relationships not well defined. In the clinic, treatment of GH deficiency in children to optimise growth potential is met with variable outcomes. Although this variability in treatment efficacy is multifactorial, recent work has shown that epigenetic regulatory processes may be a key determinant underpinning how an individual responds to GH therapy (Ouni et al. 2015).

In both humans and rats, IUGR has effects on systemic GH-IGF-1 homeostasis via disrupting the epigenetic regulation of hepatic IGF1 gene transcription and normal developmental increases in hepatic IGF-1 expression observed during early life (Alvarez-Nava and Lanes 2017). In particular, IUGR in the rat disrupts normal developmental epigenetic processes involving distal GH response elements (GHREs) on the hepatic IGF-1 gene (Fu et al. 2015). Maternal undernutrition can alter the methylation status of the GH responsive promoter 2 of the IGF-1 gene (Oberbauer 2013) and IUGR is associated with persistent hypermethylation of the IGF-1 promoter in rats and therefore can amplify GH signalling impairments in the neonate (Fu et al. 2009). In the lamb, there is a sexually-dimorphic difference in hepatic IGF1 DNA methylation and this was shown to be independent of IUGR status (Carr et al. 2015). Further studies examining epigenetic regulation of IGF-1 in IUGR rats suggest that large numbers of CpGs in GHRE loci show differential patterns of methylation (Alvarez-Nava and Lanes 2017) leading to perturbations in the normal histone signature pattern (Fu et al. 2009, 2015).

It is well known that IUGR accompanied by rapid catch-up growth can result in an increased propensity for obesity in later life and is mediated, in part, by persistent reductions in IGF-1. Using a model of thromboxane A2 to induce IUGR, Fung et al.

showed that growth restriction prevented the age-dependent upregulation of IGF-1 in weanling male mice (Fung et al. 2015). In this study, IUGR resulted in hepatic IGF-1 epigenetic modifications in both male and female offspring (including reduced transcription in the P1 promoter region of the IGF-1 gene and increased P1 DNA methylation). However, at the time of weaning, IUGR males had been unable to correct for the prenatal reduction in IGF-1 mRNA and protein—possibly arising to a more perturbed IGF-1 chromatin structure than that observed in females. Further work in the rat showed that epigenetic regulation of IGF-1 could also be modulated by the rate of catch-up growth with alterations in expression of hepatic IGF-1 mRNA and histone structure in IUGR offspring showing differential regulation between those that showed rapid versus delayed catch-up growth (Tosh et al. 2010).

GH has been shown to induce rapid and marked changes in hepatic chromatin at target promoters with the chromatin signature of Igf1 appearing to differ from that of other GH- and Stat5b-dependent genes (Chia and Rotwein 2010). IUGR, in addition to a decrease in circulating IGF-1 and IGF-1 mRNA variants, is also associated with perturbations in chromatin accessibility, including that of H3K36me3 at the hepatic *IGF1* locus. Thus the pattern of histone modifications of GHREs during development can be affected following IUGR and consequently alter the epigenetic profile of hepatic *Igf1* along its entire length (Alvarez-Nava and Lanes 2017). These effects appear to persist well into postnatal life and are associated with decreased circulating protein levels and hepatic Igf1 mRNA (Fu et al. 2009).

Interestingly, in the setting of maternal hyperglycemia, there is also disruption at H3K36me3 of the IGF-1 gene concomitant with decreased hepatic IGF-1 mRNA variants. It was speculated that such changes in histone markers reflected sensitivity to alterations in glucose in the prenatal environment thus changing patterns of IGF-1 gene expression and potentially increasing susceptibility to later life insulin resistance (Zinkhan et al. 2012). Of note, GH treatment in the rat can result in acute alterations in chromatin structure at both IGF-1 promoters, concomitant with transcriptional activation in the liver (Chia et al. 2010).

Imprinted (parent of origin genes play a key role in the regulation of fetal demand for nutrients and the placental supply line. Although not developmental programming per se, the most cited illustration of developmental epigenetic imprinting is that of IGF-2 which has been shown in animal models (Gong et al. 2010) and human studies (Huang et al. 2012) to be important in modulating fetal nutrient transport (Fowden et al. 2011; Reik et al. 2003) with evidence for placental-specific IGF-2 as a key modulator of placental and fetal growth (Constancia et al. 2002). Imprinting disorders mediated by altered epigenetic regulation of the IGF-2/H19 region have been associated with distinct alterations in growth patterns including changes in adipose deposition (Huang et al. 2012). The IGF2 gene encodes a fetal and placental growth factor affecting birth weight with DNA methylation at the *IGF2*/*H19* genes locus and acts as a modulator of fetal growth and development within normal range (St-Pierre et al. 2012). In the human, placental size is known to be associated with IGF-2 methylation and is linked to changes in placental transport capacity and reduced birth weights (Haggarty et al. 2013). Both maternal high fat nutrition and maternal undernutrition have been shown to result in a marked downregulation of

hepatic IGFBP-2 expression (Smith et al. 2013). Given that the IGFBP-2 promoter region is CpG rich and exhibits a high level of conservation across mammalian species (Hoeflich et al. 2001), it has been suggested that altered methylation may mediate IGFBP-2 expression. However, this was shown not to be the case with no changes in IGFBP-2 methylation patterns across the different dietary groups with generalised hypomethylation (Smith et al. 2013). In addition to models of global changes in nutritional intake, a maternal low protein diet has also been shown to alter expression of the hepatic IGF-2/H19 genes in male offspring and was associated with hypermethylation of the IGF-2/H19 imprinting control region (Gong et al. 2010).

There is a relative paucity of data on maternal adiposity and its' potential impact on gene expression in members of the GH gene family or on associated hormone concentrations during pregnancy. Work by Mitsuya et al. suggested epigenetic regulation of the GH gene cluster with both pregnancy complications and adverse fetal outcomes in the setting of maternal obesity linked to an altered DNA methylome and may be part of a feedback loop controlling maternal and placental metabolism and ultimately fetal growth (Mitsuya et al. 2017). In addition to altered nutrition, maternal stress during human pregnancy is also associated with altered DNA methylation of IGF-2 (Vangeel et al. 2015) and other complications of pregnancy, including preeclampsia, have been associated with altered IGF-2 methylation and may represent a mechanism behind the association between intrauterine exposure to preeclampsia and high risk for cardiometabolic disorders in these infants in later life (He et al. 2013).

A primary focus to date has been on alterations in DNA methylation and histone modifications and less focus has been on the potential role of miRNAs in the setting of the GH-IGF axis in developmental programming. MicroRNAs (miRNA) are short non-coding transcripts of around 22 nucleotides in length that regulate the expression of specific messenger RNA (mRNA) targets. Deficiency of IGF-1 during a critical early life period has been shown to result in persistent changes in post-transcriptional miRNA-mediated control of genes related to later vascular well-being in a murine model (Tarantini et al. 2016). Maternal protein restriction in rats during pregnancy and lactation results in alterations in expression of miR-29 which is inversely related to hepatic Igf1 mRNA and bodyweight in offspring postnatally. These changes appear to persist into adult life as post-weaning nutritional restoration in these offspring did not prevent long-term growth impairment (Sohi et al. 2015). In other complications of pregnancy, such as pre-eclampsia, there is some evidence for effects of altered IGF-1 regulation mediated by miRNAs—overexpression of miR-30a-3p affects apoptosis and trophoblast invasion via targeting IGF-1 (Niu et al. 2018).

Although beyond the scope of the current overview, there is a need to recognise the potential for paternally mediated effects on the GH-IGF axis on programming of offspring phenotype with an increasing number of studies linking paternal health with developmental outcomes. As an example, paternal obesity is associated with IGF-2 hypomethylation in the newborn (Soubry et al. 2013). Experimentally, expression studies in the fetal brain revealed that paternal folate deficiency, at the time of conception, can influence fetal brain DNA methylation patterns and expression of IGF-2, despite maternal folate status being adequate during the period of gestation

(Kim et al. 2013). Further, there is evidence that some tissues may retain an "epi-memory" of early life events. As an example, it has been suggested that the capacity of skeletal muscle to respond to an altered postnatal environment, either adaptively or maladaptive, is dependent upon prior early life exposures and retention of epigenetic information (Sharples et al. 2016).

5.5 Strategies to Reverse Early Life Impacts on the GH-IGF Axis

Commencing in 1985, recombinant GH has been widely used in the clinical setting for the treatment of GH deficiency. Although some initial concerns had been raised around the potential for GH treatment leading to an enhanced risk of T2DM in treated individuals in later life (Cutfield et al. 2000), data to date would suggest that current paradigms around GH use are safe and previous concerns raised may simply relate to dosing and treatment duration. Moreover, based on current dosage practises, recent studies would suggest a positive long-term influence in GHD children following GH administration across a broad range of outcomes that include normalisation of blood pressure, body composition, lipid metabolism, bone health and β-cell secretory capacity (Sas et al. 2000; Baronio et al. 2016; Cutfield et al. 2006; Horikawa et al. 2017). Less has been done around IGF-1 as a potential treatment modality due to potential issues raised around increased cancer risk (Cohen et al. 2000; Schernhammer et al. 2006) and links between IGF-1 and progression of diabetic retinopathy (Chen et al. 2012).

In additional to clinical use of GH, there have been a number of animal studies across a range of experimental paradigms highlighting the potential efficacy of GH and the IGF-IGFBP system in reversing or ameliorating the adverse consequences of developmental programming (Reynolds et al. 2017). A number of studies in rodents have examined GH treatment in both mother and neonates although the outcomes appear to be dependent on the severity of the experimental insult and nature of the model used. Using a model of moderate maternal undernutrition (50% of *ad libitum* intake), GH administration in the pre-weaning period has been shown to reverse a number of adverse outcomes observed in offspring including normalisation of body weight, fat mass, blood pressure, inflammatory responsiveness and endothelial function (Reynolds et al. 2013a, b; Gray et al. 2013, 2014; Li et al. 2015). GH treatment was also shown to correct the programming-induced reduction in hepatic IGFBP-2 and restore expression to that seen in offspring of control pregnancies (Smith et al. 2013). In a model of maternal low protein diet, similar aberrant changes in the IGF-2/IGFBP-2 axis in offspring and have been shown to be ameliorated with maternal folic acid supplementation (Gong et al. 2010). Using a model of severe maternal undernutrition (30% of *ad libitum* intake) neither administration of GH or IGF-1 to pregnant rats undernourished throughout pregnancy prevented IUGR or blood pressure elevations in adult offspring (Woodall et al. 1999). Of note, using a sim-

ilar model of severe maternal undernutrition, it has been shown that both GH and IGF-1 treatment to the adult offspring of these undernourished mothers can lead to a reversal of the programmed phenotype (Vickers et al. 2001b, 2002). Combination treatment approaches have also shown efficacy in treatment of programmed disorders including co-treatment with GH and a lipid lowering agent (acipimox) which resulted in enhanced linear body growth in offspring following IUGR (Vickers et al. 2006). Interestingly, in a dwarf rat model of developmental GH-IGF-1 deficiency, it has been shown that altered programming of the GH-IGF axis during key early developmental periods can determine the capacity for cellular DNA repair via changes in the transcriptional regulation of DNA repair-related genes. These alterations can lead to changes in cellular resistance [e.g. responsiveness to environment stressors] and can be normalised with early GH treatment (Podlutsky et al. 2017).

It is important to note that the observed differences in experimental outcomes from GH intervention studies in rodents may, in addition to dose and duration effects, reflect the type of GH used and non-homologous approaches. Most studies have utilised either bovine GH (bGH) or human GH (hGH) which have differing amino acid sequence and function with bGH binding specific to somatogenic sites whereas hGH is able to bind to both lactogenic and somatogenic and binding sites (Reynolds et al. 2017). As regards fetal interventions, there are currently no available effective intrauterine treatments to improve growth in the growth restricted human fetus (Alberry and Soothill 2007). A number of studies have been undertaken in the sheep and these have been reviewed previously by Harding and Bloomfield (Harding and Bloomfield 2004). GH treatment in the periconceptional period has been shown to alter fetal growth and development in lambs with changes in the GH-IGF axis that persist postnatally (Koch et al. 2010). In a normal sheep pregnancy, infusion of GH to the fetus during late gestation does not alter growth of the fetus nor markers of metabolic function (Bauer et al. 2000). However, in the setting of fetal growth restriction, a similar GH treatment paradigm leads to normalisation of IGF-1 concentrations in the fetus but no impact upon fetal growth was observed and this suggested that the observed changes in IGF-1 reflected reduced clearance as opposed to increased production (Bloomfield et al. 2006). These results are not unexpected given that GH plays little role in fetal growth regulation with IGFs, primarily IGF-2, regulating fetal growth independently of GH secretion (Kadakia and Josefson 2016). Interestingly, in a sheep model of overfeeding, treatment with GH in late gestation has been shown to increase fetal weights, largely a result of increased adipogenesis and suggests a direct *in utero* effect of GH on adipose tissue (Wallace et al. 2006). Of note, using the same model, when GH was administered earlier in gestation the increase in fetal adiposity was not observed and there was an association between treatment and polyhydramnios (Wallace et al. 2004). IGF-1 to the fetus via the intramniotic fluid has shown some promise with improved growth rates following IUGR that are independent of changes in circulating IGF-1 or insulin. Work by Wali et al. reported that IGF-1 delivered weekly via amniotic fluid increased growth in IUGR fetuses and was mediated in part by the upregulation of placental amino acid transporters and suggested that amniotic IGF-1 treatment may have some clinical utility (Wali et al. 2012; Eremia et al. 2007).

As with the rodent data, data from sheep models has been variable and also reflects differences in dosing and timing/duration of treatment and in some cases adverse effects have been reported including hydraencephalic brain lesions in fetuses following treatment with GH in a model of placental embolization (de Boo et al. 2008).

5.6 Conclusions

There is clear evidence from human observations and a wide range of experimental animal models that the GH-IGF axis can be programmed by alterations in the early life environment leading to persistent changes in growth and cardiometabolic profiles in offspring in later life. These programming effects can be sexually dimorphic in nature and can also be amplified by the postnatal environment, including exposure to a postnatal obesogenic diet, and there is also evidence, albeit limited, that these effects can be transgenerational in nature (Aiken and Ozanne 2014). Epidemiological evidence has provided evidence for changes in the GH-IGF axis arising from early life adversity, including famine exposure, that persist throughout the lifecourse but little is known around dysregulation of this axis at the time of the environmental exposure itself and the data therefore remains speculative. Offspring phenotypes that arise due to developmental programming share common characteristics with those associated with GH deficiency and include an increased risk for later obesity, insulin resistance and cardiovascular disorders. Many of the experimental studies to date have examined the impact of altered early life nutrition, particularly maternal undernutrition, on changes to the GH-IGF axis although other experimental modalities, including maternal stress, have elicited similar changes in this axis in offspring. A wide range of experimental studies have shown that, with a postnatal environment with adequate nutrition, both GH and IGF-1 promote catch-up growth in offspring affected by IUGR due to maternal nutritional deprivation.

There is an increasing interest in the role of epigenetic processes in modulating the effects on the GH-IGF axis with data to date suggesting that conditions including IUGR induce changes in epigenetic developmental programming that gives rise to growth and cardiometabolic disorders in later life as a consequence of disruptions in patterns of normal developmental epigenetic marks, and consequently impact expression of GHRE-containing genes covering a wide range of functional roles (Alvarez-Nava and Lanes 2017). Although most work has examined changes in DNA methylation patterns and is largely associative in nature, there is increasing evidence for a histone modifications and miRNAs in modulating effects on the GH-IGF axis.

Extrapolation from a wide range of studies in rodents, which contain an evolutionary similar *IGF* locus gene composition to that seen in the human, can only be speculative as regards programming of disease pathophysiology. However, data from experimental models does provide some insight into the epigenetic regulation of the GH-IGF axis and may provide utility in optimising diagnosis and management of those children born SGA. As an example, increased understanding of the

normal regulatory patterns of the human *IGF1* locus may allow for identification of an accessible chromatin around this locus and may allow for lower dosing strategies to be used around GH treatment of SGA subjects (Alvarez-Nava and Lanes 2017) and therefore minimise potential dosing-related side effects including altered insulin sensitivity.

As regards treatment interventions with GH or other components of the IGF system in the clinical setting, data around long term efficacy also remain limited primarily due to the low number of treatment cases relative to the number of those with born with short stature or IUGR (Stochholm and Johannsson 2015). Despite initial concerns around the potential for GH treatment to predispose to later metabolic risk, including T2DM (Cutfield et al. 2000), the longer terms studies reported to date would indicate that GH is safe with the initial side effects potentially reflecting a short-term trade-off for longer term benefit (Reynolds et al. 2017). Less is known around IGF-1 as a programming treatment modality, partly due to initial concerns raised linking IGF-1 treatment with some cancers, a linkage which remains controversial (Cohen et al. 2000). It is clear from a range of animal studies that early life treatment with GH or IGF-1 can partially reverse the adverse metabolic sequelae that result from early life programming and thus further reinforce this early period of plasticity as a key window for intervention. Further, intervention in adulthood with GH and IGF-1, when the programmed phenotype is already manifest, also show promise in correcting the cardiometabolic disorders in offspring although longer term outcomes post-treatment have not been explored (Vickers et al. 2001, 2002; Vickers and Sloboda 2012a). It is of note that most studies using GH or IGF-1 have focussed on outcomes related to linear growth, lipolysis and changes in insulin sensitivity and very little has been examined around treatment effects related to programming of the neuroendocrine axis particularly given the feedback loops that exist between GH and key neurotrophic factors known to exert marked programming effects in early life, including that of leptin (Vickers and Sloboda 2012b; Vickers et al. 2005).

Some lack of inconsistency across the animal models as relates to dysregulation of the GH-IGF axis likely reflects the nature, severity and timing of the early life exposures in addition to sexually dimorphic responses to such exposures. Similarly, efficacy of treatment strategies to ameliorate effects of the early life environment on growth and related outcomes can differ based on the mode of delivery, dose and timing of exposure. Of note, changes that appear in the GH-IGF-1 axis arising from nutritional insults in early life do appear to be relatively consistent across a range of model species and nutritional exposures studied (e.g. low protein versus global restriction). However, it is yet to be determined whether the mechanisms underpinning the commonalities in growth and cardiometabolic dysregulation are the same and whether treatment effects will be similar across the models. Given that a range of environmental factors in early life (e.g. nutrition and stress) can lead to marked variations in the GH-IGF axis, more mechanistic research is required to further understand this axis in the setting of developmental programming before effective strategies to complement those existing clinical approaches to addressing growth and related metabolic disorders can progress.

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Chapter 6
Early Life Nutritional Programming of Adult Health Status

Simon C. Langley-Evans and Beverly Muhlhausler

Abstract There is increasing recognition that the risk of a broad range of non-communicable diseases, including obesity, cardiovascular disease and type 2 diabetes, are related not only to genetic predisposition but also to adaptive changes to environmental exposures during development. This concept, referred to as the Developmental Origins of Health and Disease (DOHaD) hypothesis, means that exposure to a sub-optimal environment during critical periods of development is associated with persistent changes to tissue morphology and function. This impairs the capacity of organ systems to adapt to physiological stressors, including ageing, in postnatal life and ultimately results in poor adult cardiometabolic health. The early DOHaD studies focussed primarily on the impacts of inadequate maternal nutrition and/or low birth weight and established the link between sub-optimal intrauterine growth and risk of poor adult cardiovascular and metabolic health. However, in contemporary Western societies, maternal over-nutrition, overweight and obesity are far more common nutritional issues and this has led to an increased focus of the field on the long-term consequences of exposure to these stimuli in early life. This Chapter will focus on exploring our current understanding of the impact of exposure to maternal overweight, obesity and poor quality Western-style diets on both the mother and her offspring. We will present evidence from both human epidemiological studies and animal models, and out forward practical suggestions for potential strategies to improve outcomes.

Keywords Maternal obesity · Fetal programming · Cardiovascular disease · Pregnancy · Metabolic syndrome

S. C. Langley-Evans (✉)
School of Biosciences, University of Nottingham, Sutton Bonington, Loughborough LE12 5RD, UK
e-mail: Simon.Langley-Evans@Nottingham.ac.uk

B. Muhlhausler
Food and Nutrition Research Group, Department of Food and Wine Sciences, School of Agriculture, Food and Wine, University of Adelaide, Waite Campus, PMB 1, Glen Osmond, SA 5064, Australia
e-mail: Beverly.Muhlhausler@Adelaide.edu.au

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6.1 Introduction

Standard models of health and disease postulate that interactions between adult lifestyle and genetic factors are the main drivers of disease risk with ageing. Thus, individuals with particular gene polymorphisms that might favour heart disease, diabetes or cancer, are at greater risk than those with non-disease promoting genotypes but that risk is dependent upon quality of their diet, physical activity and use of alcohol, tobacco and other harmful agents (Young et al. 2005; Ordovas 2006). Such a model does not, however, tell the whole story as a large and robust body of epidemiological evidence, compiled from populations all around the world, indicates that risk of non-communicable diseases in adult life is also determined by the environment encountered before birth and in early infancy (Gluckman et al. 2008). Major health conditions such as cardiovascular disease and type 2 diabetes are more prevalent in older people who were of lower birth weight, who were fed infant formula rather than being breast-fed, or who showed rapid catch-up growth in childhood (Forsén et al. 1999; Fall et al. 1998; Eriksson et al. 2001; Ravelli et al. 2000). These epidemiological findings are supported by animal studies designed to directly assess the impact of nutritional variation during key developmental stages on long term cardiometabolic outcomes (McMullen and Mostyn 2009; McMullen and Swali 2013; Langley-Evans 2015). Thus, rodent models of caloric restriction, reduction of macronutrient intake and micronutrient deficiency in pregnancy and lactation show that this compromises cardiovascular function and metabolism, renal function and longevity in the associated offspring. For example, offspring of rats fed a low protein diet in pregnancy have high blood pressure from the time of weaning, become insulin resistant with ageing and have a shorter lifespan that offspring of rats consuming diets containing adequate levels of protein (Langley-Evans et al. 1996, 1999; Ozanne and Hales 2004; Bellinger et al. 2006) (Fig. 6.1).

These observations have led to the development of the Developmental Origins of Health and Disease (DOHaD) hypothesis (Barker 2007). This asserts that states of health or disease at any stage of life are the result of cumulative exposures to the environment at every preceding stage. This means that overlaid onto genetically determined risk factors for disease are adaptive responses to the early life environment that become fixed and irreversible. The high plasticity of organs and tissues during major phases of development and rapid growth (primarily the fetal and early postnatal periods) means that exposure to poor diet, high levels of psychological stress, disruption of endocrine axes or infection during these periods, either directly or via maternal exposure to these stressors can alter tissue morphology and function in the developing organism. These changes become permanent as developmental stages are completed.

Studies of the offspring of animals subject to varying forms of undernutrition (e.g. iron deficiency, low protein diets, global caloric restriction) during pregnancy confirm that even, at a gross level, organ structure is altered by the experience (Swali et al. 2011; Snoeck et al. 1990; Bennis-Taleb et al. 1999). For organs such as the kidney or pancreas, where development is largely complete around the time of birth

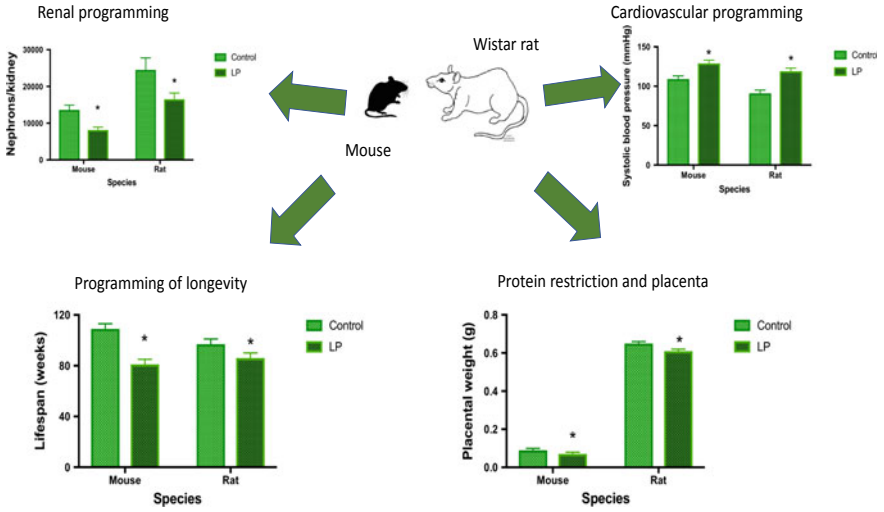

Fig. 6.1 Broad programming effects of a maternal low protein diet during pregnancy in rats and mice. Feeding a low protein diet during pregnancy, with transfer to a standard diet for lactation, is associated with reduction of nephron number in the kidneys and higher blood pressure in adult offspring. These offspring have a shorter lifespan than animals exposed to a protein-adequate diet in fetal development. The same outcomes are noted in studies of both rats and mice, demonstrating that the effects cut across species and opening up the possibility to move from the original rat model to access the superior molecular tools and transgenic strains that are available with mouse studies. Many of these programming effects are also observed in rodents subject to maternal iron deficiency, food restriction and high fat feeding. Data has been redrawn from published material (Langley-Evans et al. 1996, 1999; Ozanne and Hales 2004; Bellinger et al. 2006; Barker 2007; Swali et al. 2011)

in humans, any deficits in key functional units (e.g. nephrons in the kidney, islets in the pancreas) cannot be recovered, permanently altering their structure. Early in the life-course (childhood, adolescence and young adulthood), the individual will still have the capacity to fulfil organ function. However, as organ function naturally declines as part of the ageing process, these organs can no longer meet demands, leading to renal failure, cardiovascular disease and metabolic disturbances. Thus, the early nutritional environment sets functional capacity and determines the functional profile for ageing (Calder et al. 2018).

Much of the existing DOHaD literature has focused upon relationships between undernutrition during pregnancy and infancy and disease in later life. This is an inevitable consequence of the epidemiological approaches that were first taken to identify the fact that early nutrition is a determinant of later health and disease, which relied on retrospective follow-up of historical cohorts. Contemporary nutritional issues are far more focused upon maternal over-nutrition, overweight and obesity and so this Chapter will focus upon these states and how they influence pregnancy outcomes and the long-term growth, development and health of the offspring.

6.2 Obesity and Pregnancy

6.2.1 The Increasing Prevalence of Maternal Obesity

Across the world an increase in the prevalence of being overweight (body mass index; BMI 25–29.99 kg/m^2) and obese (BMI > 30 kg/m^2) is being observed across all age groups in the population. In all developed countries, and increasingly in developing countries, there are high levels of obesity among women of childbearing age. In the UK, 19% of 25–34-year-old women and 26% of 35–44-year-old women were estimated to be obese in 2017 (National Statistics Office 2018) and similar figures were reported for Australia (Australian Institute of Health and Welfare 2017). In the United States an obesity prevalence of 36.5% was reported for women aged 20–39 in 2015–2016 (Hales et al. 2018). The World Health Organisation reports that among women aged 15–49 years obesity prevalence also increased markedly in developing countries between 1994/2004 and 2005/2013 and that 45% of women in Latin American countries were classified as obese in 2016 (Fig. 6.2a) (World Health Organisation 2016). The lowest rates of obesity among young women are noted in Japan, South Korea and Italy (less than 10% prevalence) (Organisation for Economic Co-operation and Development).

In addition to high rates of overweight and obesity in the population, a dramatic increase in the prevalence of severe or morbid obesity has occurred in young women. In 2009, approximately 5% of all pregnant women in England and Wales had a BMI > 35 kg/m^2, and approximately 2% had a BMI > 40 kg/m^2 (Fig. 6.2b) (Centre for Maternal and Child Enquiries (CMACE) 2010). In addition to the high prevalence of

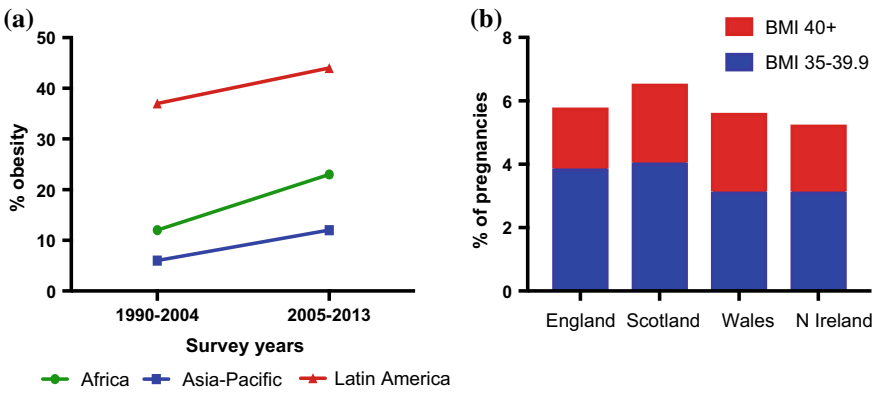

Fig. 6.2 **a** Prevalence of obesity is rising in developing countries. Data are shown for World Health Organisation regions, focused on the poorest 20% of women aged 15–49 years living in urban areas. African data represents 24 countries; Asia-Pacific 6 countries and Latin America 5 countries. Drawn from data provided by WHO (2016). **b** Prevalence of morbid obesity (BMI > 35 kg/m^2) in the UK. *Source* CMACE (2010)

obesity among pregnant women, pregnancy is recognised as a period during which women are vulnerable to excessive weight gain. Many women struggle to lose this excess weight after delivery, which increases the risk of complications in subsequent pregnancies and impacts negatively on their longer-term health. In order to reduce the risk of pregnancy complications and to control the impact that pregnancy may have on future obesity risk in the child, many countries follow the US Institute of Medicine guidelines on weight gain for pregnancy (Institute of Medicine 2009). These suggest that weight gain should be dependent on weight status going into pregnancy, with underweight (BMI < 18.5 kg/m^2) women targeting a gain of 13–18 kg; normal weight (BMI 185–24.9 kg/m^2) 11–16 kg; overweight (BMI 25–30 kg/m^2) 7–11 kg; and obese (BMI>30 kg/m^2) women targeting a gain of no more than 9 kg. The majority of women exceed these guidelines and this is thought to increase risk of obesity in their offspring.

6.2.2 Maternal Obesity and Adverse Pregnancy Outcomes

Obesity and overweight are recognised as having strong associations with poor pregnancy outcome and excessive weight gain is known to increase risks to future pregnancies. Having a high BMI going into pregnancy and/or gaining excessive weight through gestation increases the likelihood of complications for the pregnancy and of abnormal labour and delivery (Fig. 6.3).

Women who are overweight or obese may have difficulties becoming pregnant (Gourmerou et al. 2003). Elevated production of leptin from adipose tissue has a suppressive effect upon the hypothalamic-pituitary-ovarian axis and this puts overweight women at greater risk of anovulation, amenorrhoea and oligorrhoea (Gourmerou et al. 2003). Risk of polycystic ovary syndrome is also greatly increased by obesity (Moran et al. 2012). It is commonplace for women undergoing assisted reproductive treatments to be asked to reduce body weight before treatment begins to increase chances of success. Once pregnant, being obese also appears to be associated with an increased risk of miscarriage in some groups of women. Thus, while one of the greatest risk factors for miscarriage is underweight (Maconochie et al. 2007), for women who have conceived through in vitro fertilization, the risk of miscarriage is significantly increased by maternal overweight, with the level of risk being proportionate to the degree of excess adiposity (Wang et al. 2002). Obesity is also associated with a 25–37% increased risk of miscarriage in women with polycystic ovary syndrome (Cavalcante et al. 2018).

Normal pregnancy is a state of insulin resistance, which is necessary to drive glucose across the placenta towards the fetal circulation. As a result, maternal glucose concentrations achieve a greater peak after consuming food and fasting glucose is elevated compared to the non-pregnant state. For 2–3% of women this insulin resistant state progresses to gestational diabetes mellitus (GDM), and this is more likely in women who have either a family history of diabetes and/or other risk factors that would increase the risk of type 2 diabetes. Foremost among these risk factors is

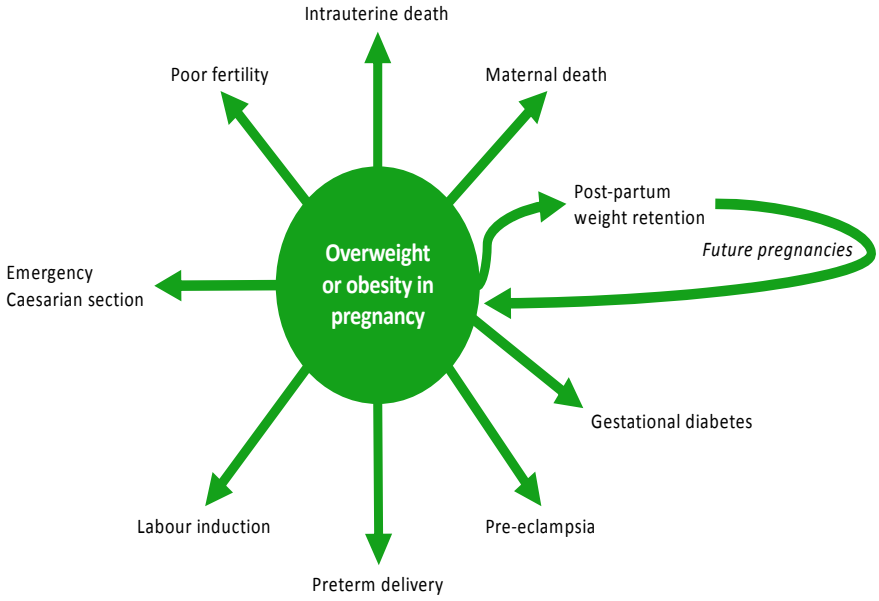

Fig. 6.3 Overweight and obesity are risk factors for poor pregnancy outcomes

obesity and the prevalence of gestational diabetes is around 15% for women with BMI > 30 kg/m^2, compared to approximately 1–2% of women with BMI < 25 kg/m^2 (Castro and Avina 2002).

The chronic low-grade inflammation that is associated with excess adiposity is likely to be both a driver and a consequence of GDM and may also be the link between this condition and other pregnancy complications commonly encountered in obese women, including hypertensive disorders. The fetus is directly impacted by GDM, since the elevated maternal glucose concentrations that are characteristic of GDM result in increased glucose transfer across the placenta and elevated fetal glucose concentrations. This, in turn, leads to more rapid growth and adipose tissue deposition, enhanced deposition of calcium in bone—which can lead to hypocalcaemia—and disruption of growth hormone and insulin-life growth factor axes (Hussain et al. 2007). The longer-term consequences of this will be explored later in this chapter. Women who have developed GDM are also at risk of longer-term health issues; 50% of these women go on to develop the condition in future pregnancies (Reader 2007) and they are also at greater risk of developing type 2 diabetes post-partum.

The increased blood volume in pregnant women and requirements to perfuse the placenta and increase blood flow to the kidneys mean that maternal blood pressure normally rises from early pregnancy. For some women, these increases in blood pressure exceed thresholds of 140/90 mmHg and this is termed gestational hypertension. While such elevated blood pressure has little bearing on pregnancy outcome per se, 2–7% of pregnant women develop a condition known as pre-eclampsia, which

can be life-threatening. In addition to uncontrollable increases in blood pressure, pre-eclampsia is also characterised by a cluster of other issues, including proteinuria. Left untreated pre-eclampsia progresses to eclampsia which can result in maternal renal collapse, placental abruption and death of both mother and baby. As a result, women with pre-eclampsia are generally delivered preterm, which may potentially expose these infants to the health issues associated with prematurity as well as maternal obesity.

Pre-pregnancy BMI and weight gain during pregnancy are the major modifiable risk factors for pre-eclampsia. Jensen et al., reported that women with BMI > 30 kg/m^2 were 3.8-fold more likely to develop pre-eclampsia than women with BMI < 25 kg/m^2 (Jensen 2006). There is some evidence that interventions that limit pregnancy weight gain in severely obese women can greatly reduce the risk of pre-eclampsia. Weight loss prior to pregnancy can also confer benefits; in women who have suffered from pre-eclampsia, post-partum weight loss has been shown to significantly reduce their risk of developing pre-eclampsia in a subsequent pregnancy (Walsh 2007). There is also some evidence that interventions that limit pregnancy weight gain in severely obese women can substantially reduce the risk of pre-eclampsia. As with GDM, the relationship between obesity and pre-eclampsia appears to be driven by inflammatory processes which, in this case, result in endothelial dysfunction in the uterine arterial system (Gammill and Roberts 2007).

Obesity during pregnancy is also associated with minor complications which, although they do not threaten the viability of the pregnancy or have a major developmental impact, cause extreme discomfort to women and increase costs associated with their management. Denison et al. reported that among 651 pregnant women in Scotland, obesity increased risk of heartburn, chest infections and symphysis pubis dysfunction by as much as fourfold (Nohr et al. 2007). The latter can be extremely debilitating due to pelvic pain that limits routine activities requiring standing, walking or weight bearing.

Preterm delivery is a major risk for neonatal morbidity and mortality and the risk of delivery before 37 weeks gestation is strongly linked to maternal weight status at both ends of the spectrum (i.e. both under- and overweight). Obesity has been reported to increase the prevalence of spontaneous preterm birth by 50% (Faucett et al. 2016) and this appears to be largely driven by GDM and insulin resistance. The inflammatory state associated with obesity can also favour premature rupture of membranes and preterm delivery (Denison et al. 2009). Preterm delivery by caesarean section is also indirectly associated obesity, as women with pre-eclampsia are generally delivered early to avoid the more serious implications of eclampsia.

The course of normal term labour can also be impacted by maternal overweight and obesity. GDM may result in babies being large-for-gestational age and this can result in longer, more traumatic labours with a greater likelihood of instrumental assistance (forceps or ventouse) or surgical intervention. Large-for-gestational age babies, particularly those who are macrosomic (>4,000 g), are also at risk of shoulder dystocia during a normal vaginal birth (Weissmann-Brenner et al. 2012). Relative to a women of BMI 20–24.9 kg/m^2 the likelihood of caesarean section is also twofold greater in women with BMI 30–34.9 kg/m^2 and threefold greater with BMI > 35 kg/m^2

(Borghesi et al. 2017). Whilst this is partly explained by the need for intervention for pregnancy complications, it is also recognised that uterine contractility is abnormal with obesity and that this causes labour to falter, increasing the need for medical interventions (Muir et al. 2018).

The loss of a pregnancy at any point after 20 weeks gestation is termed stillbirth and obesity is considered to be one of the most important modifiable risk factors for this late intrauterine death. A systematic review and meta-analysis of 96 studies concluded that maternal BMI > 25 kg/m^2 was the highest ranking modifiable risk factor in developed countries (Flenady et al. 2011), increasing risk of stillbirth by up to 60% relative to women with a BMI < 25 kg/m^2. Carmichael et al., reported that increased risk applied to stillbirth at all stages of pregnancy (20–23 weeks, 24–27 weeks, 29–31 weeks, 32–36 weeks) and that for mid-term stillbirth the risk associated with obesity was increased by 3.5-fold (Carmichael et al. 2015).

The neural tube defects (spina bifida and anencephaly) are the most prevalent birth defects in humans. Risk of a neural tube defect-affected pregnancy is multifactorial and is highly associated with ethnicity, genetic predisposition and folate intakes/circulating folate concentrations (Agopian et al. 2013). Women consuming low folate diets have significantly elevated risk and this risk can be ameliorated though increased folate intake, achieved either via folate supplementation or folate fortification of staple foods. Obesity is the other major modifiable risk factor, increasing the risk of spina bifida by more than twofold (Stothard et al. 2009). GDM is also a risk factor for a neural tube defects, but this is almost certainly an indicator of obesity-mediated risk, as GDM will typically develop long after the critical point in gestation when these defects develop (4–5 weeks gestation) (Reece 2012). Studies which have examined the efficacy of folate supplementation in preventing neural tube defects also indicate that obese women respond less well to this prevention strategy (Wang et al. 2013). This coupled to the fact that unsupplemented obese pregnant women have lower circulating folate concentrations than women with a healthy BMI, suggests that obesity modifies folate metabolism, metabolism and storage.

Maternal obesity significantly increases the risk of maternal death during pregnancy and labour. Burlingame et al., for example, reported that in Hawaii maternal death was most commonly due to heart failure and that this was strongly related to obesity (Burlingame et al. 2012). Hypertensive disorders and diabetes, either pre-existing or developing during the pregnancy, are also complications that increase the likelihood of maternal death. Major postpartum haemorrhage is also a potential cause of death associated with either spontaneous vaginal delivery or with interventions such as Caesarean section. Obesity is associated with greater prevalence of postpartum haemorrhage. In the UK the Confidential Enquiries into Maternal Deaths (CEMACH) noted that more than half of maternal deaths between 2003 and 2005 were of women who were overweight or obese and that 15% were of women with BMI > 35 kg/m^2 (Weindling 2003).

6.3 Maternal Obesity and Programming of Later Disease

6.3.1 Epidemiological Evidence Linking Maternal Obesity to Later Outcome

In addition to the negative impacts of maternal overweight and obesity on pregnancy and neonatal outcomes, there is now compelling evidence that maternal obesity is also associated with long-term adverse health outcomes in the child (Catalano and Ehrenberg 2006; Catalano 2003). The most profound effects of maternal obesity appear to be on cardiometabolic health outcomes, and children of obese mothers are at increased risk of obesity, cardiovascular disease and type 2 diabetes through the life-course. This has thus given rise to an intergenerational cycle of obesity and poor metabolic health in many populations world-wide.

Some of the earliest evidence for the link between maternal BMI and risk of overweight and obesity in the child came from a large epidemiological study conducted by Parsons and colleagues in the early 1990s (Parsons et al. 2001). In this study, over 10,000 individuals who had all been born in the same year in Hertfordshire, UK, and for whom detailed birth records were available, were followed up for assessment of BMI at 33 years of age. Using these data, the authors identified a J-shaped relationship between birth weight and BMI at age 33 in both men and women, such that those individuals who were heavier at birth had a higher BMI, and were thus at higher risk of overweight, in adulthood. Importantly, the authors demonstrated that this relationship between birth weight and adult BMI was almost entirely explained by maternal BMI, but was not influenced by other factors, including paternal BMI or smoking (Parsons et al. 2001). Thus, this study provided evidence that heavier mothers give birth to heavier infants who go on to be heavier adults, thus leading to the propagation of an intergenerational cycle.

The findings of Parsons and colleagues have since been replicated in a number of other large cohort studies. These studies all show a similar J-shaped relationship between birth weight and adult BMI, such that BMI is increased slightly in individuals of low birth weight, but that heavier babies have a greatly elevated prevalence of overweight and obesity in adolescence and young adulthood. The results of a survey of 7981 girls and 6900 boys who were part of the Growing up Today Study (GUTS) in the US at 9–14 years of age, for example, indicated that the odds ratio for adolescent overweight was 1.4 (95% CI: 1.2–1.6) for each 1 kg increment in birth weight (Gillman et al. 2003). This estimate was also not markedly altered following adjustment for other factors implicated in obesity, including physical activity, television watching, energy intakes and breastfeeding duration (Gillman et al. 2003). The GUTS follow-up further suggested, in contrast to Parsons's study, that the relationship was not markedly attenuated when maternal BMI was controlled for in the analyses suggesting that, in this cohort at least, the relationship between a high birthweight and increased risk of overweight in adolescence was not mediated to a large extent by maternal BMI. It is important to note, however, that overweight in this study was assessed at a relatively young age in comparison to other studies.

Nevertheless, the majority of follow-up studies support the suggestion that parental obesity, in particular maternal obesity, is a significant risk factor for future obesity risk independent of birth weight. In a landmark study in this area, Whitaker and colleagues obtained height and weight measurements from around 8400 subjects who had been born in a specific region of Washington State, USA, and were between 21 and 29, and also reviewed the medical records of their parents (Whitaker et al. 1997). The key finding of this study was that parental obesity was the most important predictor of future risk of obesity in children under 3 years, with 2 year old children with at least one obese parent being at more than 3 times greater risk of obesity in young adulthood compared to those whose parents were not obese. In this same study, infants who were born to obese mothers (based on maternal BMI in the first trimester) were twice as likely to be obese by 2 years of age compared to infants of mothers who weren't obese, and the prevalence of childhood obesity (BMI > 95th percentile) in 2,3 and 4 year-old children born to obese mothers was between 2.4 and 2.7 times that of children of mothers whose BMI was in the normal range (Whitaker et al. 1997). Similarly, a study conducted on a northern Finland birth cohort, in which data from the mother during pregnancy as well as measurements from the child at birth, 1, 14 and 31 years of age were collected, identified maternal obesity both during adolescence and immediately prior to pregnancy as significant predictors of obesity in adult children (Laitinen et al. 2004).

The increased prevalence of overweight and obesity in individuals of high birth weight is also associated with a higher prevalence of associated co-morbidities, including insulin resistance and type 2 diabetes (Mingrone et al. 2008). While this effect is exacerbated in the presence of maternal glucose intolerance/GDM, there also appears to be an independent effect of maternal obesity per se. This was demonstrated in an elegant study by Boney and colleagues, which established that children of obese mothers with normal glucose tolerance had an almost twice the risk of developing the metabolic syndrome by age 11 compared to children born to mothers of normal weight (Boney et al. 2005). Interestingly however, a number of studies, including the US Nurse's Health Study, suggest that the J-shaped relationship between birth weight and risk of adult type 2 diabetes is attenuated when the impact of current BMI is controlled for (Rich-Edwards et al. 1999). This suggests, therefore, that while both low and high birthweight can increase subsequent risk of type 2 diabetes, the underlying mechanisms are likely to be different. Thus, for low birthweight babies, the increased risk is due to adaptations in the physiological systems that regulate glucose/insulin metabolism, while for higher birth weight babies it appears that the increased type 2 diabetes risk is secondary to increases in BMI and body fat mass. It also appears that the metabolic deficits in infants of obese mothers emerge very early in the life course, and are likely to be driven by an increased accumulation of body fat in utero. Catalano and colleagues conducted an elegant series of studies that established that the higher birth weight in infants of obese mothers was largely due to a greater accumulation of body fat. In one of these studies, Catalano also demonstrated that infants of obese mothers also have higher insulin resistance at birth, as measured by the HOMA-IR index based on measures of glucose and insulin in the umbilical

cord blood, and that this was also directly related to neonatal adiposity (Catalano et al. 2009).

The compelling epidemiological evidence linking maternal obesity to increases in the risk of obesity and its associated metabolic co-morbidities in the child has led to considerable efforts to understand the mechanistic basis of this relationship. This, in turn, has required the development of animal models of maternal obesity, to conduct the detailed physiological and molecular studies required, and to explore and test potential interventions to break the intergenerational cycle of poor metabolic health.

6.4 Animal Models of Maternal Obesity

Within the DOHaD field animal models have been widely used to provide evidence of the relationship between maternal diet during pregnancy and/or lactation and disease states in the resulting offspring (McMullen and Mostyn 2009; McMullen and Swali 2013; Langley-Evans 2015). Such studies have utilized a wide variety of species ranging from small rodents (rats and mice) through to large domestic species (sheep and pigs) and non-human primates. In addition to confirming the principle that modifying aspects of diet (restricting intakes of food or specific macro- or micronutrients) has a permanent programming effect on the developing fetus, these animal models provide a platform to examine the mechanistic basis of the programming. For example, studies of the long-term impact of maternal protein restriction in rats and mice have shown that offspring of protein restricted dams develop high blood pressure from an early age and that with ageing, males develop chronic kidney disease which leads to premature death (Langley-Evans et al. 1996, 1999; Ozanne and Hales 2004; Bellinger et al. 2006). The mechanistic basis of this has been shown to be an impairment of the formation of nephrons during organogenesis, which means that normal function cannot be maintained (Swali et al. 2011; Snoeck et al. 1990).

Perturbation of gene expression in response to maternal diet in the developing fetus is the primary driver of the renal impairment (Swali et al. 2011). Epigenetic modifications are also implicated in the long-term response to maternal diet and are thought to influence the adult response to diet and the environment (Lillycrop and Burdge 2015). Again, the offspring of pregnant rats fed a low protein diet provide a good example. In early adulthood these animals are resistant to obesity due to repression of key genes that regulate lipogenesis (SREBP-1c and fatty acid synthase), but with ageing this repression is lifted resulting in the development of an insulin resistant phenotype with increased adiposity (Erhuma et al. 2007).

For a long time the focus of animal models of early life programming was on maternal undernutrition, but with the recognition that maternal obesity is the most important contemporary issue in pregnancy nutrition, researchers have increasingly focused on models of maternal obesity. As will be described below this is not a straightforward process as rodents in particular are highly efficient regulators of

energy balance and it is challenging to induce an obese state. Moreover, rodent models of obesity typically depend on feeding a single food item with high energy content, whilst in contrast human obesity is the complex product of genetic predisposition, sedentary lifestyle and the consumption of a highly varied range of energy dense food and beverages.

6.4.1 High Fat Feeding

The typical approach to inducing obesity in rodents is to feed a high fat diet. The standard laboratory diets that are fed to rats and mice are specifically formulated to prevent excessive weight gain and typically contain 3–4% fat by weight (~15% fat as a percentage of energy). Experimental diets to induce obesity increase this to 30% or even as high as 60% energy as fat (Armitage et al. 2005; White et al. 2009). The typical response of the test animals is to overconsume for a relatively short period (around a week) and then to reduce food intake so that the excess energy consumption is minimised. Weight gains are often modest, but changes in body composition are generally consistent with obesity.

Despite the relatively subtle changes in the weight gain of the of mothers, feeding high fat diets during rat and mouse pregnancy elicits programmed responses in their offspring, which are not heavily dependent upon the level of fat. Armitage et al., fed rats a 20% lard diet and this led to increased aortic stiffness and endothelial dysfunction in resistance arteries of adult offspring (Armitage et al. 2005). A protocol with 40% of dietary energy provided as fat led to an insulin resistant phenotype and altered pancreatic morphology (Cerf and Louw 2014) and a similar protocol was associated with increased body weight, adipocyte hypertrophy, hyperinsulinaemia and hyperleptinaemia (Segovia et al. 2018). A number of studies have utilized maternal diets with 60% of dietary energy provided as fat and similarly show increases in fat mass and reduced insulin sensitivity (White et al. 2009), hyperglycaemia and raised blood pressure in adult offspring (Desai et al. 2014). Krasnow et al. showed that some of these changes were present in neonates exposed to high fat diets for a relatively short period in pregnancy and that the effects were occurring in the absence of maternal obesity and were therefore driven by dietary composition (Krasnow et al. 2011).

Although the high fat feeding protocols vary in terms of detail of the amount and type of fat that they use, it is clear that there are consistent programming effects on offspring cardiometabolic health. No clear mechanism has been identified to explain these effects, although there are suggests that maternal insulin resistance (Isganaitis et al. 2014) or hyperleptinaemia (Makarova et al. 2013) impact directly on fetal tissues. It has also been proposed that the maternal diet impacts upon the placenta and thereby modulates the transfer of hormones and substrates from mother to fetus. A diet delivering 60% of energy as fat fed to rats was shown by Stuart et al., to impact upon the placental transcriptome, with particular effects on angiogenesis and endothelial functions (Stuart et al. 2018).

In a variation on standard high fat feeding, Samuelsson and colleagues fed female mice a diet that consisted of an obesogenic formulation (10% simple sugars, 20% lard) combined with sweetened condensed milk (55% simple sugars, 8% fat) (Samuelsson et al. 2008). After a 6 week pre-mating feeding period the diet was maintained throughout pregnancy and the suckling period. Mice fed in this way increased body weight by approximately 25% in the pre-mating period and had developed hyperinsulinaemia, hyperglycaemia and hypercholesterolaemia by the time that their offspring were weaned (Samuelsson et al. 2008). The effects of exposure to this protocol on the offspring were significant, with increased abdominal adiposity, reduced muscle mass, impaired glucose tolerance, hyperinsulinaemia, elevated blood pressure and dysfunction of resistance arteries by 6 months of age (Samuelsson et al. 2008). The same protocol led to hyperphagia and the development of non-alcoholic liver disease (Kirk et al. 2009).

When working with small animal models of obesity, one of the challenges is determining whether programming effects on the offspring are a consequence of the maternal obesity or the diet used to induce the obesity. Similarly it is difficult to establish whether the critical timeframe in which the offspring are exposed to obesity lies in fetal development or during postnatal development. Shankar et al, addressed these issue by feeding non-pregnant rats with a liquid high-fat diet fed by intragastric cannulation (Shankar et al. 2008). This induced obesity and the animals were then transferred to a non-obesogenic diet for pregnancy. The resulting offspring were cross-fostered to lean dams at birth. Compared to control animals, the offspring of obese dams exhibited increased adiposity and insulin resistance, therefore demonstrating an effect of maternal obesity in the fetal period. This was independent of the maternal diet, which was in complete contrast to the diet dependency shown by Krasnow et al. (2011).

6.4.2 Cafeteria Feeding

While high-fat diets have been and are still widely used, there has been increasing recognition in recent years that high-fat diets are not entirely reflective of the composition of the typical diets consumed by humans. In particular, these diets fail to replicate the increased palatability created by combining fat and sugar as well as including a variety of different foods and their fatty acid composition is often markedly different to what is seen in human diets (Sampey et al. 2011). The limitations of laboratory high-fat diets have led to an increasing use of 'junk food' diets, also referred to as 'cafeteria diets' in studies investigating the impact of maternal obesity on offspring outcomes. These diets typically include a range of human junk foods and have been used extensively in rodents to model the effects of overconsumption of junk food in humans. In this context, 'junk foods' refers to any food which is high in fat, sugar and/or salt, energy dense, nutrient poor, as well as highly palatable, with the key feature being the lack of nutrient density in relation to energy content (Anderson and Patterson 2005).

While cafeteria diets are designed to replicate some aspects of poor quality Western-style diets, they are generally somewhat more extreme (i.e. with a higher caloric density and poorer nutritional quality) than the typical Western diets consumed by humans. Nevertheless, the use of junk food or cafeteria diets in animal research has been shown to produce a phenotype more comparable to the features of diet-induced obesity in humans than experimental rodent diets which are based on standard rodent feeds with the addition of extra fat or sugar (Johnson and Kenny 2010; Martire et al. 2013). Studies using junk food/cafeteria diets also take advantage of the ability of highly palatable foods to act as natural rewards, by activating central reward processing pathways.

Providing dams with cafeteria diets prior to mating is associated with substantial increases in daily fat, particularly saturated fat, intakes and induces a steady increase in both body weight and body fat mass. Four weeks of cafeteria diet feeding is typically associated with around a 20% increase in body weight and increased accumulation of both subcutaneous and visceral fat of a similar magnitude (Ong and Muhlhausler 2011; Akyol et al. 2009). Thus, dams fed on cafeteria diets are heavier and fatter during pregnancy compared to dams fed on nutritionally balanced chow diets. While the effect of the maternal cafeteria diets on maternal weight and fat gain is relatively consistent between studies, the impact on birth weight of the offspring is not. Some studies reporting reductions in birth weight of the offspring (Gugusheff et al. 2013a; Nivoit et al. 2009), while other studies have reported either increases (Akyol et al. 2009) or no differences (Ong and Muhlhausler 2011) in the birth weight of offspring of junk food dams compared to controls. This is likely to be a reflection of the different compositions of the cafeteria diets used in different studies and which particular foods the animals choose (or choose not to) consume. The protein content of the individual foods provided and consumed is likely to be of particular importance, since lower maternal protein intakes are typically associated with reduced birth weights, even when these occurs in conjunction with a higher overall caloric intake (Langley-Evans 2015). Unlike laboratory high-fat diets, cafeteria diets also tend to be deficient in a number of key micronutrients, and this nutritional deficit may also contribute to the poorer growth of fetuses of mothers consuming these diets.

In line with the different effects of maternal cafeteria diets on birth weight, the impact of maternal cafeteria diets on body weight of the offspring after birth also differs between studies. Some studies have reported an increase in bodyweight from birth and continuing throughout the life course (Kirk et al. 2009) while others have reported either no difference or reduced body weights at weaning in the offspring of junk food fed dams (Akyol et al. 2009; Bayol et al. 2007; Ferezou-Viala et al. 2007). The lower body weight at weaning in offspring exposed to a junk food diet is perhaps counterintuitive, given that the increased amount of energy being consumed by junk food dams in most of these studies. However, the deficits in pup growth may be related to reductions in the quality or quantity of the dam's milk, since maternal junk food consumption and obesity has been associated with impaired milk production/lactation performance in both humans and animals (Donath and Amir 2000) or impacts of the cafeteria diet on maternal care (Connor et al. 2012).

Despite differences between studies in the observed effects on offspring body weight, however, all studies have consistently demonstrated that offspring of junk food fed dams have a significantly higher percentage body fat at and after weaning compared to offspring of control dams (Ong and Muhlhausler 2011; Sun et al. 2012) (Fig. 6.4). Thus, irrespective of effects on body weight, perinatal junk food exposure is associated with increased fat deposition in early life. In addition, studies in which the offspring have been provided with access to a cafeteria or high fat/high sugar diet after weaning have demonstrated that offspring of junk food dams have an increased susceptibility to diet-induced obesity, and that this persists throughout the life course. The greater susceptibility to obesity following perinatal exposure to a cafeteria diet appears to be the result of programmed alterations to the expression of key adipogenic and lipogenic genes within key adipose depots. Increases in mRNA expression of the key lipogenic transcription factor Peroxisome Proliferator Activated Receptor gamma (PPARγ), in neonatal fat depots have been reported in pups of rat dams fed a junk food diet during pregnancy and lactation (Bayol et al. 2008). In another rodent study, mRNA expression of another major driver of fat deposition, insulin-like growth factors 1 (IGF-1) in the perirenal fat depot was increased in female offspring of junk food fed dams, in conjunction with an increased mass of this fat depot (Bayol et al. 2008). These studies suggest, therefore, that the programming of obesity by maternal cafeteria feeding is driven by altered expression of key regulatory factors within the adipose tissue, which persists after birth and which drives an increase in both the number of adipocytes that initially form, and the capacity of these individual adipocytes for storing lipid.

Maternal cafeteria diets have also been shown to programme alterations to both food intake and food preferences, in particular an increased preference for fat and sugar. Using the approach of monitoring the food selections of offspring who are provided with free access to both a cafeteria diet and nutritionally balanced chow, studies have demonstrated that both male and female offspring of cafeteria-fed dams consume a greater amount of junk food compared to their control counterparts, and this effect is observed from the time the animals are weaned until at least 3 months of age in these studies (Ong and Muhlhausler 2011) (Fig. 6.4). It also appears that the increased preference for junk food persists even when offspring are provided with a nutritionally-balanced diet after weaning, in an attempt to 'wash out' the effects of the earlier junk food exposure. This was demonstrated in a study in which offspring of dams fed a junk food diet during pregnancy and lactation were provided with a nutritionally balanced standard rodent feed from weaning until 6 weeks of age, after which their access to the cafeteria diet was reinstated and food preferences in all offspring monitored over the subsequent 14 days. The results clearly showed that both male and female offspring of junk food dams consumed significantly greater amounts of the cafeteria diet and more dietary fat and carbohydrate compared to controls (Bayol et al. 2010; Ong and Muhlhausler 2014). They also gained more weight and had a higher fat mass than control offspring, indicating a higher propensity to diet induced obesity (Bayol et al. 2010; Ong and Muhlhausler 2014). Similar results have been obtained in other rodent studies in which offspring of junk food fed dams were weaned onto a standard diet, but still exhibited an increased preference for fat/sucrose as adults (Vucetic et al. 2011; Teegarden et al. 2009). A study of offspring of dams

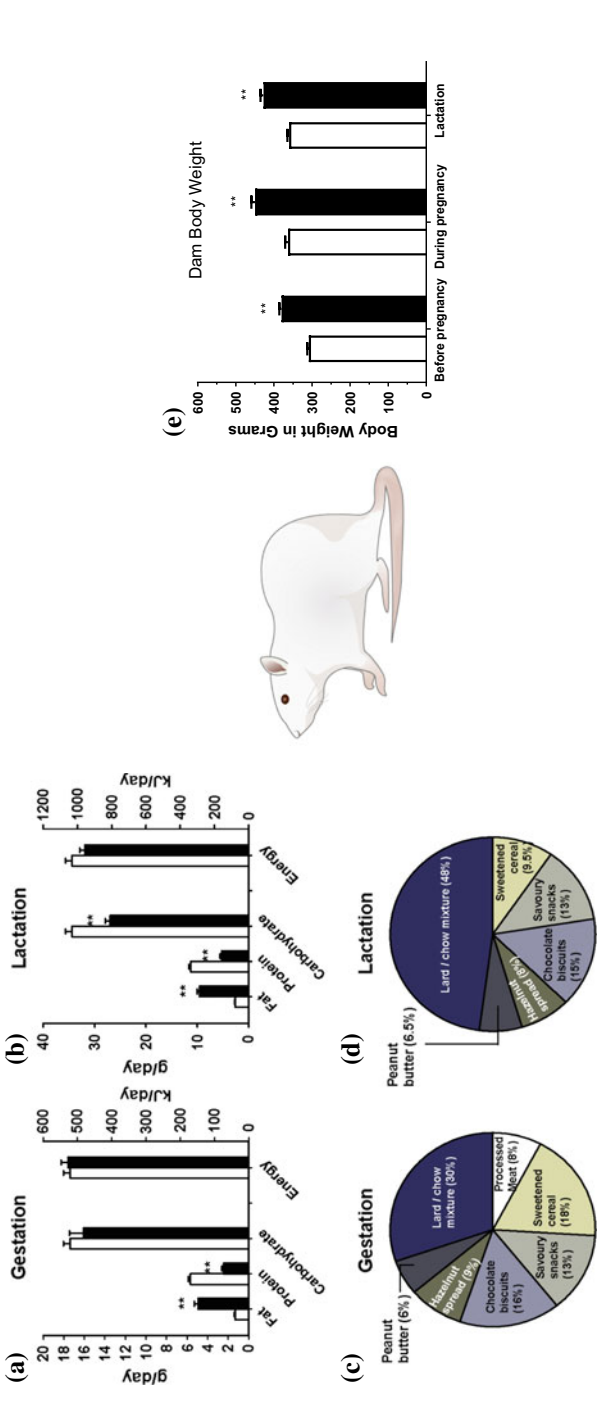

Fig. 6.4 Examples of typical energy intakes (**a**, **b**) and consumption of individual 'junk foods' (**c**, **d**) of dams during gestation and lactation when fed on cafeteria diets, and effect on dam body weight (**e**) at mating, during pregnancy and during lactation. Adapted from Ong and Muhlhausler (2011), Vithayathil et al. (2018)

exposed to a cafeteria diet during lactation also established that adult females took longer to achieve satiety in a behavioural satiety sequence experiment (Wright et al. 2011).

Further studies demonstrate that the alterations to food preferences are a consequence of altered gene expression within the central mesolimbic reward pathway, which governs the response to rewarding stimuli, including palatable foods (Nestler 2005). Activation of this pathway results in the release of endogenous opioids that bind to opioid receptors in the ventral tegmental area (VTA) in the midbrain and ultimately increases dopamine synthesis and the pleasurable sensation that characterises the response to reward. Termination of dopamine signalling occurs through active reuptake of dopamine through high affinity membrane carriers, known as dopamine active transporters (DAT) (Nestler 2005). Maternal cafeteria diets have been associated with a reduced expression of the mu-opioid receptor at weaning in both male and female offspring (Fig. 6.5). Importantly, this has functional consequences for opioid

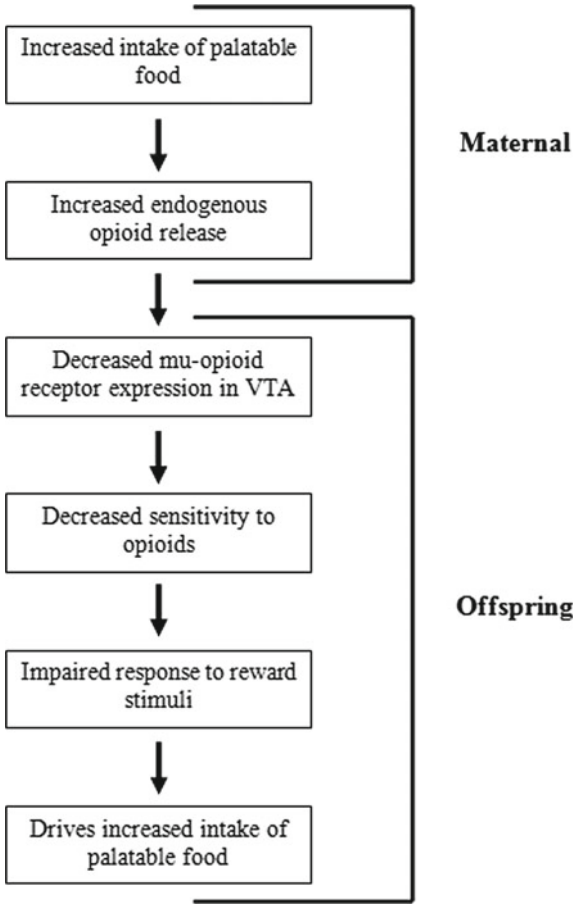

Fig. 6.5 Summary of proposed mechanism through which a maternal junk food diet could establish the preference for palatable food in offspring

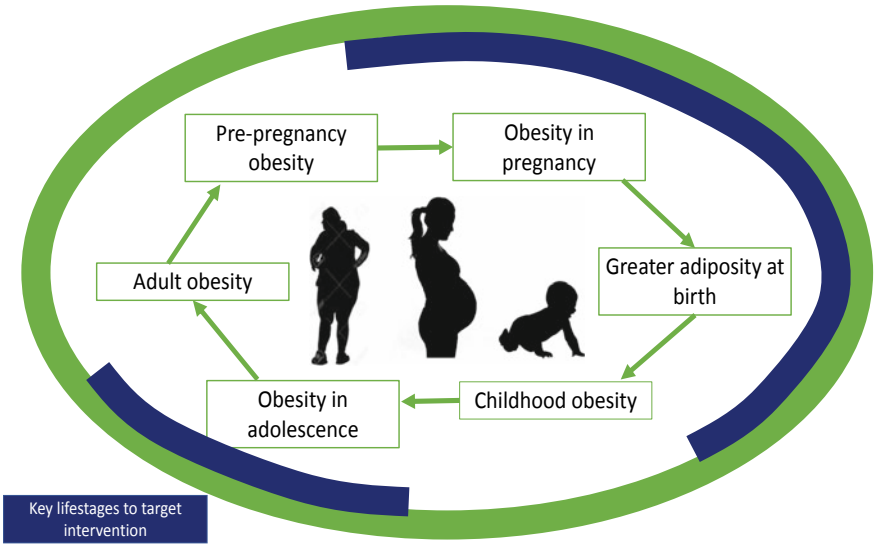

Fig. 6.6 The intergenerational cycle of obesity. Childhood obesity tends to track through to obesity in adulthood. In women, this compromises reproductive healthy and passes a predisposition to obesity and metabolic disorders on to the next generation

signalling in these offspring, and this is likely to contribute to their increased propensity to seek out and overconsume highly palatable diet (Gugusheff et al. 2013a). The lower mu-opioid expression does not appear to be present before weaning and may be more pronounced in females than in males (Gugusheff et al. 2016). When offspring of dams fed on cafeteria diets are given access to cafeteria diets after weaning, then different changes within the reward pathway are observed. At 3 weeks after weaning, expression of the mu-opioid receptor is increased and that of DAT is decreased in offspring of cafeteria fed dams compared to controls (Ong and Muhlhausler 2011). Feeding dams a cafeteria diet only during lactation has also been associated with perturbed hypothalamic dopamine metabolism (Vucetic et al. 2011). These observations imply that the effects of maternal junk food diet consumption on the reward pathway of the offspring may not be set at birth, but that reward pathway development is also susceptible to nutritional/environmental influences in early postnatal life, and this is an important area for future research (Fig. 6.6).

6.4.3 Clinical Studies

Clinical studies which evaluate the effect of maternal diet during pregnancy and breastfeeding on later food preferences in the child are complicated by difficulty of obtaining reliable food intake data and the confounding effects of shared food

environments/parental influences over child feeding behaviour. Nevertheless, a study in 5717 mother-child pairs and 3009 father-child pairs from The Avon Longitudinal Study of Parents and Children (ALSPAC), demonstrated a strong correlation between maternal fat intake during pregnancy and the child's preference for fat at 10 years of age (Brion et al. 2010). Importantly, the child's food preferences were not related to paternal diet at any time, or to maternal fat intake after pregnancy. In support of this, a smaller study involving 428 children from the United Kingdom showed that the children of obese parents had a higher preference for junk food and lower preference for vegetables than those born to lean parents (Wardle et al. 2001). Despite the paucity of studies conducted to date, the available data is consistent with the results from animal models, reinforcing the relevance of the cafeteria diet feeding model.

6.5 Obesity and Infant Feeding

6.5.1 The Role of Early Infant Nutrition: Breastmilk Versus Infant Formula

In addition to the intrauterine environment, nutritional exposures during the early infant period also have the potential to substantially alter short-and long-term health outcomes. This is powerfully demonstrated by cross-fostering studies in animal models, in which pups born to one dam are reared by a foster dam. This approach, which can only be achieved in animal models, allows researchers to study the separate influences of nutritional (and other) exposures during the fetal and suckling periods, without the potential for 'carry over' effects. Using this paradigm, researchers have been able to demonstrate that cross-fostering pups born to mothers fed an obesogenic diet before and during pregnancy onto a control mother with normal nutrition completely normalised fat mass at weaning, glucose tolerance and prevented hyperphagia (in males) and increased fat deposition (in females) when pups were provided with free access to an obesogenic diet in young adulthood (Vithayathil et al. 2018; Gugusheff et al. 2013b). Further evidence of the role of the lactation period in cardiometabolic programming is provided by studies by Wlodek and colleagues using a rodent model of fetal growth restriction. In these studies, growth restriction, induced by uteroplacental insufficiency in late gestation, programs sex-specific adult dysfunction including glucose intolerance, impaired first-phase insulin secretion, reduced nephron endowment and hypertension (Tare et al. 2012; Wadley et al. 2008; Wlodek et al. 2008). Uteroplacental insufficiency was also associated with impaired mammary development, reduced milk yield and altered milk composition in the mother, exposing the pups to a sub-optimal nutrition during suckling, as well as before birth (O'Dowd et al. 2008). However, when these growth restricted pups were cross-fostered onto mothers with normal milk quality and composition all these cardiometabolic organ deficits and dysfunction were prevented or ameliorated (Black et al. 2012; Siebel et al. 2008; Wlodek et al. 2007). These findings therefore imply

that, at least in rodents, the nutritional environment experienced during the lactation period is a more important determinant of short- and long-term cardiometabolic outcomes than exposure before birth.

In a human context, the most significant nutritional factor that influences infant growth and development is whether, and for how long, the infant is breast-fed. Infants who are fed on infant formula grow more rapidly in the early infant period than those who are exclusively breast-fed, and the results of systematic reviews and meta-analyses of studies in this area provide strong evidence that these infants also have a higher risk of overweight and obesity in childhood and adulthood (Arenz et al. 2004; Horta et al. 2015; Zalewski et al. 2017). The protective effect of breastfeeding against obesity in childhood appears to be related to the duration of any breastfeeding, rather than necessarily the duration of exclusive breastfeeding (Arenz et al. 2004). Thus, breastfeeding is protective against the development of obesity, and the benefits increase the longer the infant is breast-fed (Hassiotou and Geddes 2014).

There are several key differences between infant formula and breastmilk which have been suggested to explain the different growth trajectories of formula-fed and breast-fed infants. In terms of macronutrient content, infant formulas traditionally contained significantly higher levels of protein compared to breast milk. Protein intake during infancy has been positively associated with infant growth in observational studies, and thus this higher protein content is thought to be a major factor contributing to the accelerated growth rates of formula fed infants in the pre-weaning period (Tang 2018). The important role of protein was clearly demonstrated in the results of a randomised controlled trial by Koletzko and colleagues, in which 1138 healthy infants were randomly assigned to receive an infant formula containing either lower or higher levels of protein for the first year after birth (Koletzko et al. 2009). At 2 years of age, the weight for length z-score (a measure of adiposity in this age group) was significantly lower in infants who received the low protein formula compared to the high protein formula. The weight for length z-score in the lower protein formula group at 2 years were also not different from that of the reference group (infants who were exclusively breast-fed for the first 6 months) (Koletzko et al. 2009). These results strongly implicated the higher protein content of infant formulas in promoting excess growth and obesity and, together with evidence from other trials, has led to a reduction in the recommended levels of protein in infant formulas.

In addition to differences in protein content, however, there are other key differences in the composition of breast milk and infant formulas which have the potential to impact on short and long-term growth and body composition of the infant (Ballard and Morrow 2013). The presence of metabolic hormones in breastmilk, which are known to play a role in appetite control and energy balance in adults, is likely to be particularly important in this regard. Thus, the appetite-regulating hormone, leptin (which induces satiety), gut hormone ghrelin (which promotes food intake), as well hormones involved in promoting insulin-sensitivity (adiponectin) and insulin resistance (resistin) have all been identified in human milk (Ballard and Morrow 2013). While there has been limited research investigating the specific roles of these breastmilk compounds in regulating infant feeding behaviour, there is evidence that breast milk leptin concentrations are inversely related to infant weight gain in human

infants (Savino et al. 2009). Animal studies have also demonstrated that increasing leptin concentrations in the milk resulted in increased fat mass, hypertension and glucose intolerance in the adult offspring, suggesting the possibility of longer-term effects on infant cardiometabolic health (Hue-Beauvais et al. 2017; Briffa et al. 2017). The mechanism underlying the relationship between breastmilk leptin and infant growth is not entirely clear, however, since leptin does not appear to regulate feeding behaviour of infants in the short-term (Cannon et al. 2017). However, it is possible that leptin is important for promoting the development and expansion of neural networks in the appetite regulating pathway—something which has been demonstrated both in vitro and in rodents (Bouret and Simerly 2004). Adiponectin concentrations in breast milk have also been related positively to infant growth up to 2 years of age (Brunner et al. 2015).

Breastmilk composition is also highly dynamic, and changes both across lactation and even over the course of a single feed (Hassiotou and Geddes 2014). The change in fat content of the milk across a feed (increasing from the start to the end) is also thought to promote satiety, and the ability of the infant to regulate the volume of milk ingested during a breastfeed also assists them in developing their own internal satiety cues. In contrast, formula fed infants are often encouraged to consume a specific volume of formula at each feed, which may in fact be insufficient or excessive to meet that infant's requirements. The composition of formula also remains constant at each feed and across a single feed.

6.5.2 Obesity and Infant Feeding

Breastfeeding is widely recognised as the gold standard for infant nutrition, and several national and international health agencies, including the World Health Organisation, recommend that all infants, including infants of obese mothers, are exclusively breast-fed for the first 6 months after birth. Despite this, however, women who are overweight and obese are much less likely to breastfeed compared to women of normal weight (Donath and Amir 2000). Overweight and obesity during pregnancy, and the associated metabolic disturbances, affect the development of the mammary gland, and this can result in difficulties in both initiating and maintaining breastfeeding. Several studies have reported a delay in lactogenesis II (or initiation of copious milk production) in obese women, which is thought to be related to a combination of behavioural, physiological and anatomical factors. A lower proportion of obese women report the intention to breastfeed their infant, and this may have psychological effect on milk "let down" (Donath and Amir 2000). Obese women have also been shown to have a lower prolactin response to suckling, which can negatively impact on milk production (Rasmussen and Kjolhede 2004). The large breast size obese women may also contribute, since in some cases this can make it more difficult for the infant to achieve good attachment. In a retrospective analysis of ~2000 women in the 1995 Australian National Health Survey, mothers with a BMI > 30 were significantly less likely to initiate breastfeeding, and those that did breastfeed did so for a

significantly shorter period. In addition, these differences persisted after controlled for a range of sociodemographic factors, including maternal smoking (Donath and Amir 2000). These findings are supported by the results of a systematic review of around 15 studies, conducted in several different countries (Amir and Donath 2007). Thus, women who are obese are less likely to breastfeed and to breastfeed for a shorter duration than normal weight women, and this is likely to further contribute to the increased risk of obesity in infants of obese mothers.

There is also increasing evidence that breastmilk composition is altered in women who are overweight or obese. A number of studies have reported higher protein, leptin and insulin levels in breastmilk from overweight and obese women in comparison to women of normal weight (Andreas et al. 2014; Kugananthan et al. 2017). In one study, levels of both protein and leptin in human milk were shown to be positively correlated with maternal BMI and percentage body fat, independent of the stage of lactation (Kugananthan et al. 2017). These differences in breastmilk composition have the potential to impact on infant growth, fat deposition and the long-term propensity to overweight and obesity. Elevated protein content (Grunewald et al. 2014; Perrella and Geddes 2016) and adiponectin and ghrelin concentrations (Kon et al. 2014) in human milk have been associated with excessive growth in exclusively breast-fed infants. The link between specific factors in breast milk and infant growth is also supported by larger cohort studies, including a study of 641 mother-infant pairs in which levels of protein and fat in human milk samples at 4–8 weeks' post-partum were positively (in the case of protein) and negatively (in the case of fat) related to infant BMI/adiposity at 12 months (Prentice et al. 2016). Concentrations of insulin, leptin and adiponectin in human milk in early lactation have also been correlated with weight and body fat/fat-free mass of the infant up to 2 years of age (Brunner et al. 2015; Fields et al. 2017).

Maternal diabetes also affects milk composition, including the concentrations of glucose and insulin and fatty acid composition (Whitmore et al. 2012). Importantly, there is evidence that these changes in composition may impact on the risk of obesity in the offspring. This was demonstrated by a study in which infants born to mothers with diabetes were fed either their own mother's milk or banked milk (from women without diabetes) for the first 7 days after birth, and their intake of these respective milk sources was closely monitored in a hospital setting (Plagemann et al. 2002). This study demonstrated that the volume of their own mother's milk the infants had consumed during this period was positively correlated with their risk of overweight at 2 years of age (OR 2.47, 95% CI: 1.13–4.87) (Plagemann et al. 2002). In pregnancies complicated by both maternal obesity and maternal diabetes, the impact on mammary development, ability to initiate and maintain lactation and the composition of the milk is likely to be even more pronounced, and further studies are needed to investigate this in more detail.

6.6 Making a Difference

As the preceding sections of this Chapter have shown, the relationship between maternal diet, infancy diet, obesity and long-term health and disease is well-established. There is a growing understanding of the mechanisms which link early life factors to physiological and metabolic functions in adulthood (Langley-Evans 2015). Despite this knowledge of how early life programming determines lifelong health and disease, little has translated to the clinic in terms of providing individuals with either early warning of susceptibility (based on readily measurable biomarkers), or interventions to prevent adverse programming. In the latter case, it is reasonable to target maternal weight loss, or limiting pregnancy weight gain as a means of avoiding long-term consequences of maternal obesity.

Pregnancy is often considered to be a 'teachable moment' where women come into greater contact with health professionals and are open to advice on how to optimise their pregnancy outcomes. Mothers are generally more open to health education messages, and in particular messages relating to diet (Ritchie et al. 2010; May et al. 2014; Wilkinson et al. 2015) For example, May et al., reported that when health care providers initiated discussions about diet with pregnant women, those women were significantly more likely to improve their general health behaviours (May et al. 2014). As such, this stage of life should be a point at which we can intervene to improve the quality of nutrition and contribute to promotion of longer-term health.

At present, the main strategy for avoiding the detrimental impact of maternal obesity upon pregnancy outcome and the development of the fetus is largely focused upon reducing weight before conception. For example, in the UK the National Institute for Healthcare and Clinical Excellence recommends that health professionals should use any opportunity to provide women with a BMI of 30 kg/m^2 or more with information about the health benefits (for themselves and the baby they may conceive) of losing weight before becoming pregnant (National Institute for Healthcare and Clinical Excellence 2018). Weight loss is not recommended during pregnancy as this may impair fetal nutrition, which in itself could have an adverse programming effect. After conception the emphasis shifts to controlling antenatal weight gain, where there are well-defined guidelines on what is appropriate for women of different BMI at conception (Institute of Medicine 2009), but there is little evidence-based guidance that clinicians can offer to women on how to achieve that appropriate weight gain. Moreover the issue of body weight is a sensitive matter, so even initiating a conversation about limiting weight gain can be difficult without offending, patronising, or scaring women.

The advice currently available during pregnancy may not help with weight management. Information sources are focused on diet and physical activity advice with a view to risk management rather than positively framed health promotion. There is lots of advice on what not to eat and drink (due to high levels of certain micronutrients or potential contamination) and exercises to avoid (due to risk of injury). Although useful, this information doesn't empower women or convey how they will benefit from behaviour change, or address the underlying drivers of dietary and exercise

behaviours. Against this complex background, interventions designed to limit the effects of obesity during pregnancy have had a history of poor outcomes.

Isolated randomized controlled trials targeting weight gain in pregnancy as a primary outcome have reported some positive effects. For example, Thornton and colleagues ran an intervention in which women were prescribed a nutritional regimen and closely monitored over the last two trimesters of pregnancy (Thornton et al. 2009). In these women with a pre-pregnancy BMI > 30 kg/m^2, the intervention successfully limited weight gain and weight regain over the first 6 weeks after delivery. However, the broader literature in this area suggests that effects of interventions depend heavily on the nature of the intervention and how it is delivered (Thangaratinam et al. 2012). Interventions that specifically target maternal dietary change are generally effective in reducing pregnancy weight gain, and appear to prevent complications of pregnancy such as pre-eclampsia and GDM. Interventions which target physical activity also reduce pregnancy weight gain, but to a lesser extent than dietary interventions, but have no impact on pregnancy complications. Interventions which mix dietary change with physical activity appear ineffectual beyond small reductions in weight gain (Thangaratinam et al. 2012).

The largest examples of such an intervention are provided by the LIMIT study, in South Australia (Dodd et al. 2014a) and the UPBEAT study from the UK (Briley et al. 2014). LIMIT randomised 2212 women with BMI > 25 kg/m^2 to either standard care or a researcher-led lifestyle advice intervention focused on increasing physical activity and improving the quality of maternal nutrition. The intervention successfully improved maternal diet and activity (Dodd et al. 2014b), but had no impact on maternal weight gain and minimal effects on pregnancy outcomes (Dodd et al. 2014a). The UPBEAT trial, based in inner city populations in the UK, recruited 1555 women with BMI > 30 kg/m^2 to either take part in standard antenatal care or a behavioural intervention comprising weekly sessions with a health trainer focused on setting dietary and physical activity goals. The programme did not impact upon any of the primary outcomes (GDM and large-for-gestational age babies) but did limit gestational weight gain (Poston et al. 2015). As with all of the interventions that have been used to limit weight gain and obstetric complications, there has been no published follow-up of the infants born in UPBEAT or LIMIT beyond the first 6 months postnatal age, so it is unclear whether these interventions may have impacted upon fetal programming of later health and disease. Although there was evidence of reduced fat deposition in utero (Grivell et al. 2016) LIMIT reported that the intervention had no impact on anthropometric measures of body composition in newborns (Dodd et al. 2016) or 6-month-old infants (Dodd et al. 2018).

The complexities and challenges of delivering a successful antenatal programme to limit maternal weight gain are well-illustrated by the Bumps and Beyond programme from the UK (McGiveron et al. 2015). Bumps and Beyond was designed to work with women with severe obesity and was first implemented in the city of Lincoln. Among women whose pre-pregnancy BMI was >35 kg/m^2 a programme of 7 one-to-one sessions with a health educator, focused on improving dietary quality and increasing physical activity significantly reduced pregnancy weight gain and the prevalence of obstetric complications (McGiveron et al. 2015). When the same pro-

Table 6.1 The efficacy of interventions to limit the impact of maternal obesity may be context-dependent: Bumps and Beyond intervention

	Odds ratio [95% CI] for intervention versus non-intervention	
	Gestational diabetes	Pre-eclampsia
Nottingham intervention	1.97 [0.50–1.73]	4.96 [0.42–5.83]
Lincoln intervention	0.58 [0.32–0.94]	0.19 [0.05–0.82]

The Bumps and Beyond intervention was implemented in two cities in the English East Midlands. Nottingham is a culturally diverse city and the intervention was largely delivered by midwives and dietetic staff. Lincoln has a predominantly white Caucasian population and the intervention was delivered by healthcare assistants, with previous experience of delivering a smoking cessation programme. Data are shown as odds ratio {95% confidence intervals) comparing women who completed the intervention with those who did not attend

gramme was rolled out in Nottingham, but targeting women with BMI > 30 kg/m^2 there was no positive impact on either weight gain in pregnancy or obstetric outcomes (Table 6.1). The difference in success between the two sites may be due to ethnic and cultural differences in the population, the nature of the staff delivering the health education or the severity of the women's obesity and hence their openness to make lifestyle changes.

As described above, infancy is a life stage during which dietary exposures can exert a long-term impact on health. Breastfeeding has been demonstrated to confer protection against obesity and related metabolic disorders (Arenz et al. 2004; Horta et al. 2015; Zalewski et al. 2017; Hassiotou and Geddes 2014). There are widespread concerns about rates of breastfeeding in developed countries. In the UK, for example, whilst 81% of women initiate breastfeeding, the majority will switch to formula feeding within a few weeks after giving birth (McAndrew et al. 2010). The WHO recommends exclusive breastfeeding for the first 6 months of life (World Health Organisation 2010), but in the UK the exclusive breastfeeding rate is only 1%. Other countries fare rather better. For example in Sweden exclusive breastfeeding to six months is followed by 20% of women, and in most developing countries the practice is followed by up to 50% of mothers (World Health Organisation 2010; Yngve and Sjöström 2001).

Given the potential for breastfeeding to have long-term health benefits for pregnancy, it is desirable to increase breastfeeding rates, support women to continue breastfeeding for longer periods and to target breastfeeding to populations where risk is already higher. For example, the Bumps and Beyond intervention (McGiveron et al. 2015) was shown to successfully increase breastfeeding initiation among severely obese women from 49.5 to 75%. The most effective interventions for promoting and supporting breastfeeding tend to be based around social networks of peer support (Sudfeld et al. 2012; Kaunonen et al. 2012).

6.7 Conclusion

There is no doubt that nutrition during early life is able to programme long-term health and disease and is a key factor in the aetiology of cardiovascular and renal disease and metabolic disorders. Whilst effects of maternal undernutrition during pregnancy are already well understood, an equally significant quantity of data is emerging to demonstrate associations between maternal obesity and later disease.

Animal studies are providing a strong foundation for not just demonstrating the biological plausibility of associations between maternal obesity during pregnancy and long-term health of offspring, but also the mechanistic basis of those associations. Developing understanding of these mechanisms enables the identification of important developmental pathways play a causal role in disease and hence the future design of novel therapeutics for use in prevention and treatment of cardiovascular and metabolic diseases (McMullen et al. 2012). Furthermore, the discovery of genes, proteins and pathways which are involved in early life programming of disease will enable identification of biomarkers of programming which could be used as predictors of disease and harnessed in personalised medicine programmes.

Applying findings from mechanistic studies of early life programming to development of personalised medicine or novel drugs is, however, still very much a dream for future medicine. At present there is a global obesity crisis which is showing little sign of abating. Excessive body fat is, of course, harmful to the health of obese individuals, but the new evidence linking it to health in the next generation is more troubling and needs to be factored into global health policy and interventions in order to break the intergenerational cycle of obesity. Childhood obesity is a particular health concern as the growth in numbers of children who are overweight or obese is predicted to result in a sharp rise in obesity-related health conditions in adults. There is evidence that obesity can track from childhood through to adulthood, but it is clear that if the progression from being an obese child to an obese adult can be prevented, there are no lasting health effects of childhood obesity (Lloyd et al. 2010, 2012). Adolescence appears to be an especially critical time in the setting of long-term weight and metabolic profile (Lloyd et al. 2010, 2012) and is also an ideal time to target interventions that are of relevance to reproductive health. The evidence summarised in this Chapter should therefore make a compelling case for governments and global health policymakers to focus on the broader significance of obesity in young women.

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Chapter 7
The Interplay Between Dopamine and Environment as the Biological Basis for the Early Origins of Mental Health

Barbara Barth, André K. Portella, Laurette Dubé, Michael J. Meaney and Patricia Pelufo Silveira

Abstract A vast amount of evidence has shown that exposure to prenatal or early postnatal stress can impact the developing individual, increasing the susceptibility to several unfavorable outcomes later in life. It seems that these adversities induce adaptations, altering the metabolism to favor survival at critical periods, but at the expense of the individual's health as a trade-off. These exposures increase the risk for non-transmittable diseases like type II diabetes, but also psychiatric conditions like ADHD or depression, and these common developmental risk factors suggest overlapping underlying mechanisms. In this chapter, we will explore the idea that the co-morbidity between conditions such as ADHD and metabolic dysregulation occurs, in part at least, because of the influence of metabolic neuroendocrine signals on mescorticolimbic dopamine neurons, especially in individuals exposed to early life adversity. These neurons regulate cognitive-emotional states, notably impulsivity, and reward-based decision-making, thus defining psychiatric phenotypes and contributing to intensify behaviors that in turn promote metabolic disturbances. We will also apply the concept of differential susceptibility, an evolution-informed theoretical framework, to the understanding of the role of dopaminergic pathways on the interplay between environmental adversity, altered metabolism and risk for disease across the life span.

B. Barth · M. J. Meaney · P. P. Silveira (✉)
Integrated Program in Neuroscience, McGill University, Montreal, QC, Canada
e-mail: patricia.silveira@mcgill.ca

B. Barth · P. P. Silveira
Department of Psychiatry, Faculty of Medicine and Ludmer Center for Neuroinformatics and Mental Health, McGill University, Montreal, QC, Canada

A. K. Portella · L. Dubé
Desautels Faculty of Management, McGill Center for the Convergence of Health and Economics, McGill University, Montreal, QC, Canada

M. J. Meaney · P. P. Silveira
Douglas Hospital Research Centre, 6875 Boulevard LaSalle, Montreal H4H 1R3, QC, Canada

M. J. Meaney
Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research (A*STAR), Singapore, Singapore

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7.1 Introduction

The knowledge that conditions existent during the perinatal period have persistent effects on individuals' functioning, health and disease patterns across the lifetime is well established in the literature (Silveira and Manfro 2015; Sørensen et al. 1997). This is evident as the decline in neonatal mortality, especially since mid-1960's, took place (David and Siegel 1983), resulting from the improvement of perinatal medical care and subsequent reduction in mortality rates (Kessel et al. 1984). One large study from Finland, that covered 96% of all children born in the region in 1966 and followed them up until 14 years of age, is one of the first consistent retrospective studies to demonstrate that perinatal conditions have persistent effects on children's neurodevelopment. Among the 12,058 participants, 411 children were considered as having low birth weight (< 2500 g) and this group had a higher incidence of cerebral palsy, epilepsy, severe hearing defects and educational problems (Rantakallio and von Wendt 1985). A Danish retrospective cohort study involving 4300 participants born between 1973 and 1975 demonstrates a relationship between low birth weight and poor cognitive performance (Sørensen et al. 1997). Still along those lines, a study using data from 357,768 Swedish military conscripts born between 1973 and 1981 describes that being born small for gestational age (SGA) increases the risk for subnormal intellectual and psychological performance in males (Lundgren et al. 2004), even after adjusting for maternal and socioeconomic factors (Bergvall et al. 2006). A more recent example comes from a 240,351-sample size Western Australian population-based cohort study reporting a U-shaped association between fetal growth and the risk for intellectual disability (Leonard et al. 2007).

Besides the early evidence related to cognitive performance, other studies have identified that adversity such as exposure to stress, infections or malnutrition in early life compromises the quality of growth and development, and increases the risk for chronic, non-transmittable diseases in the offspring in the long term. For instance, increased rates of coronary heart disease and cerebrovascular disease later in life have been observed in subjects born with poor fetal growth (Barker et al. 1989). Poor fetal growth has also been associated with glucose intolerance, less capacity to secrete insulin and increased risk for type II diabetes (Barker et al. 1993; Phipps et al. 1993). Early adverse conditions exposure also increases the individuals' risk for developing attention deficit hyperactivity disorder (ADHD), schizophrenia and major depression (Lahti 2014; Murphy et al. 2017).

It is thought that these effects could be connected to the concept of developmental plasticity, defined by a critical window during development when a system is plastic and sensitive to the nutritional, hormonal and metabolic environment. For most organs and systems, the critical period occurs in utero and early postnatal life, and may give rise to a range of different physiological or morphological states in

response to a variety of conditions existent during development (Barker et al. 1989). In the presence of adversity, the fetus/newborn responds through specific adaptations, increasing allocation of energy to favor the brain, heart and adrenal glands development, but reducing the blood flow to other organs and producing lifelong changes in blood pressure and metabolism (Visentin et al. 2014). Variability and plasticity of physiological and behavioral responses help the growing organism to adapt effectively to the uncertainty of later environmental conditions. This plasticity allows the emergence of phenotypes that are better suited to their surrounding conditions, being more efficiently adapted than it would be possible if the exact same phenotypes were to be produced for all environments. But this process is done at the expense of the individuals' health (Barker 2004). Indeed, healthy subjects born at term with poor fetal growth show impaired vascular endothelial function already in infancy (Rich-Edwards et al. 2005; Davis et al. 2017), disturbed vascular regulation, premature stiffening of the carotid artery (Martin et al. 2000), and left ventricular hypertrophy (Wang et al. 2017). Early life adversities impose a change in the individual's developmental trajectory, altering its metabolism and susceptibility to several outcomes.

Although studies on the influences of environmental variation during the perinatal period on development have mainly focused on being born small for a given gestational age (SGA) or being exposed to intrauterine growth restriction (IUGR) as indicators of prenatal adversity, this concept of early life adversity can be broader, and not necessarily involving differences in fetal growth, also impacting an infant's development and wellbeing (Silveira et al. 2017). The developmental origins of health and disease (DOHaD) hypothesis suggests that intrauterine signals affect the individual predisposition to specific health outcomes, thus shaping individual differences in the risk for chronic illnesses across the lifespan (O'Donnell and Meaney 2017).

Exposure to early life adversity increases the risk for non-transmittable diseases like type II diabetes, but also psychiatric conditions like ADHD or depression, and these common developmental risk factors suggest overlapping underlying mechanisms. Although the co-morbidity between metabolic disease, poor cognitive performance and psychiatric disorders is well-established, the mechanisms are poorly understood. In this chapter we will explore the idea that the co-morbidity between conditions such as psychiatric outcomes and metabolic dysregulation occurs, in part at least, because of an influence of metabolic neuroendocrine signals on the development of the mescorticolimbic dopamine (DA) pathway. The neurons in this pathway regulate cognitive-emotional states, notably impulsivity, and responsivity to environmental challenges through reward-based decision-making, thus defining behavioral phenotypes that in turn can contribute to promote metabolic disorders.

7.2 The Dopaminergic System

Dopamine (3-hydroxytyramine; DA) is a catecholamine neurotransmitter that is synthesized in the brain, as DA does not pass through the blood brain barrier. Instead, its

precursor amino acid L-3,4-dihydroxyphenylalanine (L-DOPA) crosses the blood-brain barrier and is converted into DA. Tyrosine hydroxylase converts tyrosine to L-DOPA, that in turn is converted into DA by aromatic amino acid decarboxylase (AADC). DA is then transported by VMAT (vesicular monoamine transporter) to inside the neurotransmitter vesicles. Vesicles containing DA move towards the presynaptic membrane as an electrical impulse arrives at the terminal and the vesicle fuses with the presynaptic membrane, releasing the neurotransmitter into the synaptic cleft. There, DA can bind to specific proteins called dopamine receptors on the membrane of the postsynaptic neuron. Dopamine transporter (DAT), which is a membrane-spanning protein, pumps DA out of the synaptic cleft back into the presynaptic cytosol and vesicle. Dopamine reuptake by DAT provides the primary mechanism through which DA concentration in the synaptic cleft is balanced. Moreover, DA receptor D2 acts as a presynaptic auto receptor and also plays a role in regulating the dopaminergic system by providing feedback inhibition. This controls cell firing, and the synthesis, release, and uptake of DA (Ford 2014; Beaulieu and Gainetdinov 2011; Brady 2011).

There are four distinct pathways of DA signaling. The tuberoinfundibular pathway refers to a group of DA neurons in the arcuate nucleus of the hypothalamus that projects to the median eminence. There, DA is released into the portal vessels, acting to inhibit the secretion of prolactin from the anterior pituitary. The nigrostriatal pathway originates in the substantia nigra, and projects to the dorsal striatum. Degeneration of these projections has been shown to cause Parkinson's Disease, impairing planning, initiation, and control of movements, and for that reason this area is thought to be implicated in motor activity (Hopes 2016). The mesocortical pathway, and the mesolimbic pathway also referred to the mesocorticolimbic system projects from the midbrain to the striatum, limbic and frontal cortical regions. Particularly the mesocortical pathway projects from the ventral tegmental area (VTA) to the frontal and temporal cortices, especially the anterior cingulate, entorhinal, and prefrontal cortices. The mesolimbic pathway also originates in the VTA but instead innervates the ventral striatum, including the nucleus accumbens. This mesocorticolimbic system is involved in cognitive-emotional states, namely reward-based decision-making, and the experience of pleasure, impulsivity, concentration and executive functions (Bear et al. 2016; Dunlop and Nemeroff 2007) and for that reason it is the focus of this chapter.

Alterations on the dopaminergic pathways can lead to increased sensitivity to reward and impulsivity (Bear et al. 2016) and consequently to poor decision-making processes, prompting non-adaptive behaviors such as addiction and altered eating behavior (Wilson 2010; Loxton and Tipman 2017; Robbins and Clark 2015). Evidence deriving from the fact that drugs including amphetamine and methylphenidate, known for being dopamine enhancers, improve behavioral symptoms of most children with ADHD, suggests that the DA systems plays a role on the onset and maintenance of this condition. In fact, DA system genes were described as candidate genes for the well-established heritability of ADHD (Li et al. 2006). In the field of schizophrenia research, it is understood that an abnormal neurochemistry related to presynaptic striatal hyperdopaminergia is the common pathway that explains the

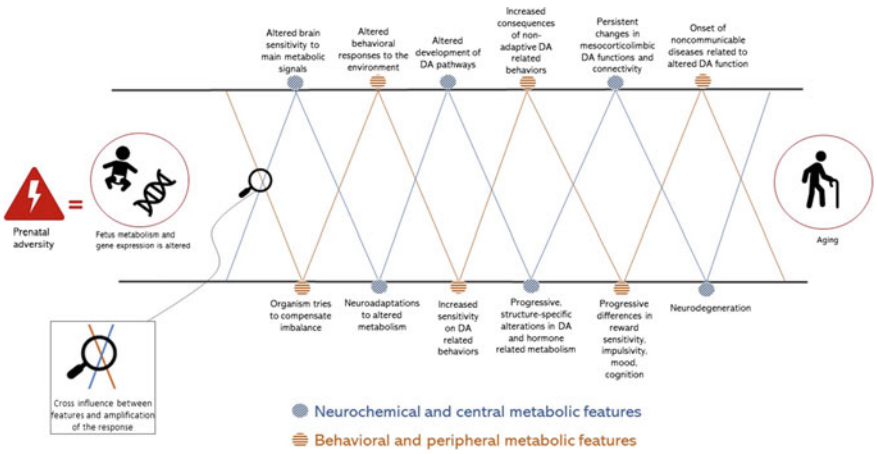

Fig. 7.1 Theoretical framework on the interplay between environmental adversity, altered metabolism and DA altered function across development

disease symptoms (Howes and Kapur 2009). Finally, DA is thought to play a role, at least to some extent, in major depression symptoms, since impairments in motivation, psychomotor speed, concentration and anhedonia are all related to the disorder, and also regulated in part by the dopaminergic systems (Dunlop and Nemeroff 2007). Thus, DA dysregulation seems to be the basis of several neurological and behavioral disorders.

Besides that, there is evidence that both prenatal and post-natal adversity are linked to alterations in the dopaminergic pathways, in humans as well as in animal models (Howes and Kapur 2009). DA pathways seem to play a role on the interplay between the influence of the environment and the development of non-communicable diseases during the life-course (see Fig. 7.1).

7.3 The Development of Dopaminergic Pathways

There is evidence that the development of DA pathways is prolonged, reaching maturation at around early adulthood (Reynolds et al. 2018) alongside the maturation of the pre-frontal cortex (PFC). DA is one of the most important PFC neuromodulators, given its role on reward-based decision making. Studies performed in animal models have quantified the density of dopaminergic afferents to the pre-frontal cortex (PFC) during development, describing that it begins as early as the embryonic development, starting with axon extensions from the VTA and increasing during neonatal, juvenile and adult periods (Willing et al. 2017).

In humans, mesocorticolimbic DA axons continue to grow during adolescence towards the PFC (Hoops and Flores 2017) and there is evidence that netrin-1 recep-

tor DCC is responsible for coordinating this maturation. Work by Reynolds et al. (2018) in animal models has demonstrated that DCC acts as a guidance cue receptor, controlling the extent of growth by determining the axons' final target in the PFC. Changes in this growth trajectory can significantly modify PFC structural and functional development (Reynolds et al. 2018). Interestingly, these axons are especially vulnerable to environmental effects (Hoops and Flores 2017), increasing the individuals' susceptibility to develop several disturbances when exposed to stress or adversity during development.

In conclusion, DA pathways, especially the mesocorticolimbic pathway, finish their development later in life when compared to other neurotransmitter systems, suggesting that this pathway is susceptible to the influence of the environment for a longer period of time, being an obvious candidate for a biological mechanism involved in the programming by prenatal and postnatal adverse conditions. This idea strongly corroborates with the concept of DA genes being considered as "plasticity genes" (see below) and points the importance of studying this system when investigating the impact of environmental adversities on neurodevelopment.

7.4 Early Life Adversity: Beyond Low Birth Weight

As mentioned above, environmental conditions existent during early developmental stages have a dramatic influence on the health/disease patterns of the individual over the life course. The measure of low birth weight has been used in the literature as a marker of exposure to fetal adversity, although it is known that fetal adversity not necessarily impacts birth weight. For instance, the presence of multiple psychosocial stressors during pregnancy is associated with higher systolic and diastolic blood pressure in children aged 5–7 years (van Dijk et al. 2012). Higher prenatal stress during the first 20 weeks of pregnancy is a predictor, among adults, of mood dysregulation, lower overall gray-matter volume, and lower gray-matter volume in mid-dorsolateral frontal cortex, anterior cingulate cortex, and precuneus (Mareckova 2018). Social adversity during the prenatal period is a risk factor for elevated inflammation in adulthood, independently of the exposure to adversities during childhood (Slopen et al. 2015). Fetal exposure to maternal depression during pregnancy also has persistent effects on immune function of the young adult offspring (Plant et al. 2016). Despite the large amount of evidence, studies exploring the relationship between prenatal adversity and risk for disease in the offspring focus either exclusively on the prenatal social environment (Slopen et al. 2015), maternal mental health (O'Donnell et al. 2014; Pearson et al. 2013) or biological risk (Lahti 2014; Raikkonen et al. 2008; Laursen et al. 2007), but these conditions are highly inter-correlated in the lives of children, and have yet to be considered in a cumulative manner.

To tackle the issues described above, Silveira et al. (2017) conducted a study in two community birth cohorts and created a cumulative prenatal adversity score, accounting for information on health during pregnancy, birth weight, gestational age, income, domestic violence/sexual abuse, marital strains, as well as maternal smoking,

anxiety, and depression. As a result of the effort to improve the representation of the early adversity environment, they were able to demonstrate that the cumulative adversity score was a better predictor of neurodevelopmental outcomes than any single factor in isolation. The knowledge about the interplay between components that represent an adverse environment is crucial to design better and more precise preventive measures and interventions to improve neurodevelopment and physical health in the general population.

7.5 Genetic Studies Inform About Biological Functions

Genetic studies contribute vastly to our knowledge of the etiology and mechanisms underlying different diseases. Although association studies between variation in the environment, human behavior and specific outcomes can inform about risk factors, they do not apprise which biological processes are implicated. Genetic studies enlighten about how gene expression can modulate these associations and contribute to the understanding of the link between the functionality of a system and a specific outcome.

Earlier studies using genes to better understand the etiology and mechanism of a particular disease involved candidate genes, that focused on testing the association between a specific variant (e.g. a single nucleotide polymorphisms, SNP) and a given disease (Auer and Stitziel 2017). Those studies made a significant impact in the scientific community, but also raised questions on the extend of the contribution of this method to complex questions, including the onset of noncommunicable diseases such as obesity. Considering the millions of existing SNPs on the human genome, it is very unlikely that a single SNP could explain much of the variation on the risk to develop a specific condition, or on a behavioral trait. It is now clear that complex phenotypes such as obesity and mental conditions arise from the cumulative influence of multiple genetic variants (Lee et al. 2011; International Schizophrenia et al. 2009).

This shift in the understanding of disease risk, together with advances in genomic technologies, has led to larger and better powered genome-wide association studies (GWAS) that have permitted large scale analyses of common markers, by associating SNPs inside a gene with a specific outcome. For example, in a large sample size study conducted to find susceptibility loci for coronary artery disease (CAD), SNPs significantly associated with this outcome were able to explain approximately 10.6% of CAD heritability (Consortium 2013). The use of methods of genomic risk profiling is consistent with the idea that the genetic contribution to a certain condition is derived from a combination of small effects from many genetic variants. To consider the effects of many SNPs, a new concept of polygenic risk score (PRS) was introduced. The PRS summarizes individual's genetic risk for a specific condition (Hachiya et al. 2017), characterizes subject's response to therapy (Natarajan et al. 2017), or describes variation in specific measures associated with a disease. A polygenic risk score is calculated for each subject in the target sample as a sum of the risk alleles count, weighted by the effect size described in a discovery GWAS

(Wray et al. 2014; Dudbridge 2013). The specific alleles that compose the PRS also come from GWAS studies, like the CAD study mentioned above, that have remained significant after multiple comparison corrections. As an example, Scott et al. (2012) performed a GWAS for fasting insulin, adjusting for age, sex and body mass index (BMI), compiling data from 108,557 individuals from 56 studies. They demonstrated that loci associated with fasting insulin concentrations also show an association with lipid levels and fat distribution, suggesting a relationship between genetic variation in these loci and cardio-metabolic risk. GWAS studies have identified several variants associated with complex traits, although still leaving questions open, especially regarding the mechanisms involved in these associations. This approach neglects the fact that genes operate in networks and code for precise biological functions in specific tissues. Besides that, since the significant SNPs come from GWAS studies, only the ones that "survive" calculations to adjust for multiple comparisons will end up being recognized as significant, resulting in strong genetic main effects and leaving no space for the potential environmental variability contained in the sample.

More recently, new methods are accounting for mechanisms that can further explain variations in biological processes associated with unfavorable outcomes. For example, gene expression is composed by three main constituents: a genetically determined component, a trait-related component, and a component determined by the remaining factors, including the environment (Gamazon et al. 2015). To represent the genetically determined component of gene expression, these authors created an algorithm called Predixcan, proposing a gene-based association method that directly tests the molecular mechanisms through which genetic variation affects phenotype. This is done by estimating the amount of gene expression that is determined by an individual's genetic profile and correlating this biologically imputed gene expression with the trait of interest. More specifically, genotype information from a sample of interest is compared to a reference dataset that has both genotype and gene expression information, then a tissue-specific prediction model involving a machine learning algorithm is used to estimate the genetically determined component of gene expression from the subjects of the target sample (Gamazon et al. 2015). One example of the use of this method can be found on the work by Huckins et al. (2017) in which data from 40,299 schizophrenia cases and 65,264 47 matched controls were used to predict gene expression levels in 12 brain regions. They found 413 genes associated with schizophrenia across 12 brain regions, being the Dorsolateral Prefrontal Cortex (DLPFC) the one with higher number of associated genes.

Although the focus on the function of a single gene is interesting, it is known that genes operate in networks, and code for precise biological functions in specific tissues. We recently developed a novel approach to genomic profiling, informed by biological function, and characterizing gene networks based on the levels of co-expression with a determined gene in a specific tissue. This genetic score is called ePRS (Silveira et al. 2017; Hari Dass et al. 2019; Miguel et al. 2019). The principle of gene networks considers that gene expression is co-regulated by other genes, and consequently genes involved in the same network are expected to have similar expression profiles (Gaiteri et al. 2014). Analyzing genomic data through gene sets defined by functional pathways represents a potentially powerful and biologically-

oriented link between genotypes and phenotypes (Ramanan et al. 2012). Recent advances in this field comprise the assessment of spatial and temporal transcriptomes in the human brain by the BrainSpan (Miller et al. 2014) and HBT (Human Brain Transcriptome) datasets (Kang 2011) and the integration of genetic variation with gene expression in the brain by the Genotype-Tissue Expression (GTEx) project (Consortium 2013; Lonsdale et al. 2013). Using these online databases, matrices of co-expression can be generated, and the genetic variation and association with gene expression in the genes that compose the network can be used to reflect the function of the machinery involved in that biological process. An example of the application of such method is the work by Silveira et al. (2017). A tissue-specific (hippocampal) ePRS score was created for the SLC6A4 or serotonin transporter gene, which has been related to the responsivity to environmental adversity and effects on psychopathology across the life span. Using a cumulative environmental score of prenatal adversity, they searched for interactions between the SLC6A4 ePRS and environmental quality on neurodevelopmental and socio-emotional outcomes. The ePRS reveled significant interaction effects that were not identified with the use of candidate polymorphism 5-HTTPLR variant.

These new genomic approaches integrate information from molecular neurobiology with GWAS technology to develop biologically-informed polygenic scores based on gene co-expression or genetically predicted gene expression in specific brain regions, creating novel measures to identify vulnerability for childhood behavioral phenotypes that predict later neuropsychiatric conditions in community-based samples, and gene network by environment interactions.

7.6 Diathesis Stress Versus Differential Susceptibility

As shown on the previous section, genes modulate the cellular response to environmental variation. Although discrete and potentially differential gene by environment interactions are difficult to be detected using simple association studies, some theoretical paradigms guide the understanding of these relationships. The dominant paradigm on gene by environment interaction studies is based on the diathesis-stress hypothesis, which states that some individuals are more vulnerable than others to the negative effects of the environment (e.g., insensitive parenting, childhood maltreatment, poverty). However, this theoretical framework does not consider variations in resilience, for instance, raising an intriguing question on why would natural selection craft an individual to be more susceptible only to the negative effects of the context?

The alternative differential susceptibility hypothesis (Belsky 1997; Boyce and Ellis 2005), firstly observed in psychiatric-genetic research (Belsky and Pluess 2013), suggests that individuals vary both in relation to how much they are negatively affected by environmental adverse events (Caspi et al. 2002, 2003) and how much they are positively influenced by the provision of resources and support (Blair 2002) or the simple absence of contextual adversity (Belsky et al. 2009). In fact, it has been proposed that individuals should vary in their susceptibility to environmental

influences (Belsky 1997) based on an evolutionary perspective, where the future is uncertain. In order to maximize the probability of survival/reproduction, natural selection would favor systems/genes that are able to respond to both poor as well as rich environmental conditions, so that the offspring would be "hedging their bets" against an unclear future.

This theoretical framework has advantages since it considers a broader spectrum of environmental influences. One applicability of this concept can be seen on the proposed idea of "plasticity genes", in which DA is one of the main "plasticity systems" that may have been set up as a form of preparation of the individual to vary its responses according to diverse environmental conditions (Belsky et al. 2009). This enhanced sensitivity to the environmental context, therefore, increases the range of phenotypic possibilities, and from the research stand point, moves the interest not only to specific vulnerabilities, but to identify both the several patterns of environmental sensitivity, and the significant factors involved in the manifestation of these patterns (Moore and Depue 2016).

A study from our group showed, for instance, that girls carrying the 7-repeat allele of the *DRD4* gene and living under adverse socioeconomic conditions have higher fat intake, while those carrying the same gene variant but living in a healthy environment have lower fat intake when compared to non-carriers (Silveira et al. 2016). This suggests that the previously considered obesity "risk allele" (DRD4 7-repeat) (Levitan et al. 2004) in fact determines openness to environmental modification and/or intervention. A metanalysis conducted with data from 15 studies also revealed results that corroborate the idea of dopamine genes functioning as "plasticity genes". Bakermans-Kranenburg and Van Ijzendoorn (Bakermans-Kranenburg and Van Ijzendoorn 2011) described that children with a larger number of less efficient dopamine-related variants performed worse in negative environments but also profited the most from positive conditions, in comparison with children with a lower number of these variants.

Shifting from a "vulnerability" to a "differential susceptibility" paradigm not only enables the study of the full range of negative and positive G versus E interactions, but also has the potential to bring more impactful and targeted interventions to improve health outcomes of the individuals who are also the most vulnerable.

7.7 Evidence of Dopamine as the Biological Bases of Early Life Programming

As mentioned above, early life adversity could include many different types of adversities happening pre or postnatally. In the past, we have studied the effects of intrauterine growth restriction on behaviors involving sensitivity to reward and impulsivity in different human cohorts. We have shown, for instance, that poor fetal growth is linked to alterations in the hedonic responses to sucrose as early as the first day of life in human newborns (Ayres et al. 2012), a finding corroborated by Rotstein et al. (2015)

and Laureano et al. (2015). We also demonstrated that 3-year old girls born SGA are more impulsive towards a sweet reward using the Snack Delay Task (Silveira et al. 2012), a behavioral feature that is associated with fat preferences and higher body mass index later in childhood (Silveira et al. 2012). Similarly, another study demonstrated that SGA children at 10 years of age have significantly higher percent energy intake derived from fat when compared to controls, which is associated with higher waist circumference, insulin and HOMA-IR levels (Crume 2014). Our group showed that adult women born with severe growth restriction have a higher intake of carbohydrates, and increased carbohydrate to protein ratio in their diets (Barbieri et al. 2009). The association between being born low birth weight and having specific food preferences later in life, initially described by our group (Barbieri et al. 2009; Disease 2006), was later replicated in several different human cohorts around the world (Kaseva et al. 2013; Stein et al. 2009; Lussana et al. 2008; Perälä et al. 2012; Kampmann et al. 2018; Ester et al. 2019).

Although consistent, the studies in humans are correlational. "Bedside-to-Bench" translational approaches with relevant animal models hold the promise of (1) establishing causal relations and (2) identifying underlying mechanisms. The latter is critical for developing objective measures of risk at the level of the individual child. We have explored the long-term effects of poor fetal growth using a rat model based on caloric restriction of 50% initiated at gestational day 10 (Desai et al. 2005). Pups from food restricted and controls dams are fostered by control dams within 24 hours of life, which ensures growth restriction only during the fetal period (Alves et al. 2015; Cunha et al. 2015; Dalle Molle et al. 2015). The experiments reveal a higher preference for palatable foods in food restricted (FR) animals with a choice between standard and palatable chow (diet with higher contents of sugar and fat) (Dalle Molle et al. 2015; Alves et al. 2015). The behavioral phenotype of increased palatable food consumption in FR rats is comparable to that described in humans (Ayres et al. 2012; Silveira et al. 2012; Barbieri et al. 2009; Portella et al. 2012; Silveira 2014; Portella and Silveira 2014; Dalle Molle and Silveira 2015; Laureano 2015; Reis et al. 2016). Following our findings of altered taste reactivity to sucrose in human newborns (Ayres et al. 2012), we also saw that FR rat newborns demonstrate more persistent hedonic responses to sucrose when compared to control pups (Laureano et al. 2016) already in the first day of life. FR animals also have reduced conditioned place preference to sweet food when compared to controls (Dalle Molle et al. 2015), which combined with the behavioral profile described above strongly suggests that FR affects the functioning of the dopaminergic mesocorticolimbic pathway, closely associated with appetite regulation and eating behaviours.

Indeed, we described robust alterations in tyrosine hydroxylase (TH), an enzyme involved in DA synthesis, as well as phospho-tyrosine hydroxylase (pTH) levels in the NAcc of FR rats (Dalle Molle et al. 2015), and in the orbitofrontal cortex (OFC) in response to sweet food intake (Alves et al. 2015). FR rats have reduced levels of dopamine type 2 (D2) receptors in the NAcc when compared to controls (Dalle Molle et al. 2015), which explains FR rats' inability to condition their preference to a place paired with palatable food (Smith et al. 2002).

In humans, much of the evidence suggesting DA as a biological basis for early life programming was generated in gene by environment interaction studies. For instance, we recently saw an interaction between a multilocus score reflecting DA signaling capacity and poor fetal growth on spontaneous sugar intake in 48-month children. Using five polymorphisms to create a composite score, the hypofunctional variants (TaqIA-A1 allele, DRD2-141C Ins/Ins, DRD4 7-repeat, DAT1-10-repeat, Met/Met-COMT) received the lowest scores. While in IUGR children there was a correlation between the genetic score and the consumption of sugar, no association was found in non-IUGR children (Silveira et al. 2018).

Levitan et al. (2017) showed in two birth cohorts (one from Canada and another from Netherlands) a significant interaction between maternal sensitivity and the presence of the 7-repeat allele (7R) of DRD4, predicting higher body mass indices (BMI) and/or obesity risk. When exposed to poor maternal sensitivity, 7R carriers have a higher chance of being obese or overweight, especially in Canadian girls or in Dutch boys. The presence of 7R is also associated with higher body mass index (BMI) in women who had seasonal affective disorder and were born in the spring (Levitan et al. 2006), suggesting a fetal programming effect.

As mentioned above, we have shown that variations in this specific mutation of the DRD4 gene interacts with socioeconomic status (SES) according to the differential susceptibility framework, to predict fat intake in girls at 4 years of age. In other words, the same individuals who are genetically more prone to develop obesogenic behaviors when raised in low SES conditions, are also more predisposed to eat less fat when raised in a supportive, high SES environment (Silveira et al. 2016). As a follow up study, we used the entire genotype information in the same cohort to calculate the genetically predicted gene expression of DRD4 in the prefrontal cortex, evaluating the differential responsivity to positive scenarios on eating outcomes. There was a significant interaction between the exposure to positive environments and the predicted prefrontal DRD4 gene expression on emotional over-eating measured by the Children Eating Behavior Questionnaire applied at 48 months. This interaction also followed the differential susceptibility framework, in which the children that have high predicted DRD4 gene expression and show elevated emotional eating in a less positive environment, have less emotional eating symptoms in more positive environments (Barth et al. submitted). This highlights the idea of dopamine genes acting as "plasticity genes", as noted by Bakermans-Kranenburg and Van Ijzendoorn (2011) meta-analysis, proposing the dopamine-related genes as markers of differential susceptibility, and other studies showing that variations in genes that code proteins implicated in the dopamine pathways are sensible to environmental variation (Nikolova et al. 2011; Stice et al. 2012).

In the previously mentioned study from our group, reporting significant interactions between a score for cumulative prenatal exposure to adversity and the ePRS based on the serotonin transporter (SLC6A4) on neurodevelopmental outcomes (Levitan et al. 2017), an enrichment analysis of the genes represented in the polygenic score also suggests the involvement of DA in these fetal programming effects. The most significant biological process enriched in the score was the dopaminergic neuron differentiation, which can be explained by the common source for monoamin-

ergic progenitors during neurodevelopment (Abeliovich and Hammond 2007; Cheng et al. 2010).

It is known that early adverse conditions increase the risk for many different psychopathologies, including ADHD (Lahti 2014; Murphy et al. 2017). Based on that, Neuman et al. (2007) described that children carrying specific variations of the DAT1 and DRD4 genes, when exposed to prenatal smoking, are more likely to be either diagnosed or have symptoms of ADHD in comparison with non-exposed, non-carrier children. This once more suggests a role of the dopaminergic pathways on modulating the relationship between early environmental exposure to adversity and the development of psychopathology.

Following the idea that genes operate in networks, Miguel et al. (2019) created an expression-based polygenic score that reflects variations in the function of the dopamine transporter DAT1 gene network (ePRS-DAT1) in the prefrontal cortex (PFC). Using data from two prospective birth cohorts (Canadian based Maternal Adversity, Vulnerability and Neurodevelopment—MAVAN; and GUSTO Growing Up in Singapore Towards Healthy Outcomes), they evaluated differences in cognitive flexibility according to the exposure to hypoxic-ischemic conditions at birth. More intense exposure to hypoxic-ischemic conditions was associated with longer latency to respond and lower accuracy in the attentional set shifting paradigms—measures related to attentional flexibility—but only in the high DAT1 ePRS group. In addition, the relationship between these genes involved in the machinery associated with prefrontal DAT1 function and the PFC and thalamic gray matter volumes was different between children exposed or not to hypoxic-ischemic conditions. These findings indicate that variations in the function of the DAT1 gene network seem to be important for attention flexibility and its deviances, especially in the context of early life adversity like poor oxygenation levels at birth.

Being born small for gestational age (SGA), a proxy of a poor intrauterine environment, is associated with higher risk of hospitalization for all mental disorders, higher risk of anxiety and adjustment, personality and psychotic disorders (Monfils Gustafsson et al. 2009). At least until young adulthood, individuals born SGA are at increased risk of severe mental disorders such as schizophrenia (Abel et al. 2010) and suicide attempts and completeness (Niederkrotenthaler et al. 2012), independently of their gestational age at birth. Schizophrenia is linked to altered dopamine signaling (Howes and Kapur 2009), suggesting once more a possible link between early life adversity, altered DA signaling and risk for later mental health disturbances.

All the above findings indicate that exposure to early life adversities could modulate the behavioral phenotype over the life course, inducing neurochemical responses and adaptations that are, again, reflected in altered behaviors. This could, in the long term, lead to unfavorable outcomes. Figure 7.1 outlies the proposed theoretical framework on how early adversity affects an individual's development. Exposure to prenatal adversity leads to fetal altered metabolism and gene expression (O'Donnell and Meaney 2017). This prompts the organism to compensate, and neuroadaptations occurring in response to the altered metabolism take place as a trade-off (represented by the orange dots and lines). Because of these neuroadaptations, very specific behavioral features appear already early in life, for instance altered hedonic responses to

sucrose (Ayres et al. 2012; Laureano et al. 2015). These small, persistent alterations in the behavioral response help shaping the development of the DA mesocorticolimbic pathways, affecting neurotransmission and the connectivity between the striatal and prefrontal regions (Hajnal and Norgren 2001). These in turn trigger altered behaviors such as increased impulsivity (Silveira et al. 2012; Reis et al. 2015, 2016) altered reward sensitivity (Bear et al. 2016) and preferences for palatable foods (Crume 2014; Barbieri et al. 2009; Kaseva et al. 2013; Migraine et al. 2013; Perälä et al. 2012). All these progressively contribute to generate consequences of non-adaptive DA related behaviors, and these in turn lead to structure-specific alterations in DA and hormone-related metabolism. The continuation of this process, perpetuated by the behavioral features (e.g. chronic increased intake of high fat, high sugar foods), leads to systemic overload and exhaustion, loss of homeostasis, chronic diseases such as type II diabetes (Hajnal and Norgren 2001; Ravelli et al. 1998), cardiovascular disease (Visentin et al. 2014), atherosclerosis (Giussani et al. 2013), mood disorders (Monfils Gustafsson et al. 2009; Niederkrotenthaler et al. 2012), Alzheimer's disease (Cai et al. 2015; Rani et al. 2016) and neurodegeneration (Verdile et al. 2015).

7.8 Conclusions and Final Overview

We gathered evidence of the role of dopamine pathways on modulating the relationship between environmental adversities and later health outcomes. There is an intricate cascade of successive metabolic and behavioral events that feed each other forward and seem to contribute to both metabolic disarrangements and psychiatric disease/neurodegeneration in the long term. This life course approach represents a major change in how we think and study human lives, adding new dimensions of recurring interactions between context, and sensitivity/resilience (plasticity) in biological processes. Beyond understanding the biological factors behind dopaminergic plasticity effects, this approach also highlights the importance of understanding the key environmental factors that trigger such plastic adaptations. Our focus on dopamine genes as "plasticity genes", and the view of differential susceptibility hypothesis as an important player in this phenomenon, opens up the possibility of both identifying vulnerability but also opportunities for prevention.

Prenatal adversity is associated with higher risk of hospitalization for mental disorders, higher risk of anxiety and adjustment disorders, personality and psychotic disorders (Monfils Gustafsson et al. 2009), schizophrenia (Abel et al. 2010), suicide attempts and completeness (Niederkrotenthaler et al. 2012), type II diabetes (Phipps et al. 1993; Hales and Barker 1992), hypertension (van Dijk et al. 2012), cardiovascular disease (RichEdwards et al. 1997) and atherosclerosis (Martin et al. 2000). The cost to society should focus not only on health outcomes, but also poor academic achievement and reduced human capital (Currie 2005; Reichman 2005; Strauss 2000). Our studies of the biological basis for developmentally-determined co-morbid metabolic and psychiatric conditions represent a novel approach to understanding the pathophysiology of common, chronic illnesses. These studies have direct

implications for targeted preventive measures against metabolic and mental health diseases associated with the exposure to early life adversity.

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Chapter 8
The Developmental Origins of Osteoporosis

Clare Shere, Cyrus Cooper and Elaine M. Dennison

Abstract Osteoporosis is a disease characterised by poor bone strength and microarchitecture, causing bone fragility, which leads to an increased risk of fractures. Although primarily seen as a disease of old age, evidence is accumulating that in utero and early life environment can set an individual on a trajectory for osteoporosis and fragility fracture in later life. The development of osteoporosis is dependent on peak bone mass, and the subsequent rate of loss. The peak bone mass achieved by the third decade of life has been shown to be a powerful predictor of osteoporosis; although peak bone mass is partly genetically determined, the remaining majority contribution is attributable to environmental exposures in early life and modifiable lifestyle factors through life. Current osteoporosis management focuses on bone loss later in life, but it is important to consider strategies earlier in the lifecourse. This review will focus on events operating in utero, or early in post-natal life that influence bone health of the individual.

Keywords Developmental origin · Osteoporosis · Early life environment · Peak bone mass · Fragility fracture

8.1 Introduction

Osteoporosis is a disease characterised by poor bone strength and microarchitecture, causing bone fragility, which leads to an increased risk of fractures. Although primarily seen as a disease of old age, evidence is accumulating that in utero and early life environment can set an individual on a trajectory for osteoporosis in later life. Osteoporosis represents a considerable burden in terms of morbidity and even mortality. It is estimated that globally, in over 50s, 1 in 3 women, and 1 in 5 men will suffer an osteoporotic fracture in their lifetime (Cooper et al. 2017). Hip fracture confers an 8–18% increase in mortality within one year (Haentjens et al. 2010).

C. Shere · C. Cooper · E. M. Dennison (✉)
MRC Epidemiology Lifecourse Epidemiology Unit, Southampton General Hospital, University of Southampton, Southampton SO16 6YD, UK
e-mail: emd@mrc.soton.ac.uk

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The development of osteoporosis is dependent on peak bone mass, and the subsequent rate of loss. The peak bone mass achieved by the third decade of life has been shown to be a powerful predictor of osteoporosis, such that a 10% increase in peak bone mass decreases the risk of osteoporotic fracture in late adulthood by 50% (Hernandez et al. 2003), supporting the vital role of early life factors to reach an optimum peak. Although peak bone mass is partly genetically determined, the remaining majority contribution is attributable to environmental exposures in early life and modifiable lifestyle factors through life. Osteoporosis risk is also impacted by the rate of bone loss in older age, exacerbated in women after the menopause. Current osteoporosis management focuses on this aspect, but based on the evidence for the key role of early life on the attainment of peak bone mass, it is important to consider strategies earlier in the lifecourse. This review will focus on events operating in utero, or early in post-natal life that influence bone health of the individual.

8.2 The Developmental Origins of Health and Disease (DOHaD) Hypothesis

The Developmental Origins of Health and Disease theory was first proposed in the 1990s, based on the finding that infants of low birth weight are affected by a greater incidence of cardiovascular disease in adulthood (Barker 1995). The underlying concept is of developmental plasticity, where environmental conditions experienced at critical windows during development can induce adaptive changes which become fixed and persist into adult life. This foetal programming of metabolic and endocrine systems puts the individual on a trajectory that can influence future disease risk, independent of adult lifestyle factors. There is a compelling body of evidence for the DOHaD theory, with early life environment influences on the development of cardiovascular disease, insulin resistance, type 2 diabetes and obesity as well as osteoporosis (Barker 1995).

Developmental plasticity is thought to represent an evolutionary mechanism enabling a myriad of phenotypes to arise from a single genotype, allowing adaptation to a predicted environment, based on the environment experienced during intrauterine and early life. However, if there is a mismatch between the predicted and actual adult environment, these phenotypic alterations may become deleterious, and predispose to later disease. For example, adverse early life conditions may induce a “thrifty phenotype”, well suited to an environment with sparse resources, but if the adult environment is plentiful, the individual is maladapted, with associated susceptibility to disease that only manifests in later life. At a practical level, this points towards the importance of a lifecourse approach to target public health interventions at early stages to reduce the risk of osteoporosis and therefore fracture risk, and improve long term health at a population and individual level.

8.3 Skeletal Development

The foetal skeleton is formed via two processes: primarily endochondral ossification, with intramembranous ossification forming the skull. Endochondral ossification occurs using a cartilage frame that begins to form at around 5 weeks gestation through sequential differentiation of mesenchymal stem cells into chondrocytes. Chondrocytes hypertrophy and secrete extracellular matrix, forming a microenvironment rich in regulatory cytokines and matrix metalloproteinases, encouraging proliferation, differentiation, angiogenesis and vascular invasion of the structure. Finally, osteoclasts and osteoblasts invade, for remodelling and mineralisation. The majority of mineral transfer across the placenta occurs during the third trimester of pregnancy, with roughly 30 g of calcium required for the foetal skeleton. The skeleton continues to develop post-natally, with rapid growth in infancy (Mackie et al. 2008). Pubertal sex steroids initiate fusion of long bone epiphyses, to slow appendicular skeletal growth, while accelerating axial skeletal growth. Skeletal development continues until the attainment of peak bone mass up to the third decade of life (Cooper et al. 2006).

8.4 Epidemiological Evidence

Evidence for the DOHaD model in osteoporosis has emerged through retrospective cohort studies, as well as prospective mother-offspring cohort studies. Low birth weight is used as a crude marker of adverse environmental conditions. Cohort studies have looked at these relationships at different stages of the lifecourse. Below we detail some of these studies.

8.5 Developmental Plasticity at Work in Childhood to Peak Bone Mass

One of the first such studies investigated a cohort of females born in Bath, UK, in the 1960s, finding a positive association between body weight at 1 year old and peak BMC at the lumbar spine and femoral neck at 21 years old, which remained after adjustment for current body weight (Cooper et al. 1995). This suggested an independent effect of intrauterine conditions on later bone mass. Subsequent cohort studies in Norway (Christoffersen et al. 2017), Lebanon (El Hage et al. 2010), the Gambia (de Bono et al. 2010) and America (Callreus et al. 2013) have similarly found positive associations between birth weight and bone mass during adolescence and around the attainment of peak bone mass.

Birth weight alone is a rather crude measure of foetal growth and extrapolated in utero environment. Therefore, studies have looked at growth in utero using ultrasound measures, and growth in childhood for a more longitudinal view, with the aim to

pinpoint the critical time points where environment exerts the greatest effect on later bone health. Studies on a Dutch cohort and a British cohort have shown in utero growth as well as infant growth as important predictors of childhood bone mass accrual. The Dutch group showed that foetal growth from 20 weeks gestation to birth, as well as growth from birth to 4 years, was positively associated with BMC, BA and BMD at age 6 (Heppe et al. 2014). Results from the Southampton Women's Survey showed foetal growth from 11 to 34 weeks gestation as well as growth from birth to 4 years old was positively associated with BMC and BMD, independent of current weight, height and bone size. The most important period of growth for bone mass at birth was during early gestation, and for bone mass at 4 years old was growth during late gestation (Harvey et al. 2010a, 2012). Both these studies found the strongest association between growth from birth to 1–2 years old and bone mass, potentially suggesting that this early post-natal period is key to childhood bone health. In fact, those born small for gestational age, suggesting intrauterine adverse conditions, who displayed catch up growth in the first 1–2 years of life showed similar bone measures to those born in the normal range of birth weight by 2 years old. This ability of bone mass to recover by early compensatory growth highlights this as vital window of development for future bone health. A Portuguese cohort study looked at different growth trajectory patterns through to age 7, and found that children with persistent weight gain had the greatest bone mass and density aged 7, and lean mass was more important than fat mass for childhood bone mineralisation (Monjardino et al. 2017). These findings point towards the influence of early life environment on bone health through adolescence and up to the attainment of peak bone mass.

8.6 Developmental Plasticity at Work in Old Age

The influence of early life environment is still evident at older ages. In the Hertfordshire cohort, for whom extensive birth records exist, weight at 1 year was associated with spine and hip bone area, as well as bone mineral content (BMC) at the hip and femoral neck. The relationships persisted after adjustment for adult lifestyle factors and adult weight and height (Cooper et al. 1997; Dennison et al. 2005). Birth weight and weight at 1 year predicted bone strength in both males and females at around age 70, measured using peripheral quantitative computed tomography (pQCT) of the radius and tibia, and was found to influence femoral geometry, with poor infant growth associated with a narrower femoral neck, corresponding to reduced mechanical strength (Javaid et al. 2006). In one of the first studies to consider gene-environment interactions, an interaction was observed concerning the vitamin D receptor (VDR) gene, for which polymorphisms are known to be associated with osteoporosis risk. In those with the lowest birth weights, genotype BB individuals had higher spine bone mineral density (BMD), whereas genotype BB individuals of the highest birth weights had lower spine BMD (Dennison et al. 2001).

In a separate British cohort, comprised of births during one week in March 1946, birth weight was positively associated with bone cross sectional area (CSA) and

strength at age 60–64 (Kuh et al. 2014). Similar findings were observed in an American cohort, where low birth weight was associated with decreased BMC in males age 70 (Yarbrough et al. 2000). The Helsinki birth cohort showed those with greatest height gains in childhood (between the ages of 2–7) had greater bone strength aged 68–80, and males with the lowest growth velocities were at increased risk of hip fracture in old age, although this association with hip fracture risk was not seen in females. These findings may be particularly relevant in terms of environmental impacts, as this population are likely to have been affected by wartime food shortages during childhood (Mikkola et al. 2017).

The relationship between early life factors, and hip fracture, has been explored in Scandinavian cohorts. In the Helsinki cohort, risk factors for later hip fracture were identified as tall maternal height, low childhood BMI, and poor childhood growth velocity aged 7–15. It was noted that those who had sustained fractures were shorter at birth, but of average height at age 7, which may suggest that in these individuals, skeletal growth was prioritised at the expense of optimal mineralisation, leading to higher fracture risk (Cooper et al. 2001; Javaid et al. 2011). However, in two Swedish cohorts, although birth weight was positively associated with total body BMC, no association was found between birth weight and hip fracture risk aged 50–94 (Byberg et al. 2014). It should however be noted that a greater proportion of these cohorts were male.

The fact that these associations remain after adjustment for confounders including lifestyle factors known to contribute to bone density, and the effect of current body weight and height show that there are other factors at play. Twin studies offer an opportunity to control for the genetic contributory element. The crucial role of intrauterine environment is evidenced by the finding of a relationship between differences between sets of twins' birth weight and their BMC in their late 40s, after adjustment for current height and weight, even in monozygous twins (Antoniades et al. 2003). As these individuals are genetically identical, the differences in birth weight are likely a result of differences in placental function and nutrient delivery to the foetus, pinpointing the role of adverse in utero environment as an influence on later bone health.

Systematic reviews and meta-analyses have consistently evidenced birth weight and early growth as more important determinants of BMC, rather than BMD, such that a 1 kg increase in birth weight is associated with a 1.49 g increase in hip BMC (Alexander et al. 2014; Baird et al. 2011). This points towards these factors exerting their effect through influencing the size of the skeletal envelope during development. Therefore, the environment in utero, reflected by birth weight, in concert with genetic factors determining growth, influences bone health through adolescence, to the attainment of peak bone mass and into old age, with an impact on fracture risk.

8.7 Intrauterine Life

8.7.1 Maternal Nutrition and Lifestyle

Maternal factors are key to provide the developing foetus with the nutrients and environmental stimuli required for skeletal development, via the placenta. It has been proposed that signals indicating environmental conditions can be passed across the placenta, which induce changes and program foetal metabolic and endocrine control systems to set a trajectory for skeletal development, adapted to these environmental conditions. These signals may be communicated via direct levels of key nutritional elements, but also via endocrine signals from the mother. Pregnancy is a particularly energetically demanding period, especially the last trimester, where 80% of bone mineral is transferred across the placenta (Forestier et al. 1987). Any scarcity or imbalances in these minerals in the maternal diet, or factors impacting utero-placental function, can have profound impacts on foetal bone development, which track through the lifecourse. Factors limiting the mother's ability to supply nutrients impose maternal constraint, which operates in all pregnancies to an extent. Maternal constraint may also have evolutionary origins, to limit foetal growth to allow passage through the birth canal. The placenta is the vital link between the mother and foetus, its efficacy dependent on healthy blood supply and function of nutrient and mineral transporters; specifically relevant to bone development, calcium transporters. Supporting this, placental size at 19 weeks gestation is positively associated with neonatal bone size and mineralisation (Holroyd et al. 2012). Children of pregnancies affected by pre-eclampsia, a disorder of placental function, show reduced hip BMD at birth, which is still apparent at 17 years old. Pre-eclampsia may influence bone health in a variety of ways, through placental insufficiency and reduced calcium transport, but is also complicated by shorter time in utero, as these babies are usually delivered pre-term, reducing time for placental mineral transport in the critical last trimester, as well as the ability to mechanically stress bones in the unique intrauterine environment (Hannam et al. 2015).

Maternal pre-pregnancy characteristics, including maternal birth weight, height and parity are positively associated with neonatal bone mass, as are characteristics during pregnancy, of maternal fat stores at 28 weeks gestation, and a lower level of physical activity in late pregnancy. Maternal fat stores reflect maternal nutrition, and the apparent negative impact of physical activity in late pregnancy may represent increased demand for limited minerals for the maternal skeleton, at the expense of the foetal skeleton. Maternal smoking during pregnancy is associated with reduced neonatal spine and whole body BMC, independent of placental size, suggesting an influence on placental function, or toxins crossing the placenta (Godfrey et al. 2001; Harvey et al. 2010b). This effect has been shown to persist into childhood, with smoking in pregnancy associated with reduced bone mass in their children at the femoral neck and lumbar spine at age 8, even after adjustment for current body size (Jones et al. 1999).

8.7.2 Paternal Influences

In the Southampton Women's Survey, paternal birth weight was associated with neonatal bone mass (Godfrey et al. 2001). The father's skeletal size, assessed by DXA, was closely associated with DXA indices in daughters, but not sons. The differential influence on daughters and sons may indicate the action of imprinted genes, of which only either the paternal or maternal allele is expressed (Harvey et al. 2008).

8.8 Diet and Nutritional Status

Although retrospective observational studies have shown birth-weight and weight gain in infancy to be positively correlated with bone mass in later life, we are now seeing an epidemic of childhood obesity, which is emerging as potentially detrimental to bone health. Obese children, with higher proportions of fat to lean mass have lower BMD when adjusted for height and weight, and an increased childhood fracture risk (Dimitri 2018). In a Tasmanian cohort, greater maternal fat mass, and a higher dietary fat intake in the third trimester of pregnancy were associated with reduced childhood BMD at the femoral neck and lumbar spine, which was still apparent at age 16 (Yin et al. 2010). It appears that not only the quantity, but also the quality of maternal diet is important for the bone health of their children. Perhaps, just as nutritional scarcity programs a thrifty phenotype, nutritional abundance programs a wasteful phenotype, associated with poor use of nutrients and metabolic dysfunction, equally impacting bone health in later life.

Maternal diet, assessed using food questionnaires in pregnancy, is associated with childhood and adolescent bone mass. The Southampton Women's Survey found a more "prudent" diet in late pregnancy (a diet high in fruit, vegetables and wholemeal cereals, and low in processed food) is associated with greater whole body and lumbar spine BMC, reflecting greater skeletal size, as well as BMD in offspring at age 9. This relationship remained after adjustment for factors including the child's height, sex and vitamin D status, as well as socioeconomic status and maternal smoking (Cole et al. 2009). Investigation of a range of nutrients (protein, fat, calcium, phosphorus, magnesium, potassium and folate) in maternal diet and their children's bone indices in a Tasmanian cohort and a large British cohort (ALSPAC) have found only weak associations for individual nutrients, which often disappear after adjustment for height and weight (Yin et al. 2010; Tobias et al. 2005; Jones and Dwyer 2000). In the ALSPAC cohort, maternal folate intake was associated with the child's spine BMD, but the authors evidence this as a marker of good overall nutrition, rather than a key individual nutrient (Steer and Tobias 2011). The Pune Indian cohort group also found serum folate status at 28 weeks pregnant was associated with higher offspring spine and total body BMD age 6 (Ganpule et al. 2006). In a Dutch cohort, maternal dietary phosphorus and homocysteine levels were associated with higher absolute

bone mineral accrual in their children, and maternal dietary protein intake and vitamin B12 levels were the strongest predictors of their offspring's bone mass age 6 (Heppe et al. 2013). The conclusion from these studies is that a balanced nutritious diet is associated with childhood bone mass, rather than a specific dietary nutrient.

8.9 Vitamin D

Studies have explored effects of calcium intake and vitamin D levels, key contributors to bone homeostasis and development. The majority of vitamin D is produced endogenously in the skin, dependent on UVB exposure from sunlight, and a smaller proportion is obtained from the diet. The active form is 1,25-dihydroxy vitamin D [1,25 $(OH)_2D_3$], and is stored as 25-hydroxy vitamin D [25 (OH)D], which is used to measure vitamin D status. The foetus is entirely dependent on the mother for vitamin D, so low maternal levels may program foetal metabolic and endocrine systems to be adapted to low sunlight levels, the predicted environment as signalled by maternal vitamin D levels, to acquire maximal vitamin D, and use it efficiently to build and maintain the skeleton. Extremes may represent an insult that pathologically impairs skeletal development, which the foetus is unable to adapt to. This is illustrated in the example of severe maternal vitamin D deficiency resulting in neonatal rickets and hypocalcaemia, but there is evidence for a graded programming effect on the developing skeleton.

Given that production of vitamin D is UVB dependent, sunlight exposure may be expected to influence bone health. Osteoporosis shows a distribution skewed towards more northerly regions, with the highest rates of osteoporotic fracture seen in Scandinavian countries (Cooper et al. 2017). Low maternal sunlight exposure may exert a programming effect. In a Korean population, infants born in winter had a lower whole body BMC than those born in summer. This was related to lower umbilical cord 25 (OH)D, 1,25 $(OH)_2D_3$ and calcium, and higher markers of bone resorption in those born in winter. This may indicate that low foetal vitamin D is related to increased bone resorption, resulting in lower neonatal bone mass (Namgung et al. 1998).

Studies have consistently found a high prevalence of vitamin D deficiency in pregnancy. The Southampton Women's Survey found 18% of women were vitamin D deficient at 34 weeks gestation (<25 nmol/L), and maternal 25 (OH)D levels were positively associated with whole body and lumbar spine BMC in their children at 9 years old (Javaid et al. 2006). Analysis of ultrasound measures of foetal skeletal development showed that maternal 25 (OH)D insufficiency (25–50 nmol/L) was associated with a smaller femoral volume (Ioannou et al. 2012), and wider distal femoral metaphysis, an observation similar to that seen in neonatal rickets (Mahon et al. 2010). Similarly, children of American mothers with 25 (OH)D < 50 nmol/L had lower neonatal total BMD (Boghossian et al. 2018). In a Western Australian cohort, 38% of mothers were vitamin D deficient at 18 weeks gestation, even in a country with the potential for high sunlight exposure. Maternal 25 (OH)D levels were

positively associated with whole body BMC and BMD in their children at age 20, around the time of peak bone mass (Zhu et al. 2014). A Finnish study found that 71% of mothers and 15% of newborns were vitamin D deficient, despite mothers meeting dietary recommendations. Mothers were divided into two groups, above or below the median vitamin D level (46.2 nmol/L). Offspring of the mothers with higher vitamin D levels had greater tibial BMC and CSA (Viljakainen et al. 2010). By 14 months, children's 25 (OH)D levels were similar in the two groups. The children of mothers with lower 25 (OH)D in pregnancy had shown greater BMC gain, so the two groups had similar BMC by 14 months old. However, the higher tibial CSA seen in those born to mothers with higher 25 (OH)D persisted at 14 months (Viljakainen et al. 2011). This may indicate a role of catch up growth to ensure catch up in height and skeletal size, which is not matched by aspects of skeletal morphology, and this effect tracked through post-natal development despite normalisation of vitamin D levels.

Other cohorts have investigated the relationship between circulating vitamin D and bone health in the offspring. In a Canadian cohort with high levels of vitamin D deficiency, infants who were vitamin D deficient were heavier and longer, but had lower bone mass relative to their weight (Weiler et al. 2005). In a Gambian study, no association was found between maternal 25 (OH)D in mid or late pregnancy and the bone mass of their children up to 52 weeks old. However, it is worth noting that in this population, with high sunlight exposure, all mothers had sufficient levels of vitamin D (>50 nmol/L) (Prentice et al. 2009). In an American cohort of pregnant adolescents, maternal calcium intake and vitamin D levels were co-dependently positively associated with in utero femoral and humeral lengths on ultrasound, pointing towards the interlinking of these nutrients for bone development (Young et al. 2012). A Danish study investigated fracture risk in relation to vitamin D, in a population with marked seasonal variation in vitamin D levels. They found a greater incidence of fractures over a nine-year period in women aged 65–95 born in spring and summer (April–September) compared to those born early in the year (Jan–March). This may indicate vitamin D scarcity during early and mid-pregnancy could program foetal bone development, associated with a higher risk of fracture later in life. The effect was a weaker risk factor for fracture than age and adult lifestyle factors, but may still point towards a background influence of foetal programming (Abrahamsen et al. 2012).

These studies provide some evidence for vitamin D levels in pregnancy exerting a programming effect, which tracks into childhood, up to the attainment of peak bone mass, and may influence future fracture risk, but the evidence is inconsistent and warrants further investigation. Difficulties include different definitions of vitamin D levels representing deficiency. Disparate populations, with different baseline vitamin D levels may partly explain the differing results, as the programming effect may only become apparent when vitamin D levels are significantly low, if the effect size is small.

8.10 Intervention Studies: Vitamin D Supplementation

Considering the evidence for the beneficial influence of maternal dietary components on their children's bone, several randomised controlled trials have investigated supplementation of vitamin D in pregnancy. Trials in India (Sahoo et al. 2017), Iran (Vaziri et al. 2016) and Brazil (Diogenes et al. 2015) found vitamin D supplementation in pregnancy conferred no improvement in offspring bone mass. The UK MAVIDOS trial randomised pregnant women with 25 (OH)D levels between 25 and 100 nmol/L to 1000 IU or placebo daily from 14 weeks gestation. Supplementation increased maternal 25 (OH)D levels by 34 weeks gestation. Over winter, levels fell in unsupplemented mothers, but remained stable in the supplemented group. Furthermore, among babies born in late winter or early spring, the children of supplemented mothers had greater BMC, BA and BMD, but similar birth weight and length, compared with the placebo group (Cooper et al. 2016). These results underline the importance of late pregnancy nutrition, furthering the evidence that low vitamin D during the time of highest mineral transfer can impact upon offspring bone health, and suggests that vitamin D supplementation is only beneficial to prevent deficiency impairing bone mineral accrual.

8.11 Calcium

Findings from studies on the effects of maternal dietary calcium have been contradictory. A cohort study from Pune, India found that higher maternal calcium intake in pregnancy was associated with higher total and lumbar spine BMC and areal BMD in their children at age 6, independent of parental bone indices (Ganpule et al. 2006). In the Dutch Generation R and British ALSPAC cohort, associations between maternal dietary calcium and bone mass became non-significant after multivariate analysis (Tobias et al. 2005; Heppe et al. 2013).

Several intervention studies have investigated calcium supplementation during pregnancy. A trial in India found that calcium supplements from mid pregnancy resulted in increased neonatal BMD, measured by X-ray, compared to placebo (Raman et al. 1978). A trial in America found no difference in the BMC of neonates born to mothers supplemented with 2 g calcium a day compared with placebo. However, when stratified for dietary calcium intake, offspring of mothers with the lowest dietary calcium intake who had received supplementation had higher whole body BMC, indicating that calcium supplements were only of value in those with low dietary intake (Koo et al. 1999). Conversely, in the Gambia, where the population is accustomed to low dietary calcium, supplementation during pregnancy appeared to have detrimental effects on both offspring bone health and maternal bone health that persisted post lactation. 125 pregnant women were randomised to 1500 mg calcium per day or placebo during the second half of pregnancy. They found no benefit on infant birthweight, growth, or bone indices measured by DXA up to 1 year old, but

observed a slightly slower rate of whole body BMC and BA increase in the offspring of supplemented mothers (Jarjou et al. 2006). Furthermore, during a year of lactation, calcium supplemented women showed greater bone mineral loss at the hip, lumbar spine and radius (Jarjou et al. 2010). The effect in the supplemented mothers persisted 2–8 years post-partum. This may suggest that prolonged exposure to low dietary calcium has forced this population to develop adaptive mechanisms to enable them to meet the high demands of pregnancy and lactation, and that supplementation may disrupt this, resulting in adverse bone outcomes for the mother (Jarjou et al. 2013).

8.12 Post-natal Life: Infancy, Childhood and Adolescence

8.12.1 Nutrition in Childhood and Adolescence

Several observational studies have identified relationships between childhood and adolescent calcium intake and bone density in later life (Nieves et al. 1995; Matkovic et al. 2004). A Swiss study found that prepubertal girls supplemented with calcium for one year showed greater BMD gain compared to placebo, an effect still evident 3.5 years after discontinuation of supplementation. The greatest increases were seen in those with low baseline dietary intake (Bonjour et al. 1997, 2001). Similar persistent effects were seen in prepubertal boys (Chevalley et al. 2005). In contrast, a Chinese study found calcium supplementation for 18 months in 7 year olds, although resulting in a 17.6% increase in BMD at 18 months compared to placebo, had no lasting effect 1 year after supplementation had ended (Lee et al. 1997). A meta-analysis found that higher calcium intake improves childhood bone mass only in children with low dietary intake (Huncharek et al. 2008). These effects have also been shown to translate into later life fracture risk. A US study found that lower milk consumption in childhood was associated with lower hip BMC and BMD in adult women, and an increased risk of osteoporotic fracture (Kalkwarf et al. 2003).

8.12.2 Physical Activity

Observational studies have demonstrated relationships between high physical activity in childhood and adolescence with greater bone mass in adulthood (Mantovani et al. 2018). This is especially apparent at the extremes, where professional athletes, particularly those involved in contact sports such as rugby, who have spent their childhood and adolescence training, have higher bone mass compared with age-matched controls. This is associated with increased markers of bone formation (Elloumi et al. 2009).

8.13 Animal Studies

8.13.1 Maternal Low Protein Diet (LPD)

Animal studies offer further evidence for foetal programming of the skeleton. Multiple studies use the model of a low protein diet (LPD) in pregnancy, followed by an unrestricted diet at weaning. Offspring of rats fed a LPD exhibit growth retardation in utero, and are more prone to cardiovascular diseases and earlier mortality compared to controls. They also show lower BMC, altered bone macrostructure at the growth plate and microarchitecture, with weaker bones which are more susceptible to fracture under stress, effects which persist into adulthood (Mehta et al. 2002; Lanham et al. 2008b). These changes are associated with altered markers of bone metabolism.

At 4 weeks of age, offspring of rats fed a LPD had higher levels of alkaline phosphatase and osteocalcin, indicating increased osteoblast activity. They also had lower levels of IGF-1, which regulates chondrocyte proliferation at the growth plate. After 4 weeks, the growth rate of offspring of LPD fed mothers began to fall behind that of controls, which tracked into adulthood (Lanham et al. 2008a). Female offspring showed thinner less dense femoral heads, more closely packed trabeculae in the femoral neck, denser cortical bone in the midshaft tibia, and vertebrae with thicker denser trabeculae. The vertebrae and femoral necks were stronger, but the femoral head and midshaft tibiae weaker under mechanical loading. These changes may represent a response to utilise scarce resources to prioritise the strength of areas of the skeleton most vulnerable to life-threatening fractures, to maximise survival in a predicted nutrient-poor environment; a demonstration of the thrifty phenotype at work. The actual abundance of food available to the rat pups postnatally may have negatively impacted on subsequent bone development, with a programmed propensity to deposit bone in key areas, which may in fact make them more brittle. This was seen in the tibiae, where there was increased cortical bone, but this conferred structural weakness (Lanham et al. 2008b).

Alterations in mesenchymal stem cell (MSC) activity may be in part behind these effects. The offspring of rats fed a LPD in pregnancy showed reduced differentiation and proliferation of MSCs into osteoblasts at 8 weeks old, followed by a relative increase in osteoblast activity at 12–16 weeks. This is in contrast to the control group, where peak osteoblast activity occurred at 8 weeks, which fits with the timing of rat skeletal maturity at 13 weeks old (Hughes and Tanner 1970). The MSCs of the LPD group were not responsive to osteogenic factors including GH, IGF-1 or 1,25 $(OH)_2D_3$. These findings suggest that a maternal LPD may program the foetal endocrine and metabolic systems to delay skeletal maturity, potentially through hormonal imbalance coupled with altered sensitivity of MSCs to osteogenic signals (Oreffo et al. 2003).

8.13.2 Under and Overnutrition

A model of global foetal nutrient restriction can be created by bilateral uterine vessel ligation in pregnant rats (Romano et al. 2009). The restricted male, but not female, offspring are lighter at birth. By 6 months old, the restricted offspring have reduced cortical BMC, and smaller weaker bones compared to controls. These effects were improved, but not corrected, by good post-natal nutrition in females, but not males. These findings highlight the persisting effects of intrauterine environment, and also point towards sex-specific effects (Romano et al. 2009). Effects on bone have been found in the lambs of ewes fed a low, normal or high calorie diet during pregnancy. MSCs of lambs of mothers fed both low and high calorie diet showed a 50% reduction in proliferation, with a reduction in mitochondrial metabolic activity (Pillai et al. 2016).

8.13.3 Maternal High Fat Diet (HFD)

Much work is exploring a possible link between early life origins of both bone and metabolic disease. There is a wealth of evidence that adverse intrauterine nutritional and endocrine environments as a result of maternal diet predisposes the offspring to metabolic disease, in both human and animal studies (Hoffman et al. 2017). MSCs are the common progenitor of osteoblasts and adipocytes. Early influences pushing MSCs towards adipocyte lineages could conceivably have a detrimental effect on bone development as well as predisposing to obesity and metabolic disease.

In mice, a maternal HFD in pregnancy led to increased femoral bone marrow adiposity and altered trabecular structure in the offspring (Lanham et al. 2010). In a separate study, the offspring of mice fed a HFD one month prior to conception and then throughout pregnancy were born shorter, with shorter long bones, and displayed decreased total bone volume and average BMD (Liang et al. 2009).

8.13.4 Vitamin D

Studies of offspring of vitamin D deficient rats showed disruption to trabecular bone measured using microCT, which persisted into adulthood (Lanham et al. 2013). Piglets of vitamin D supplemented sows during pregnancy had 25% higher BMD and stronger femurs, which tracked up to 8 weeks. At birth, piglets of supplemented mothers had increased osteocalcin mRNA, indicating increased osteogenesis (Amundson et al. 2016). Furthermore, the offspring of vitamin D deficient guinea pigs have been shown to have lower osteocalcin levels, body weight and length, whole body and tibia BMC at birth and at one month old, with weaker bones. Post-natal vitamin D supplementation improved serum levels, but did not improve bone indices, suggest-

ing a fixed intrauterine programming effect (Finch et al. 2010). A further mouse study showed that maternal vitamin D supplementation improved offspring femoral and lumbar vertebral trabecular bone structure, and similarly, post-natal vitamin D supplementation was unable to correct these effects (Villa et al. 2016). In a study investigating links between vitamin D and the effects of mechanical loading on bone development, maternal vitamin D deficiency resulted in lower bone mass in the rat pups. In vivo controlled mechanical loading of the tibiae resulted in lower bone mass accrual in the pups who had been exposed to a low vitamin D environment in utero, despite adequate dietary vitamin D post-natally, which may indicate a programmed altered responsiveness of bone to osteogenic stimuli such as loading (Borg et al. 2018).

8.14 Biological Mechanisms for Foetal Programming: How Does Environment Influence Phenotype?

Epigenetics is an attractive mechanism to link the observed environmental impacts on bone mass, strength and fracture risk in adult life, as it is proposed to allow environment-genome interaction. Modification of the epigenome allows an added layer of control over gene expression, which is potentially more flexible and faster acting than changes in the DNA sequence, and therefore more amenable to transient environmental influence. This control is mediated through structural changes in DNA which impact the ability of transcriptional machinery to access DNA sequences, to thereby alter gene expression.

Epigenetic control occurs through three main mechanisms. Methylation of cytosine residues at carbon 5, so called CpG sites in the DNA sequence often located in and around gene promoters, is carried out by DNA methyltransferase (Dnmt) enzymes. This leads to conformational change of the chromatin, impeding access of transcriptional machinery, to repress gene expression. Histone modifications, including acetylation, methylation, phosphorylation and ubiquitination, also alter chromatin structure to promote [in the case of acetylation] or repress transcription. Finally, micro RNAs, short sequences complimentary to the target gene, can interfere at the level of mRNA translation to repress gene expression (Chmurzynska 2010).

Early development is a highly dynamic period, and epigenetic mechanisms are necessary to permit the transition of pluripotent stem cells to commit to multipotent, tissue specific lineages, through altered gene expression. At fertilisation, there is global demethylation of the maternal and paternal genome within the oocyte and sperm, excluding a handful of imprinted genes, followed by de novo methylation by Dnmt 3a and 3b. At this critical time point, signals received by the developing embryo relating to the environmental conditions, via intrauterine fluid and the placenta, are proposed to influence subtle differences in epigenetic patterns to regulate gene expression. Epigenetic mechanisms could even act pre-conceptually, through altered patterns on imprinted genes, resulting in preferential expression of either

the maternal or paternal allele of a gene, in the egg and sperm, which could also support the observation of paternal influences on bone parameters in their offspring, and could explain the sexual dimorphism seen in numerous studies of the impact of peri-conceptual environment on offspring bone outcomes. Through development, the activity of Dnmts and other such enzymes gradually reduces, indicating a reduction in epigenetic alterations as the individual matures, which again highlights the key period of early life, where environmental influences can permanently program metabolic and endocrine systems (Andraos et al. 2018).

Some of the first evidence that epigenetics may mediate the influence of early environment on later disease risk was found in a population affected by the 1944–45 Dutch Hunger Winter. Individuals who had been exposed to starvation in utero and during early life, who were at greater risk of developing cardiovascular and metabolic disease in adulthood, showed genome wide hypomethylation compared to controls. Specifically, reduced methylation at the IGF-2 locus, a gene involved in regulation of growth and adiposity (Heijmans et al. 2009). These findings have led to much interest in the exploration of epigenetic changes brought on by early environmental conditions, both in humans and animal models.

8.15 Hormonal Axes: GH/IGF-1 Axis

Growth hormone (GH) is vital for foetal growth, including bone development and remodelling throughout life. At the skeletal growth plate, GH stimulates production of IGF-1 by chondrocytes and osteoblasts, triggering chondrocyte differentiation and collagen synthesis for bone growth, as well as resorptive osteoclast activity for remodelling (Yakar and Isaksson 2016). In the Hertfordshire cohort, adult GH concentrations were positively associated with bone density aged 60–70 (Fall et al. 1998; Dennison et al. 2003). In men, weight in infancy was positively associated with GH concentration, which also correlated with bone loss rate over 4 years (Fall et al. 1998), pointing towards an early life programming effect that extends into later life and impacts bone health. A single nucleotide polymorphism in the human GH (GH1) gene promoter was associated with lower GH concentrations and an increased rate of bone loss in old age, showing a genetic component to this association (Dennison et al. 2004). Furthermore, in the Southampton Women's Survey, umbilical cord IGF-1 concentration was positively associated with neonatal whole body BMC, independent of maternal lifestyle and characteristics (Javaid et al. 2004). The importance of the GH/IGF-1 axis is supported by animal studies, as described previously. Offspring of rats fed a LPD during pregnancy had lower serum IGF-1, along with indications of premature skeletal maturation compared to controls, and thinner weaker femoral heads in adulthood (Lanham et al. 2008b). Furthermore, the MSCs were unresponsive to GH and IGF1 in culture, showing a programmed altered responsiveness (Oreffo et al. 2003). These early life environmental conditions can therefore induce foetal programming which tracks into later life.

8.16 Vitamin D and Calcium Homeostasis

The observed associations between maternal vitamin D levels in pregnancy and offspring bone indices, in both humans and animals, may occur through epigenetic actions on genes involved in growth and placental calcium handling. Studies on the SWS cohort have found that low maternal 25 (OH)D at 34 weeks gestation is associated with increased methylation of a CpG site in the RXRA gene in the umbilical cord at birth. In turn, a higher percentage methylation at this site, as well as four other CpG sites, was associated with reduced body size-adjusted BMC in their children age 4 (Harvey et al. 2014). RXRA is a co-factor which forms heterodimers with nuclear receptors including the vitamin D receptor (VDR), glucocorticoid receptor (GR), and peroxisome proliferator-activated receptor (PPAR) . The active form of vitamin D, 1,25 $(OH)_2D_3$, binds the VDR-RXRA heterodimer in the nucleus, causing a conformational change allowing the complex to bind vitamin D response elements in promoters of target genes and recruit transcriptional machinery, to allow vitamin D to upregulate expression of certain genes. Therefore, increased RXRA gene methylation could indicate reduced expression, and thereby down-regulation of vitamin D regulated genes, with a lasting impact on bone metabolism.

Target genes controlled by the vitamin D-VDR-RXRA complex include genes involved in placental calcium transport. Calcium is actively transported across the basolateral membrane of placental cells into the foetal circulation via four isoforms of plasma membrane calcium ATPase (PMCA 1–4). In the Southampton Women's Survey placental PMCA3 mRNA expression, as well as umbilical cord venous calcium concentration, was positively associated with neonatal whole body BMC (Martin et al. 2007). As PMCA genes contain vitamin D response elements (Glendenning et al. 2000), this could represent a mechanism for vitamin D impacting placental calcium transfer.

Expression of the placental vitamin D receptor (VDR) may also influence regulation of placental calcium transfer. In an American cohort, placental VDR expression was positively associated with in vivo materno-foetal calcium transport, measured by injecting the mother with an isotope of calcium during labour, and measuring levels in the umbilical cord at birth. In turn, VDR expression was positively associated with foetal humerus and femur length. In vitro, 1,25 $(OH)_2$D-VDR activity has been shown to upregulate calcium import and chaperone proteins, which allow calcium transfer across the apical membrane and across placental cells to the basolateral membrane, indicating a possible mechanism for increased placental calcium transport (Young et al. 2014). Taken together, these findings may indicate that maternal vitamin D levels can induce epigenetic alterations which influence the expression of genes involved in placental calcium transfer, impacting intrauterine bone mineral accrual.

8.17 Hormonal Axes: Glucocorticoid Receptor (GR)

The epigenetic effects of the maternal LPD in rats on offspring metabolic pathways have been investigated. Offspring showed greatly increased GR and PPAR expression, changes which were prevented by supplementing the mothers on LPD with folate during pregnancy (Lillycrop et al. 2005). This was related to decreased methylation of the hepatic $GR1_{10}$ promoter, with a reduced expression of Dnmt1 but not Dnmt3a or 3b, and histone modifications conferring transcriptional upregulation. The authors propose that hypomethylation occurs in the developing embryo, and decreased Dnmt1 activity leads to further hypomethylation through successive mitotic divisions. Machinery to induce epigenetic changes therefore have reduced affinity to bind the hypomethylated $GR1_{10}$ promoter, reducing histone modifications that would confer transcriptional repression, leading to increased gene expression. These changes are predicted to lead to increased gluconeogenesis (Lillycrop et al. 2007). Similarly, offspring of mothers fed a LPD in pregnancy showed overall reduced methylation of the PPARα promoter, but with differential methylation at specific CpG sites, which was prevented by folate supplementation in pregnancy (Lillycrop et al. 2008). These epigenetic changes remained stable throughout the rats' lifetime, illustrating the foetal programming concept. GR and PPARα promoters remained hypomethylated not only in the offspring of rats protein-restricted in pregnancy, but also the subsequent generation, despite a normal diet in both the F1 and F2 generations, which provides evidence for a transgenerational effect of adverse in utero environment (Burdge et al. 2007). The beneficial effect of folate supplementation could be explained by its role in the production of methyl donors, which are required for DNA methylation. Both folate and methionine are key components of S-adenosylmethionine (SAM) synthesis, a major methyl donor. Methionine is an essential amino acid, meaning it can only be obtained from the diet, so availability to the foetus is likely reduced in mothers fed a LPD (Chmurzynska 2010). Therefore, supplementation with folate may to some extent rescue the availability of methyl donors, allowing normal methylation of the genome.

8.18 Mesenchymal Stem Cell (MSC) Differentiation

Mesenchymal stem cells (MSCs) are the common progenitor of both osteoblasts and adipocytes, raising the possibility that early environmental conditions could favour differentiation towards adipocyte lineages, at the expense of osteoblast lineages, becoming a programmed stereotyped setting, resulting in metabolic dysfunction coupled with poor bone health in later life. The PPAR superfamily are nuclear transcription factors that are key regulators of metabolism, and are instrumental in regulating MSC lineage commitment during differentiation. In MSCs, long chain fatty acid binding to PPARγ triggers heterodimerisation with RXR nuclear factors, enabling DNA binding and expression of genes to tip the balance towards differ-

entiation into adipocytes rather than osteoblasts (Li et al. 2016). As demonstrated previously, intrauterine environmental conditions can modify epigenetic control of PPARα, hinting at this as a mechanism affecting bone health.

Animal studies on the maternal HFD have examined this skewed differentiation as a potential mechanism for the effect on bone indices. Foetal rat osteogenic calvarial cells [osteoblast progenitors] collected from foetuses of mothers fed a HFD showed poor maturation into osteoblasts compared to control, which was associated with hypermethylation and resulting reduced expression of the HoxA10 gene, which encodes a transcription factor with multiple regulatory effects (Chen et al. 2012). A further study showed these cells showed increased cell senescence signalling with reduced aerobic metabolism, and reduced differentiation into osteoblasts, which showed poor proliferation (Chen et al. 2016). This study also collected human MSCs from the umbilical cords of obese and lean mothers, and similarly, found increased cell senescence signalling, with a greater propensity to differentiate into adipocytes rather than osteoblast lineages, with resistance to IGF-1 and insulin in those from obese mothers (Chen et al. 2016). This appeared to be epigenetically mediated, with acetylation of histone H3K27 and subsequent increased expression of genes in this pathway, including PPARγ to increase activation of the p53/p21 cell senescence pathway (Chen et al. 2018). Epigenetic mechanisms are key regulators of commitment of MSCs to different lineages during differentiation (Mortada and Mortada 2018). These findings are supported by the findings in a human mother-offspring cohort study. In children, higher methylation of 9 CpGs in promoter regions of the CDKN2A locus from the umbilical cord at birth correlated with decreased whole body less head BMC, BA and aBMD aged 4 and 6 years old. Transcription factors were found to bind to these sites depending on levels of methylation, supporting differential methylation leading to differential gene expression. Altered methylation of CDKN2A is associated with increased adiposity, and is also implicated in differentiation of MSCs. It encodes two cell cycle inhibitors, which have effects on cell senescence pathways. Therefore, epigenetic changes of genes controlling regulatory pathways, including altered methylation of CDKN2A, induced by intrauterine conditions may favour differentiation of MSCs into adipogenic rather than osteogenic lineages, programming increased adiposity coupled with altered bone development (Curtis et al. 2017).

8.19 Leptin

Leptin is an adipokine, secreted by adipose tissue. Principally viewed as a regulator of fat metabolism and appetite, evidence is emerging that bone and fat interact, and leptin may be one mediating factor. During development, leptin can promote MSC differentiation into osteoblasts rather than adipocytes, and is key for development of organs including bone, brain and liver. Leptin is a strong contender for mediating a programming effect based on in utero conditions, and maternal nutrition can alter neonatal leptin levels. In humans, concentration of leptin in the umbilical cord at

birth was positively associated with neonatal bone mass, as well as lean and fat mass (Javaid et al. 2005).

Undernutrition may serve to disrupt the timing of the perinatal leptin surge seen in rodent models, which can lead to dysfunctional hypothalamic development, including insensitivity to leptin. In rats, this is associated with obesity. This is supported by the finding that administering leptin post-natally to the offspring of calorie restricted rats can prevent metabolic derangement. This could impact bone development through effects on sympathetic tone acting on β-adrenergic receptors on osteoblasts (Devlin and Bouxsein 2012). The effect of leptin could therefore represent a link between the observed effects of maternal nutrition on metabolic as well as bone function.

8.20 Conclusion

The available evidence suggests that intricate balances in metabolic and endocrine control systems are dependent on the intertwined influences of genetics and the environment, which interact to alter phenotypic traits with the aim of producing a finely tuned individual, expertly adapted to predicted environmental conditions, through millennia of genetic evolution and overlaid faster acting epigenetic regulation. With the advent of rapid socioeconomic and cultural change, it may be that we can no longer adapt fast enough, resulting in disease in later life.

Inherent to studies on the impact of early life environment on disease later in life is the lag time to reach the outcome measure, here osteoporotic fracture. The follow up of prospective cohort studies and intervention studies are keenly awaited, with the view to informing future bone health strategies. Perhaps the view of osteoporosis requires a paradigm shift, with a focus on the very beginnings of life, which can target our public health initiatives towards optimising nutrition and lifestyle during and even before pregnancy, with a view to improving the bone health of our aging population in years to come.

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Chapter 9
Nutrigenomics as a Strategy for Neuronal Health

Elisabetta Damiani and Rosita Gabbianelli

Abstract Nutrigenomics through gene expression and epigenetic remodeling can program adult health. Diet during pregnancy and lactation (the first 1000 days of life) can modulate offspring's epigenome leading to tissue specific variations during cell differentiation processes, and may define epigenetic marks associated with long-term effects on offspring neuronal health. Being epigenetics reversible, a healthy diet represents a fundamental opportunity, even after the first 1000 days of life, for maintaining cellular homeostasis. The positive impact of food (i.e. maternal milk, oily fish, fruit and vegetables, curcumin, tea) with its dietary flavonoids (i.e. sulforaphane, quercetin, lutein, resveratrol, carotenoids) and other bioactive compounds (i.e. docosahexanoic acid, melatonin etc.), will be reflected on chromatin structure modulation and DNA methylation which are associated with switching on/off of genes. An anti-inflammatory diet during early-life and across the whole life may represent a key strategy for influencing brain plasticity and for building an "epigenetic memory" useful in developing neuronal resilience against early-life stressors and to prevent age-related neurodegeneration.

Keywords Epigenetic programming · Brain plasticity · Nutrigenomics · Neuronal resilience · Adult health · Anti-inflammatory diet

9.1 Introduction

Nutrigenomics is the branch of science that studies how our diet can modulate gene expression directly and/or indirectly via epigenetic mechanisms. This is particularly relevant during cellular differentiation that begins at conception, proceeds during pregnancy and completes after birth up to 2 years of life. This whole period is known

E. Damiani
Department of Life and Environmental Sciences, Polytechnic University of the Marche, Ancona, Italy

R. Gabbianelli (✉)
Unit of Molecular Biology, School of Pharmacy, University of Camerino, Camerino, Italy
e-mail: rosita.gabbianelli@unicam.it

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as the first 1000 days of life and its importance in programming neuronal health can have an impact on neuro-homeostasis later in life. Neurons are the building blocks of the nervous system which includes the brain and spinal cord and when they become damaged or die, the body is not able to replace them resulting in neurodegeneration. Examples of neurodegenerative diseases include Parkinson's (PD), Alzheimer's (AD) and Huntington's (HD) which primarily affect the neurons in the brain causing problems with movement and mental functioning (dementia). The incidence of neurodegenerative diseases is rising globally due to an aging population and also to environmental stressors, such as xenobiotics. Consequently, this will also impact significantly the cost of the health care system along with the need for more public infrastructures to accommodate people with these disabilities and healthcare providers. To mitigate this tendency, it is important to adopt healthy life-style choices that may prevent or delay the onset and progression of neurodegeneration later in life. In this context, dietary choices across the whole life span play a primary role, especially considering that epigenetic marks can be reversed by appropriate dietary nutrients. This chapter will first introduce the main epigenetic mechanisms involved in programming neuronal health in early-life focusing on carbon 1 (C1) metabolism, DNA methylation and histone modifications, and on the regulatory activity of gene expression due to microRNAs (miRNAs). Secondly, the role of early-life risk factors associated with neurodegeneration will be discussed, based primarily on the evidence of both animal and human epidemiological studies. As preventive strategy against neurodegeneration, the protective role of the most important macro/micronutrients during the first 1000 days of life will be reviewed that may positively influence the epigenome. Lastly, how different nutritional choices (healthy vs. Western diet) may influence neuronal resilience from 2 years to the onset of neurodegeneration will be briefly discussed.

9.2 Epigenetic Programming in Early-Life

Epigenetic programming is a physiological mechanism involved in cell differentiation from pluripotent ones; the goal of epigenetic programming is reached through DNA methylation and histone modifications which are able to switch on/off genes leading to specialized cells in different tissues. Although all human cells have the same genome, the cells of different tissues carry out diverse functions due to this epigenetic re-modelling that occurs during early-life. The window of epigenetic plasticity is the first 1000 days of life that includes the prenatal period of life (9 months) and the 24 months of postnatal age.

DNA methylation has a key role in the regulation of tissue-specific gene expression, in genomic imprinting, X chromosome inactivation and silencing retroviral elements. Differential methylation occurs during early embryonic development, and the process is responsible for imprinting by which only one of the two inherited parental chromosomes is expressed. This DNA methylation depends on the availability of methyl groups which can be obtained from food metabolism. A folate-

rich diet, folic acid supplementation during pregnancy, and the availability of B6 and B12 vitamins are fundamental to guarantee the required methyl groups useful for DNA methylation by DNA methyltransferases (DNMTs). Folate, the carrier of methyl groups, becomes 5-methyl tetrahydrofolate through enzymatic activity of methylenetetrahydrofolate reductase (MTHFR). 5-Methyl tetrahydrofolate as well as homocysteine, in the presence of vitamin B12, are converted into methionine by 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR). The methyl group from methionine is then transferred to *S*-adenosylmethionine (SAM) by methionine adenosyltransferase (MAT) and SAM becomes the final donor of these groups utilized by DNMTs, which catalyse the methylation of the 5th carbon of the cytosine residue giving 5-methylcytosine (Fig. 9.1a). A family of DNMTs is responsible for DNA methylation; DNMT1 is known as *maintenance* DNMT because it methylates hemi-methylated DNA transferring the parental DNA methylation pattern to the newly synthesized DNA during DNA replication (Fig. 9.1b), while DNMT 3a and 3b are responsible for the de novo methylation because they methylate both replicative and native DNA (Fig. 9.1c).

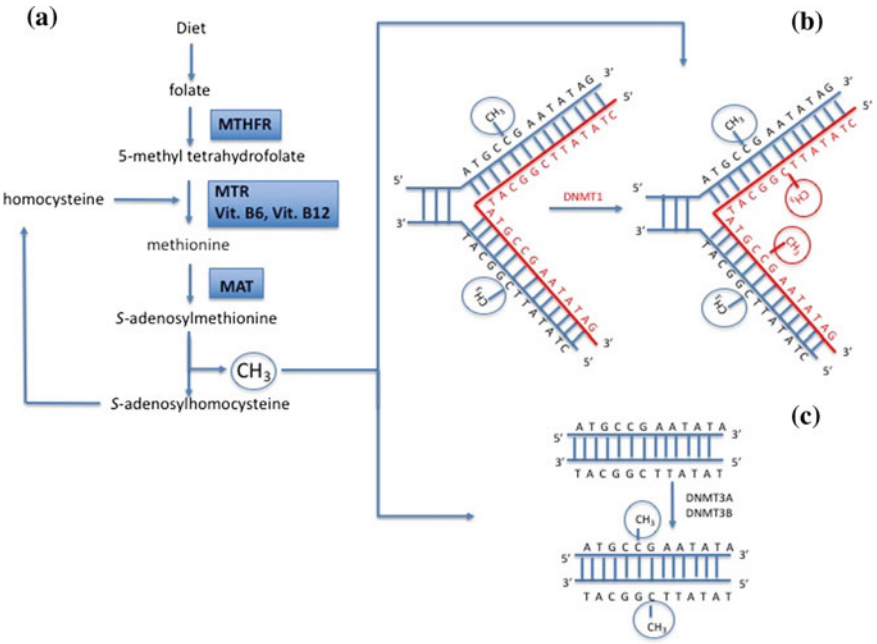

Fig. 9.1 Simplified one-carbon metabolism and methylation by DNMTs. Methyl groups produced by the folate pathway (**a**) are used by DNMTs to properly methylate DNA during its replication by DNMT1 (**b**) and to new CpG islands by DNMT3A and DNMT3B (**c**). MTHFR: methylenetetrahydrofolate reductase; MTR: 5-methyltetrahydrofolate-homocysteine methyltransferase; MAT: methionine adenosyltransferase; DNMTs: DNA methyltransferases

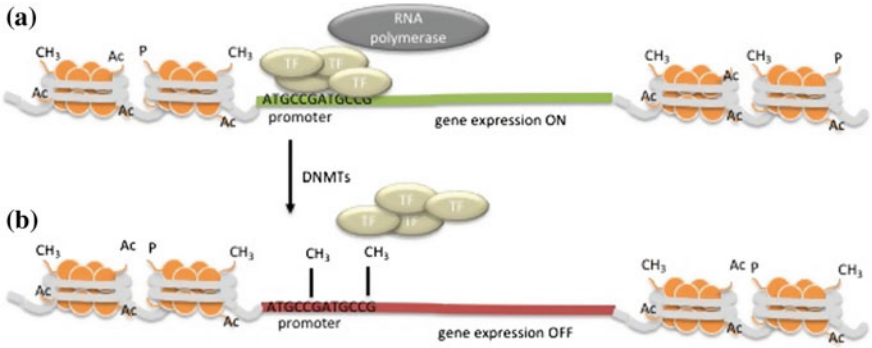

Fig. 9.2 Chromatin structure and CpG regulation of gene expression at the promoter region. Transcription factors (TFs) interaction at the promoter region identify CpG islands driving the pool of RNA polymerases to start gene expression (**a**). Cytosine methylation at CpG islands blocks TFs identification of promoter regions inhibiting gene expression (**b**)

DNMTs have an important role not only during early-life cell differentiation but across the whole life span because the DNA methylation pattern is responsible for gene regulation that should be maintained to guarantee health. DNMTs prevalently methylate cytosines located before guanine nucleotides known as CpG islands. CpG islands associated with promoters are highly conserved in humans highlighting their key role in gene expression. CpG islands within the promoter appear to be more predominant in nucleosome-free regions hence facilitating gene expression because of less DNA packaging (Choi 2010). These islands are involved in binding with transcription factors (TFs): they enhance the accessibility of DNA to the TFs promoting the recruitment of proteins required for gene expression. Methylation of CpG islands in the gene promoter region is associated with its silencing because it impairs the binding of TFs with consequent inhibition of transcription (Fig. 9.2).

The brain is a tissue with a high level of DNA methylation (Moore et al. 2013). Neurons respond to environmental stimuli through membrane depolarization which may modulate DNMTs activity. The key role of methylation during neurogenesis and neuronal maturation has been observed in knockout mice models of Dnmts; DNA methylation and demethylation on the glial fibrillary acidic protein (*Gfap*) gene promoter has been associated with the differentiation of neuronal progenitor cells to astrocytes. Knockout of Dnmt1 leads to demethylation of *Gfap* and multiple maturation deficits such as impaired neuronal excitability and dendritic arborisation, underlining the essential role of DNA methylation for neuronal maturation.

Proper DNA methylation is required also in adult brain; DNA methylation and demethylation work by modifying gene expression and synaptic plasticity consequently impacting learning and memory. DNA demethylation occurs through 5-hydroxymethyl-cytosine (5hmC) which is catalysed by ten eleven translocation (Tet) enzymes or via deamination of the amine group to carbonyl group by AID/APOBEC complex leading to thymine. Global DNA demethylation leading to 5hmC is found

in mammal tissue as an important regulatory mechanism of gene expression. Altered DNA methylation has been associated with psychiatric disorders; early-life stress due to maternal neglect increases glucocorticoid promoter methylation which is maintained in adult age in rodents (Weaver et al. 2004). Equally, abused children show increased methylation of the promoter for glucocorticoids receptors and their decreased expression (McGowan et al. 2009).

The crosstalk between DNA methylation and histone modifications is fundamental in the regulatory process of gene expression. Histone proteins can be modified by methylation, acetylation, ubiquitination and phosphorylation at specific amino acids on the histone tails leading to different chromatin packaging modulating transcription; acetylation at lysine residues is generally associated with less DNA packaging that favours transcription. Histone acetylation depends on histone acetyltransferases (HATs) which catalyse the transfer of the acetyl group from Acetyl-CoA to lysines of histone tails masking their positive charge; this acetylation reduces the electrostatic interaction between histones and DNA decreasing chromatin packaging and opening the way for TFs to recognise CpG islands at the promoter level. The activity is reversed by signals which activate the histone deacetylases (HDACs), of which four classes exist (HDAC1-4). By removing acetyl groups from the positive charge on the lysine, the histone-DNA interaction is again possible leading to DNA packaging blocking gene expression.

Other common histone modifications are phosphorylation and methylation which impact chromatin packaging differently according to the group and the type of residue modified at the histone tails. Phosphorylation at serine, tyrosine and threonine residues is mediated by kinases and phosphatases, while histone methylation requires Histone-MethylTransferase (HMTs) enzymes that depend on the FAD/$FADH_2$ ratio and on the methyl groups on SAM. All these groups are produced by oxidative metabolism of nutrients and for this reason, early-life nutrition plays a key role in epigenetic programming of adult health (Gabbianelli and Damiani 2018).

Epigenetic programming is also under the control of microRNAs (miRNAs) which work synergistically with histone modifications in controlling adaptive gene expression. miRNAs contribute to regulate synaptic connections, neuronal maturation and plasticity (McNeill and Van Vactor 2012). miRNAs are small non-coding RNA of about 22 nucleotides, with regulatory activity on endogenous mRNA. miRNAs are formed following cleavage by the enzyme Dicer in the cytosol of long double-stranded RNA (about 70–100 nucleotides) produced in the nucleus; miRNA can form hybrids with endogenous complementary mRNA inhibiting translation and/or promoting mRNA degradation (Bernstein et al. 2003). More than 2000 miRNAs have been identified in human cells and fluids (i.e. plasma, saliva, urine, milk); they can migrate from/to cells modulating gene expression and, for this reason, they are known as *miRNA hormones* (Bernstein et al. 2003). Gene expression in both developmental and mature brains is modulated by miRNA and some genes are responsible for miRNA transcription in the nucleus (Wang et al. 2012). One miRNA can target various mRNAs, likewise more miRNAs can control more mRNAs at the 3′ untranslated region (UTR). The key role of Dicer has been observed in Dicer-knockout mice which develop progressive loss of dopaminergic neurons and motor disability

in early-life (Bernstein et al. 2003); furthermore, neuronal abnormalities have been associated with loss of Dicer. miRNAs can also control DNA methylation through DNMTs regulation; Dicer-knockout mice show depletion of miRNA-290 which indirectly regulates DNMT3a and DNMT3b (Bouvy-Liivrand et al. 2017). The complex modulation of miRNAs influences neuronal communication starting from early-life across the whole life span and their imbalance differ in diseases; from this evidence, miRNAs have been suggested to be useful biomarkers for early screening of various diseases, such as neurodegenerative disorders (Roser et al. 2018).

9.3 Early Risk Factors Linked with Development of Neurodegeneration

The quality and quantity of food, a western diet (loosely defined as one high in saturated fats, red meats, empty carbohydrates, low in fresh fruit and vegetables, whole grains), exposure to xenobiotics (i.e. pesticides, metals), smoking, alcohol intake and stress during the 1000 days of epigenetic plasticity can influence neuronal development and may have an effect on the development of neurodegeneration in adult age (Gabbianelli and Damiani 2018; Modgil et al. 2014).

In Europe, pesticide residues in food are generally present within the limit permitted by the European Food Safety Authority (EFSA); however EFSA only controls if each pesticide is contained in food within the maximum residue level legally permissible, while the alarm is on excessive pesticide exposure derived from the cumulative effect of a mixture of more pesticides. At the same time, the mycotoxin control should be guaranteed. The main concern is however, related to the impact on non-target organisms because pesticides have been shown to modulate gene expression and the epigenome; strategies able to control mycotoxin content and counterbalance pesticide-induced damage are the main goals to reach for human health.

The mother's intake of food containing pesticides during pregnancy and/or lactation increases the individual risk associated with the development of PD and AD in adulthood (Tanner et al. 2014). In fact, early pesticide neuronal damage promotes genetic and epigenetic changes associated with oxidative stress, neurotransmitter imbalance, protein instability, behavioural changes, inflammation linked to pro-inflammatory cytokine production and microbiota imbalance (Faa et al. 2016; Tartaglione et al. 2016). Studies on animal models exposed to the pesticide permethrin during early-life have indicated that this xenobiotic can promote neuronal damage leading to Parkinson's-like disease development in adult age (Nasuti et al. 2017). Furthermore, an intergenerational effect of neonatal exposure during brain development has been observed in unexposed offspring in rats on DNMTs and DNA methylation, underlining the epigenetic modulation of this synthetic pyrethroid (Bordoni et al. 2015; Fedeli et al. 2017). In humans, Attention-Deficit/Hyperactivity Disorder (ADHD) has been observed in children with high levels of urine organophosphates and pyrethroid metabolites (London et al. 2012). Moreover, a decline in ver-

bal and memory functions in children of six years old has been reported when 3-phenoxybenzoic acid, the main pyrethroid metabolite, was increased in their urine (Viel et al. 2015). Therefore, the abnormal mental development observed in children born from mothers having increased urine biomarkers of pesticides may be linked to genetic and epigenetic mechanisms (Slotkin et al. 2017).

The yellow agouti (Avy) mouse model whose coat colour changes according to the methylation of the Agouti promoter, is a useful model to screen the methylation/demethylation activity (brown coat and yellow coat, respectively) of nutrients and xenobiotics. Avy has been used to test the impact of maternal exposure to bisphenol A (BPA) whose residues can be measured in food and beverages stored in polycarbonate plastic. Offspring born from mothers receiving BPA through the diet, showed a decrease in CpG methylation and a shift in coat colour towards yellow (Dolinoy 2008).

From the food chain, heavy metals can reach offspring from maternal diet. Cadmium for example is able to promote global DNA methylation, while aluminium crossing the blood brain barrier can modify chromatin structure promoting oxidative stress, and is able to induce changes in neuronal dynamics and alter homeostasis leading to neuronal damage associated with neurodegeneration (Kopp et al. 2018; Lukiw 2010; Nica et al. 2017). Iron deficiency has been related to changes in HDAC3 that modifies hepcidin expression involved in the regulation of systemic iron homeostasis and leads to permanent deficits in recognition memory and procedural memory in adult age (Pasricha et al. 2017). Furthermore, neurodevelopmental dysfunctions have been associated with hippocampal DNA methylation due to low iron during early-life (Schachtschneider et al. 2016). A link between decreased fetal neurogenesis, due to impairment of DNA methylation, and amyloid peptide formation in adulthood, has also been observed when deficits of copper and zinc occur during pregnancy and in early-life (Gerber et al. 2017; Keen et al. 2003).

Alcohol too can inhibit DNA methylation and folate absorption in the small intestine; maternal alcohol use during pregnancy and lactation may be associated with an increased risk in offspring to develop neurodegeneration in adulthood and fetal alcohol spectrum disorder in children (Ramsay 2010).

High fat diet (HFD) during pregnancy and lactation has been associated with inflammation in offspring due to production of pro-inflammatory cytokines (i.e. IL-6 and TNF-α) and increased lipopolysaccharide (LPS) which contributes to low grade inflammation. Prenatal inflammation may have negative long-term effects on neurogenesis and hypothalamic inflammation because pro-inflammatory cytokines (i.e. TNFα and IL-1β) can cross the placenta and blood brain barrier modulating fetal brain responses (Graciarena et al. 2013; Valdearcos et al. 2014). Impairment of neuronal development has been observed in animal models only if the exposure to LPS occurs during the prenatal period (Graciarena et al. 2013). High consumption of red meat, fish, eggs and other animal products, stimulates the production of trimethylamine-oxide which accumulates in the vascular wall promoting atherosclerosis and inflammatory responses mediated by macrophages (Sonnenburg and Backhed 2016).

Sweetened beverages and high dietary sugar intake, typical of junk diets, contribute to the development of metabolic syndrome, visceral adiposity, fatty liver,

hyperuricemia and cardiovascular diseases (Stanhope 2016). In particular, fructose has been associated with an increased food consumption because it does not stimulate leptin production and insulin secretion (Luo et al. 2015). Indeed, maternal sucrose or high fructose corn syrup (HFCS) use during pregnancy and lactation in rats, has been associated with increased adiposity and epatic fat content in 3 week-old rats, which disappear at 12 weeks of age, while free fatty acid levels and hepatic lipid profile are perturbed (Toop et al. 2017). Furthermore, increased risk of preterm delivery may be associated with fructose use since it increases NaCl absorption as observed in animal models (Li et al. 2015). Due to the metabolic impact of fructose, its consumption during pregnancy may increase uric acid and insulin levels leading to increased maternal acidosis. Finally, lipid peroxidation in the fetus liver has been observed following maternal fructose use (Valenzuela-Melgarejo et al. 2018).

Maternal under/poor nutrition is also associated with intra-uterine growth restriction (IUGR) due to inflammation; an increase in TNFα, IL-6 and C-reactive protein (CRP) (Visentin et al. 2014) have been observed in serum from both mother and fetus. Studies on rats show that low levels of dietary proteins is associated with increased expression of IL-6 and IL1α in white adipose tissue macrophages (Xie et al. 2017). The worrisome effect of increased production of IL-6 depends also on its capacity to modulate DNMT1 expression which might perturb the epigenome leading to long term effects (Hodge et al. 2005). Furthermore, preliminary studies have shown that placental global hypermethylation is associated with maternal obesity and with infant length and head size (Nomura et al. 2014). A correlation between body mass index and DNA methylation of genes involved in inflammatory-chronic diseases has been observed, highlighting the role of early-life in the modulation of adult healthy/unhealthy status.

9.4 Protective Role of Nutrition During First 1000 Days of Life

In the previous section, an overview is given of how improper diets, inadequate quantities of micro/macronutrients and certain xenobiotics that end up in the food chain, can influence the epigenome ultimately manifesting itself in disease. This is particularly important in the brain that begins to form at conception and reaches completion at 2 years of age. Neuropathological changes occur decades before clinically identifiable symptoms manifest themselves, providing a long window of time for the cumulative effects of environmental factors to affect brain's health. Therefore, the role of nutrition for preventing neurodegeneration during the first 1000 days of life plays a pivotal role.

The importance of how nutrition can influence epigenetic marks was first described in the Agouti mouse model in 2003 where coat colour variation is established early in development according to maternal diet (Waterland and Jirtle 2003). The Agouti viable yellow (A^{vy}) gene was silenced in female mice that were supple-

mented with extra folic acid, vitamin B12, choline and betaine, i.e. a high methyl donor diet, who delivered offspring that were brown in colour and healthy as opposed to the controls that were yellow in colour and obese. In humans, a similar case was observed following the Dutch Hunger Winter in 1944–1945, where reduced folate intake during the prenatal period lead to less DNA methylation of the imprinted insulin growth factor 2 gene (IGF2) in same-sex siblings. This epigenetic mark manifested itself decades later with overweight in men at 20 years old and glucose intolerance when they reached 50 and an increase in BMI in females at the same age (Heijmans et al. 2008). This example reinforces the notion that very early mammalian development is a crucial period for establishing and maintaining epigenetic marks even trans-generationally. In fact, it has been observed that offspring from prenatally undernourished fathers, but not mothers, were heavier and more obese than offspring from parents receiving a normocaloric diet before conception (Veenendaal et al. 2013).

The methyl donors, folate (vitamin B9), choline and methionine are all essential micronutrients for normal development and functioning of the developing brain and the aging brain. They act as epigenetic modifiers of the genome by altering neuronal gene methylation expression and activity (Bekdash 2018; Gueant et al. 2013). These nutrients together with vitamins B12 and B6 all participate in brain metabolism in the methionine/folate cycle and their lack has consequences for conversion of aminoacids to monoamine neurotransmitters. Severe maternal folate and choline deficiencies result in neural tube defects (NTDs) where brain and spinal cord fail to develop normally, and in other congenital defects (Zeisel 2009). To reduce this risk and for promoting normal embryonic growth, a red blood cell folate level >900 nmol/L is considered sufficient (Bailey 2000). Therefore, a folate-rich diet (i.e. leafy green vegetables, kale, pulses, liver, etc.) and folic acid supplementation, together with the availability of B6 and B12 vitamins, should provide an adequate supply of methyl groups for methylation to take place and is recommended prior to and *only* during the first trimester of pregnancy. Supplementation beyond this timeframe appears to be linked with the development of allergic diseases in children (McStay et al. 2017). Vitamin B12 is present only in animal food (i.e. meat, fish, eggs), hence vegans are required to take a synthetic one orally through sublingual treatment to avoid its hydrolysis by the liver.

Maternal dietary folates and other micro/macronutrients involved in epigenetic programming of offspring all pass through the gut in order to be metabolized and absorbed, hence maintenance of a healthy gut and the microbes within it that regulate various elements of the "gut-brain axis" (GBA) via immunological, endocrine and direct neural mechanisms are of crucial importance (Alam et al. 2017; Rhee et al. 2009). Consequently, gastrointestinal manifestations that disrupt this axis may be associated with neurodegenerative disorders as has already been hypothesized for PD (Mulak and Bonaz 2015). Indeed, some indicate that maternal microbiota may shape neurodevelopment of offspring paving the way to neurodegenerative diseases later in life (Natale et al. 2008). For example, alterations in the maternal gut microbiome and intestinal permeability following inflammation due to a HFD in the obese phenotype that induces increased circulatory LPS, may alter folate levels

thus affecting epigenome programming in the offspring with long-term effects. The microbiota of pregnant obese women differs from normal pregnant women by having significantly higher levels of *Staphylococcus*, *Enterobacteriaceae* and *E. coli* and fewer *Bifidobacterium, Bacteroides* and *Akkermansia muciniphila* (Santacruz et al. 2010). This could influence microbial colonization of the infant leading to metabolic consequences in adulthood, including the possible increased risk of developing neurodegenerative diseases (Contu and Hawkes 2017; Mulligan and Friedman 2017). Supporting this view are the few animal studies linking disrupted DNA methylation patterns and altered clearance of the β-amyloid peptide (Aβ), marker of AD, in the brains of adult offspring exposed to a HFD during the prenatal period and in human studies of maternal obesity, alterations have been reported in the extent of DNA methylation in cord blood and microRNA in amniotic fluid (Fuemmeler et al. 2016; Nardelli et al. 2014). Therefore, targeting the maternal microbiome may have a knock-on effect on brain development in offspring to prevent neurodegeneration later in life.

The gut microbiota composition and metabolites production depend on food intake. Dietary fibers and resistant starch actively promote the production of three important short chain fatty acids (SCFA): butyric acid, propionic acid and acetic acid which have systemic effects on the hypothalamic hunger-satiety centre, on insulin production and on lipid synthesis (Sonnenburg and Backhed 2016). Butyric acid especially, has anti-inflammatory and anti-apoptotic effects (Louis et al. 2014). Microbiota diversity and its positive impact on gut homeostasis can be promoted by a substantial intake of different vegetables and fruits rich in flavonoids and phytochemical content, and to tryptophan supplementation because of their anti-inflammatory activities exerted by inhibition of IFNγ and TNFα expression (Nikolaus et al. 2017; Tilg and Moschen 2015). This is particularly important during pregnancy since a high association has been reported between mother and offspring microbiota (Roytio et al. 2017). Good microbiota maturation in offspring is also promoted by vaginal delivery instead of cesarian-section at birth, since higher microbiota maturation is observed in the former case (Rutayisire et al. 2016). After birth, milk-feeding practices play an essential role in shaping the early pioneering bacteria in the new-born important for gut function, vitamin biosynthesis, energy retention and immune system development since the immune system of neonates is immature and requires the exposure of gut bacteria to develop properly (Zeng et al. 2016). Breast milk in healthy women contains a wider variety of viable and more beneficial bacteria, compared to formula-fed milk, as well as secretory IgA, antimicrobial peptides, cytokines, immune cells and over 200 non-digestible oligosaccharides (HMOs) which provide nutrients to the microbes colonizing the infant gut that produce specific SCFAs (Martin et al. 2007). The SCFA profiles of formula-fed infants are characterized by high proportions of acetate and lactate and a lower proportion of propionate compared to breast milk which may account for the greater propensity for metabolic syndrome, celiac disease and obesity later in life (Binns et al. 2016). Since obesity is linked to inflammation and this to neuroinflammation, then the risk of developing neurodegenerative diseases may also be reduced by breast-feeding. However, if breast milk is delivered from obese mothers that contains a different and less diverse and beneficial bacterial

community than that of normal-weight subjects (Collado et al. 2012), along with a different composition of hormones (e.g. leptin and insulin), cytokines and oligosaccharides, then infants born to these mothers will have a different neonatal microbiome in terms of composition and characteristics which may contribute to future disease risks later in life (Lemas et al. 2016). Overall, proper microbial diversity is necessary for maintenance of gut permeability to avoid any absorption of toxic compounds (i.e. pesticides and other xenobiotics) and the release of pro-inflammatory cytokines that could reach the brain via GBA and promote neuroinflammation associated with neurodegeneration. In this context, several studies on human and animal models demonstrate the key role of microbiota composition in the mediation of gut inflammatory cytokines promoting neuroinflammation in PD and AD diseases (Nasuti et al. 2016; Tremlett et al. 2017).

Controlling inflammation is a fundamental requisite for the prevention of neurodegeneration and since systemic inflammation is a consequence of obesity and a high fat diet (HFD), a maternal and toddler anti-inflammatory diet might represent a key strategy to prevent the risks associated with neurodegeneration development later in life. The daily diet should hence include food able to control inflammation and maintain a balanced redox state such as green/white/red/orange vegetables and red fruits, broccoli, curcuma, tea (Castelli et al. 2018). Members of the *Brassicaceae* family such as kale and broccoli contain sulforaphane (SF), an isothiocyanate able to inhibit COX-2, while promoting the Nrf2/ARE pathway, an indicator and modulator of oxidative stress in neurodegeneration and to have antioxidant activity (Qin et al. 2016; Tarozzi et al. 2013). It has also been shown to improve behavioural cognitive impairments and attenuate brain Aβ burden in an AD animal model (Zhang et al. 2017), therefore its use against particular signs and symptoms of AD has been suggested (Pennisi et al. 2017). Green tea consumption is also favoured for its high content in epigallocatechin gallate (EGCG), a flavonoid with significant antioxidant and anti-inflammatory activity (Xu et al. 2017). In neonatal mice, EGCG inhibited sevoflurane-induced neurodegeneration and improved learning and memory by acting on the activation of the CREB/BDNF/TrkB-PI3K/Akt signalling pathway (Ding et al. 2017). Quercetin, another flavonoid widely distributed in nature including green tea, has also been associated with a reduced risk of developing neurodegenerative disorders (Elumalai and Lakshmi 2016). Other compounds such as resveratrol and curcumin, found in the skin of red and blue berries and in turmeric powder respectively, are involved in the production of anti-inflammatory cytokines suggestive of their neuroprotective role, especially for curcumin which is able to cross the blood brain barrier, and exerts anti-inflammatory, antioxidant, and anti-protein-aggregating roles (Di Martino et al. 2017; Koushki et al. 2018). In general, all dietary polyphenols, and in particular flavonoids, may be effective in preventing neurodegeneration through their ability in protecting neurons against oxidative stress-induced damage, repressing neuroinflammation and in maintaining cardiovascular and cognitive health, recently reviewed in Castelli et al. (2018) These should therefore be part of a daily diet both pre- and postnatally and maintained throughout the life span. Carotenoids should also be part of this daily regime according to a recent meta-analysis on 52 studies that analysed plasma levels of antioxidant vitamins and carotenoids in AD patients. This study

demonstrated for the first time that these patients had significantly lower levels of lycopene, lutein, zeaxanthin and cryptoxanthin compared to the controls, suggesting how important these dietary components, found in high quantities in green leafy vegetables, could be in preventing neurodegeneration (Lieblein-Boff et al. 2015; Mullan et al. 2018).

Another interesting molecule that has come under scrutiny as a strategic compound for neuroprotection is supplementation with melatonin. This is produced by the pineal gland in animals and is a pleiotropic molecule that exerts multiple physiological functions, including reduction in ROS production and immune response enhancer, contributing to anti-inflammatory function. Investigations in animal models have shown that melatonin protects against AD (Bavithra et al. 2017; Corpas et al. 2018a; Hu et al. 2017), from damage due to high fructose diet (Valenzuela-Melgarejo et al. 2018) and that melatonin supplementation induces cognitive enhancement and brain resilience against neurodegenerative processes.

Lastly, numerous studies have shown the link between AD incidence and altered lipid status such that this neurodegenerative disease can be considered a lipid metabolism disease (Florent-Bechard et al. 2009). Consequently, modifying the lipid content and status of target tissues and the brain particularly, through nutritional strategies for preventing neurodegeneration seems obvious. Of all lipids, docosahexaenoic acid (DHA) is the most significant omega-3 (*n*-3) polyunsaturated fatty acid (PUFA) (> 90% of all *n*-3 PUFAs) in the brain, concentrated in the grey matter primarily in phosphatidylethanolamine (PE) and phosphatidylserine (PS) membrane lipids, and it affects neurological function in several ways. It is a highly essential nutrient for the growth and maturation of an infant's brain and retina and it rapidly accumulates in the brain during gestation and early infancy. The availability of DHA via placental transfer impacts the amount of DHA incorporated into neural tissues hence the mother's dietary intake of this PUFA plays a primary role not just during pregnancy, but also after through mother's milk. Indeed, DHA levels in tissues have been found to be higher in breast-fed infants when compared to formula-fed infants. Pregnant and nursing women should hence consume at least 200 mg DHA daily as its effects on growth and development of the fetus likely have a profound impact on cognitive abilities later in life (Weiser et al. 2016).Observational studies indeed indicate a preventative role of dietary n-3 PUFA (salmon, mackarel, herring, sardines) and DHA with regards to risk and incidence of AD, such that one or more servings of fish per week (or 200 mg DHA) is associated with a 60% lower risk of developing AD (Weiser et al. 2016). A recent study on newborns, showed that long-chain PUFA supplementation (arachidonic acid and DHA) from birth to 12 months positively affected brain function, structure and metabolism at age nine years, demonstrating the long-term effects of this nutrient in neuronal health (Lepping et al. 2018).

On the whole, by influencing many different signalling pathways, receptor systems, enzyme activities, membrane structure and dynamics, all the nutrients mentioned above, as well as many others not treated here, ultimately may lead to overall better development, maintenance and aging of the CNS throughout the lifespan (Fig. 9.3).

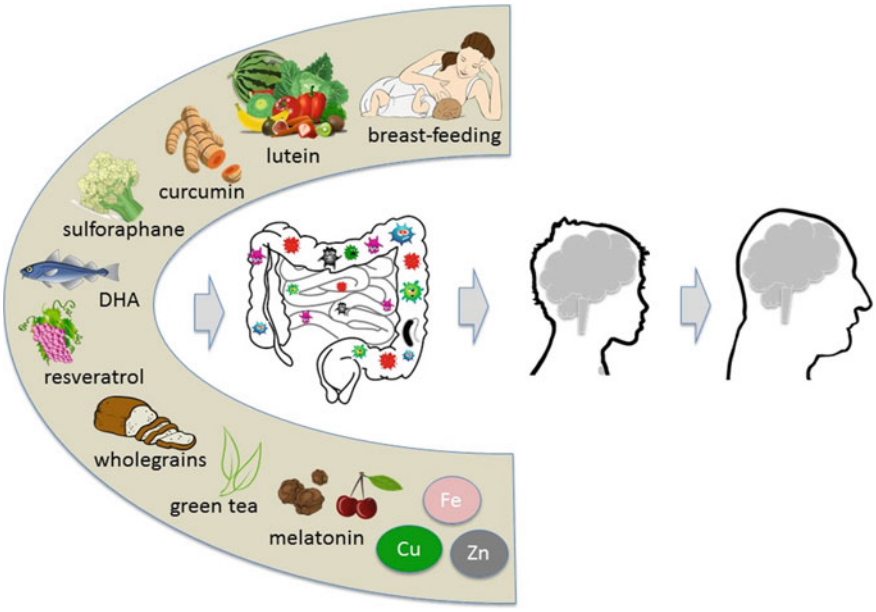

Fig. 9.3 Positive role of gut microbiota modulators and impact on brain at young and old age. Early life exposure to positive factors like breast-feeding, vegetables and fruits, curcumin, oily fish, melatonin, docosahexanoic acid (DHA), lutein, green tea, wholegrains and the correct amount of microelements (Cu, Fe, Zn) could play a key role in neuronal development mediated by gut microbiota, at young and old age

9.5 Nutrigenomics for Promoting Neuronal Resilience

Resilience refers to the capacity of an individual to avoid the consequences of stress (negative social, psychological and biological) that can compromise well-being. In this context, dietary factors during early-life and beyond may influence brain plasticity and epigenetic variability that contribute to developing an 'epigenetic memory' (Russo et al. 2012). Hence dietary choices could be determinant in building resistance to neurological challenges (Agrawal et al. 2014) and would explain why not every individual who experiences stressful events in early-life goes on to develop mental illness and neurological disorders later in life. Several positive, early-life experiences such as enrichment, quality of parental care and a balanced diet can all impact healthy neurodevelopment and adaptive responses to stressors leading to resilience (Bateson et al. 2014). In this section, we will focus solely on some recent examples of how nutrigenomics may promote neuronal resilience against early-life stressors.

Grissom et al. (2017) tested the hypothesis that early-life nutrition would impact the proinflammatory transcriptional response to a stressor. They fed pregnant and lactating dams with either a low-protein diet (LP), a high fat diet (HF), or a control diet. A panel of 20 pro-inflammatory related genes in response to peripheral

LPS administration (a physiological stressor), or 15 min restraint (a psychological stressor), in adult male offspring were then examined in four different brain regions. The data they obtained support the conclusion that early-life nutrition affects proinflammatory gene expression profiles throughout the brain in offspring, and these responses differ by brain region, by stressor, and by dietary challenge which may translate into risk or resilience to stressors. Another study performed on Sprague Dawley rats (Tyagi et al. 2015) showed that early-life exposure to dietary omega 3-fatty acids can protect the brain against the deleterious effects of switching to a western diet, since DHA is essential for proper metabolic signalling and methylation of brain-derived neurotrophic factor (BDNF), an important neurotrophin for brain function and neuroplasticity. BDNF appears to be a crucial protein in translating the effects of food on the brain and it exerts its biological function by binding to its receptor tropomyosin-receptor-kinase B (TrkB), which initiates multiple signalling cascades (Gomez-Pinilla 2008). The switch to a low omega-3 fatty acid diet promoted BDNF methylation and reduction in binding of the transcription regulator CTCF to the BDNF promoter IV. The changes in BDNF gene transcription are associated with altered BDNF protein expression that may influence neuronal function and mental health by involving PGC-1α, a mitochondrial transcription co-activator and BDNF regulator. The prior exposure to DHA appears to preserve the effect of western diet transition by promoting DNA demethylation in the BDNF promoter IV. These results support a model in which diet can build an "epigenetic memory" during brain formation that confers resilience to metabolic perturbations occurring in adulthood. Adequate levels of dietary DHA in early-life seem crucial for building long-term neuronal resilience for optimal brain performance and aiding in the battle against neurological and psychiatric disorders in adulthood but also for normal homeostasis, as confirmed in other studies (Agrawal et al. 2014; Bhatia et al. 2011). Decreased levels of BDNF and TrkB signalling in different brain regions are also involved in the depression-like phenotype of Nrf2 KO mice. By pre-treating these mice with the Nrf2 activator sulforaphane (SFN), there was a reduction in the depression-like symptoms caused by repeated social defeat, likewise with the dietary intake of 0.1% glucoraphanin (a precursor of SFN) present in food during juvenile and adolescent stages. These findings suggest that the transcription factor Keap1-Nrf2 pathway plays a key role in depression and that dietary intake of SFN-rich foods in early-life and adolescence can confer stress resilience in adulthood (Yao et al. 2016). SFN-rich broccoli sprout extract was also efficient in improving significantly social interaction, abnormal behaviour and verbal communication in young men with autism spectrum disorder and cognitive impairment in medicated patients with schizophrenia (Shiina et al. 2015). High fructose consumption has also been shown to disrupt both synaptic plasticity through the BDNF-TrkB signalling pathway and brain cell energy homeostasis (decrease in hippocampal insulin receptor signalling) along with increased protein and lipid peroxidation aggravating traumatic brain injury (TBI) in Sprague-Dawley rats. These data imply that high fructose consumption exacerbates the pathology of brain trauma by further disrupting energy metabolism and brain plasticity typical of TBI, thus reducing neural resilience and predisposing the brain toward neurological disorders later in life. This is particularly

worrisome considering the rise in consumption of high caloric foods in the WD and the number of diabetic and prediabetic persons worldwide (Agrawal et al. 2016).

Evidence for the involvement of an epigenetic signature induced by unfavourable nutritional conditions during early-life on BDNF comes from a study conducted on chicks. Fasting for 24 h at 3 days of age (D3) lead to increased methylation of lysine 27 of histone 3 (H3K27) at the putative promoter of BDNF and increased expression of its specific histone methyltransferase (HMT). When the same chicks were fasted again on D10 the reduced levels of BDNF were rescued compared to those fasting for 24 h on D10 only. This demonstrates that chicks respond to fasting with dynamic methylation at H3K27 in the hypothalamic paraventricular nucleus (PVN) during the neonatal critical period, and that this allows the PVN to form a 'molecular memory' which keeps the individual's inner environment homeostatic and resilient to future fasting over the short term (Jiang et al. 2016).

Resveratrol, mentioned in the previous section, is an epigenetic modifier that mediates its effects through SIRT1, a deactylase involved in longevity and neuroprotection. A recent study (Corpas et al. 2018b) on control non-transgenic (NoTg) and Alzheimer disease (AD) transgenic (3xTg-AD) mice showed that supplementation with 100 mg/kg of resveratrol at 2 months through to 1 year of age lead to reduced levels of Aβ and p-tau pathology in the hippocampus of 3xTg-AD mice. Furthermore, in both groups there were increased levels of the amyloid-degrading enzyme neprilysin, reduced levels of amyloidogenic secretase BACE1, and increased proteasome protein levels and proteasome activity. Collectively, the data demonstrate that resveratrol induces cognitive enhancement and neuroprotection against amyloid and tau pathologies in both healthy and AD mice, underlying a mechanism of brain resilience and defence against neurodegeneration caused by the accumulation of aberrant proteins. The same investigators (Corpas et al. 2018a) on the same animal models also showed that melatonin mitigates neurodegenerative processes by increasing brain resilience. Daily supplementation with 10 mg/kg of melatonin in 6-month-old mice up until 12 months of age reversed cognitive impairment and dementia-associated behaviors of anxiety and apathy and reduced amyloid and tau burden in 3xTg-AD mice, as well as inducing cognitive enhancement and higher wellness-like behavior in NoTg mice. Mechanistically, NF-κB and proinflammatory cytokine expressions were decreased in both groups of mice whereas the SIRT1 pathway, the ubiquitin-proteasome proteolytic system and the neuroprotective Gas6/TAM pathway were activated in both mouse strains after melatonin dosing. Therefore, melatonin induces both prevention and neutralization of neuroinflammation that may favor resilience against AD.

Lastly, the involvement of the microbiome as a key regulator of the stress response in early-life must be recognized. Bacteria are required for normal brain development (Clarke et al. 2013; Codagnone et al. 2018; Diaz Heijtz et al. 2011) as well as brain function in adulthood and any factor that influences the gut microbial community, including the maternal microbiome has thus the potential to impact neurodevelopment and stress sensitivity even in the fetus via the maternal-placental-fetal interface (Codagnone et al. 2018). Hence the quality and quantity of nutritional factors pre- and post-natally undoubtedly play an important role in this. However, it still remains to be established whether changes in maternal microbiota directly affect the susceptibility

to stress or resilience both in rodents and human infants. Therefore, future studies should aim to investigate the exact mechanistic relationship that the microbiome has in mediating brain resilience.

9.6 Conclusions

Nutrigenomics attempts to highlight the key role of macro- and micro-nutrients in the metabolic responses mediated by gene expression. Diet and parental care during early-life can modulate the "epigenetic memory" influencing stress responses and strengthening neuronal resilience. The western diet is associated with unfavourable metabolic responses due to the lack of functional groups and microelements required for proper gene expression and epigenetics remodelling, and to a suboptimal microbiome activity that are associated with inflammatory responses, impairment of neuronal development and neurodegeneration throughout the lifespan. Future research should therefore attempt to elucidate the mainstream effects of specific foods and the impact that different diets, with the same caloric content, have on gene expression and "epigenetic memory". This would aid to properly address educational programmes aimed to maintain neuronal homeostasis and to promote wellness in the future generations.

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Part III
Epidemiological Evidence

Chapter 10
Prenatal Undernutrition and Ageing and Longevity

Susanne R. de Rooij

Abstract Dietary restriction is one of the most extensively studied ways to elongate lifespan, but when species are undernourished before birth, effects are completely opposite. In the present chapter, evidence from animal experimental as well as from human studies is presented demonstrating that prenatal undernutrition increases the risk for ageing-associated diseases of the brain and the body, seems to accelerate the ageing process and decrease lifespan. The findings presented here are of importance from a public health perspective as prenatal nutrition may be a modifiable factor affecting healthy ageing. Also, understanding the processes by which prenatal undernutrition leads to accelerated ageing may provide clues on how we can detect early ageing and implement interventional approaches when conditions are still reversible.

Keywords Prenatal undernutrition · Ageing · Ageing-associated disease · Longevity · Public health perspective

10.1 Introduction: Prenatal Undernutrition and Ageing

Attempts to increase healthy lifespan have a long history and have always inspired man. In one of the earliest known works of literary writing, the Epic of Gilgamesh, the hero sets out on a long, dangerous journey to find the secret of eternal life which appears to be hidden in a plant sunk to the bottom of the sea. Nowadays, among scientists around the globe, the current worldwide ageing of the population has instigated a renewed hunt for the secret of a long healthy life. With so many people getting into old age, understanding the biology of healthy ageing is now more relevant than ever.

Up until now, the search for modifiable factors affecting the ageing process has mostly focused on a whole range of adult/postnatal lifestyle factors. Dietary restriction is one of the most extensively studied ways to elongate lifespan. However, when

S. R. de Rooij (✉)
Department of Clinical Epidemiology, Biostatistics & Bio Informatics, Amsterdam University Medical Centers, Location AMC, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
e-mail: s.r.derooij@amc.uva.nl

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diet is restricted in early life, the effects seem to be reversed completely. Early life malnutrition may even be more important for the ageing process than later life over nutrition. This was elegantly shown by studies in which mice received either a normal or a 20% protein restricted diet during gestation and/or lactation followed by either a normal or a high fat cafeteria diet (Ozanne and Hales 2004). A normal diet during the whole period resulted in a lifespan of on average 765 days, a postnatal cafeteria diet resulted in a lifespan of 715 days, while a prenatally restricted diet resulted in a lifespan of 568 days, which was even lowered to 517 days when combined with a postnatal cafeteria diet.

Suboptimal nutritional circumstances in the prenatal environment could be the starting point of an accelerated ageing process with decreased lifespan as its final outcome. In this chapter, evidence for prenatal undernutrition as an important factor in ageing and longevity will be discussed. We will start by reviewing studies which have provided evidence for a role of prenatal undernutrition in ageing of the brain, followed by studies focusing on ageing of the body. We will further discuss studies in which associations between prenatal undernutrition and age-associated diseases and mortality have been investigated. We will also consider potential underlying mechanisms, which have been examined in some human studies, but mostly in animal models. In the final part of this chapter, we will discuss the relevance of these studies for the field of ageing and how these findings can be translated to practice.

10.2 Animal Models and Famine Studies

The obvious advantage of using animal models is that they provide the opportunity to manipulate a certain element of the prenatal environment, in this case nutrition, while keeping other factors constant and to follow the offspring into old age. Most preclinical studies used rodent models where the diet of pregnant animals is manipulated by restricting calorie or protein intake. To overcome the limitation of being unable to experiment with prenatal nutrition in humans and study its outcomes, researchers have used situations in which nutritional conditions varied as a result of naturally occurring events or man-made adversities (de Rooij 2018). Although famines are of course humanitarian disasters, they can serve as unique opportunities to study the consequences of poor nutritional circumstances in utero for health in later life. Famine-based studies are observational studies, but they mimic experimental studies in the sense that people who were exposed to undernutrition can be compared to people who were unexposed to undernutrition.

Across the world, different periods of famine during different periods of time have been used to study consequences of undernutrition in early life. The most widely studied famines include the Dutch famine, which was a 4–5 month period that struck the urban western part of the Netherlands at the end of World War II, and the Chinese famine, which coincided with the Great Leap Forwards in 1959–1961 and was caused by imposed drastic changes in agriculture, economic mismanagement

combined with natural disasters. Below we will give an overview of findings from these famine-based studies on ageing associated outcomes and longevity.

10.3 Ageing Effects on the Brain

One of the most distinct manifestations of ageing is memory problems and cognitive decline, which may ultimately progress to dementia. Already in the early seventies, animal work was performed showing effects of early nutritional deprivation on brain and behavioural outcomes. Young rats that were undernourished during the perinatal period were shown to exhibit slowness in learning a maze, behavioural rigidity and high emotionality resembling the characteristics of rats at old age (Roeder and Chow 1972).

In the Dutch famine birth cohort, it was shown for the first time that prenatal undernutrition may affect cognitive function in older age. By comparing those who were exposed to the famine in early gestation to those unexposed during gestation (either born before or conceived and born after the famine), it was demonstrated that exposed people performed worse on a Stroop task at the mean age of 58 years (de Rooij et al. 2010). The Stroop task requires selective attention, which is a cognitive ability that is one of the first to decline with age and has been shown to be a strong predictor for conversion to Alzheimers' disease even before memory deficits were present (Balota et al. 2010).

These findings of decreased Stroop performance after prenatal famine exposure were replicated in a Chinese cohort, showing that men and women prenatally exposed to the Chinese famine performed worse on the Stroop task as well as on a trail making task (Li et al. 2015). Other studies in which consequences of prenatal exposure to the Chinese famine on later life cognitive function were investigated followed and showed associations with a lower IQ as measured by the Wechsler Adult Intelligence Scale, worse general cognitive function and increased cognitive decline over a 2-year period measured with short tests during telephone interviews, and worse general cognitive function in later life as measured by the Mini Mental State Examination (He et al. 2018; Xu et al. 2018; Wang et al. 2016).

Another cohort in which consequences of prenatal exposure to the Dutch famine were investigated, the Dutch Hunger Winter Families Study, showed no overall effect of prenatal undernutrition on general cognitive function in later life but did show a tendency to an effect of exposure in early gestation specifically (de Groot et al. 2011).

In a subsample of the Dutch famine birth cohort study, it was found that 68-year old men exposed to famine in early gestation showed evidence of premature ageing of the brain, as measured by BrainAGE (Franke et al. 2018). BrainAGE is a measure of the estimated age of the brain, based on structural MRI data, compared to a healthy brain model for that particular chronological age (for an overview of this concept see Franke et al. 2010).

Altogether, these findings suggest an increased risk for the development of dementia among people who were undernourished in early gestation. In line with this, Kang

et al. showed a higher prevalence of mild cognitive impairment (MCI) and dementia in elderly exposed to the Chinese famine in prenatal and/or early postnatal life (Kang et al. 2017). However, results of this study should be interpreted cautiously as the findings may be confounded by the older age of the famine exposed participants.

10.4 Ageing Effects on the Body

Another clear manifestation of ageing is impaired physical function, which is associated with increased morbidity and mortality (Hirani et al. 2015). With age, a progressive decline of muscle mass and strength occurs, which is one of the reasons physical function deteriorates (Trombetti et al. 2016). Systematic reviews have shown consistent associations between grip strength, walking speed, chair rising, and standing balance with subsequent morbidity and mortality (Cooper et al. 2010, 2011).

Animal studies have shown that prenatal undernutrition is associated with poor physical function in later life. For example, offspring of sheep that were undernourished during pregnancy showed reduced voluntary physical activity as an adult, with male sheep walking a smaller distance than female sheep (Donovan et al. 2013). Also, rats that were prenatally undernourished showed reduced locomotor activity (Duran et al. 2005).

Whereas many famine-based studies have investigated potential associations between prenatal famine exposure and cognitive function as well as with age-related diseases such as type 2 diabetes and heart disease as we will describe below, to the best of our knowledge only one study has examined physical function and frailty after prenatal famine exposure. In the Dutch famine birth cohort, it was shown that at age 68 years, men who had been exposed to the famine in early gestation had lower grip strength and a lower physical performance score, which was based on a timed walk, repeated chair stands, and a standing balance test. Frailty was not affected by prenatal famine exposure, however the sample size was small ($n = 150$) and results may have been biased by selective participation of the more healthy cohort members (Bleker et al. 2016).

10.5 Ageing-Associated Chronic Diseases

There is abundant evidence that poor prenatal nutritional conditions lead to unfavourable metabolic and cardiovascular outcomes, such as obesity, glucose intolerance, insulin resistance, hypertension and increased risk for type 2 diabetes and cardiovascular disease (see below). Metabolic and cardiovascular abnormalities are related to cognitive ageing and are known to increase the risk for dementia disorders (Bhat 2010). They are also related to decreased physical function and have a clear negative effect on lifespan (Kones and Rumana 2017). Prenatal undernutri-

tion may thus also indirectly affect ageing and longevity through programming of cardio-metabolic health.

10.5.1 Cardiovascular Diseases

There is evidence from many different famine-based studies that prenatal undernutrition increases the risk for developing hypertension and cardiovascular disease. Several studies that investigated consequences of prenatal exposure to the Chinese famine showed that individuals who were in utero during the Chinese famine have a higher mean blood pressure and more often have hypertension in middle age compared to unexposed individuals (Li et al. 2011; Wang et al. 2012). In addition, Li et al. showed that this was particularly the case for those exposed individuals who had a western style diet and/or those who developed overweight as adults (Li et al. 2011). Another study found that it was mainly women that had been prenatally exposed to the Chinese famine who suffered from higher blood pressure and hypertension (Chen et al. 2014).

The Nigerian civil war between 1967 and 1970 caused a severe famine in Biafra. People who were in utero during this period or who were small infants had higher blood pressure around 40 years of age and displayed an almost 3 three times higher chance of developing hypertension (Hult et al. 2010). Similarly, men and women prenatally exposed to the Dutch famine had higher blood pressure and a higher prevalence of hypertension in middle to late age (Stein et al. 2006).

Hypertension is a very important risk factor for cardiovascular disease and indeed one study among a Chinese cohort showed that those with hypertension had a doubled risk of developing cardiovascular disease. When also taking prenatal famine exposure into account, the risk increased to an odds ratio of almost 3.5 for those with both hypertension and prenatal famine exposure. This was especially true for women and those living in urban areas or those with central obesity (Shi et al. 2018).

Particularly relevant with respect to the ageing aspect is evidence that comes from the Dutch famine birth cohort study. Here, it was shown that people who were conceived during the famine and were thus exposed to undernutrition during the first trimester of pregnancy not only developed coronary heart disease more often, but also were on average 3 years younger at the time of diagnosis compared to controls (Painter et al. 2006; Roseboom et al. 2000a).

10.5.2 Metabolic Diseases

Instigated by the thrifty phenotype hypothesis, which proposes that the epidemiological associations between poor fetal and infant growth and the subsequent development of type 2 diabetes and the metabolic syndrome result from the effects of poor nutrition in early life, which produces permanent changes in glucose-insulin

metabolism, many famine-based studies have investigated the long-term associations between prenatal famine exposure and metabolic outcomes, including obesity, lipid and glucose metabolism and type 2 diabetes (Hales and Barker 2001). The evidence for a positive association is abundant.

Studies in cohorts of people prenatally exposed to the Dutch famine, the Chinese famine and the Biafra famine have all shown positive associations between prenatal famine exposure and obesity in later life (Hult et al. 2010; Ravelli et al. 1999; Liu et al. 2017). The same holds for lipid metabolism. Examination of lipid metabolism in people exposed to the Dutch or the Chinese famine in utero demonstrated an unfavourable effect of prenatal undernutrition on lipid metabolism, with higher levels of total cholesterol, LDL and triglycerides (Roseboom et al. 2000b; Lumey et al. 2009; Wang et al. 2017). Both the associations between prenatal famine and obesity and between prenatal famine and lipid metabolism seemed to mainly concern exposed women (Ravelli et al. 1999; Lumey et al. 2009; Wang et al. 2017).

Concerning glucose metabolism and prevalence of type 2 diabetes, the evidence that prenatal famine exposure affects these outcomes is also strong (for an extensive review see de Rooij et al. 2014). Compared to unexposed controls, glucose levels in adult life were shown to be higher in those prenatally exposed to the Dutch famine, the Chinese famine and the Biafra famine (Hult et al. 2010; Ravelli et al. 1998; Li et al. 2010). One study examined the prevalence of type 2 diabetes as measured by use of medication in a database of 325.000 Austrian patients and showed it to be higher among people who had experienced one of the Austrian famines in 1918, 1936, or 1946 around the time of birth (Thurner et al. 2013). The prevalence of type 2 diabetes based on glucose measurements was also shown to be higher after prenatal exposure to the Dutch and Biafra famines (Hult et al. 2010; Ravelli et al. 1998).

Taking all the famine-based studies together, there seems to be plenty of evidence suggesting that prenatal undernutrition leads to premature ageing of the brain and the body as well as an increased risk for cardiovascular and metabolic diseases.

10.6 Longevity

Given the abundance of evidence for the negative effects of prenatal undernutrition on ageing symptoms and ageing-associated diseases, one would expect lifespan to be reduced after prenatal undernutrition. Indeed, as already discussed in the introduction, lifespan was substantially reduced in a study in which mice were prenatally underfed (Ozanne and Hales 2004).

There have been quite a lot of human studies backing this up. Lindeboom et al. investigated a sample of Dutch individuals who were born around the time of the Potato famine in the Netherlands in 1846–1847. They showed that exposed men lost on average 4 years and exposed women lost on average 2.5 years of life after age 50. Those in lower social classes were more affected than those in higher social classes (Lindeboom et al. 2010).

In the Dutch famine birth cohort study, women prenatally exposed to the 1944–1945 famine seemed more vulnerable than men, at least up to the age of 63 years. At that age, women exposed to famine in early gestation had died more often than unexposed women, predominantly from cardiovascular diseases and cancer (van Abeelen et al. 2012). A very large study of men born around the time of the Dutch famine, showed that at the age of 63 years, men exposed to the famine in early gestation did not show higher mortality due to cardiovascular disease or cancer, but did show higher mortality due to other natural causes and also due to external causes (Ekamper et al. 2015). Additional analyses in this cohort revealed that those from lower social background or education died at a younger age, but that the associations between prenatal famine exposure and mortality were independent of these variables (Ekamper et al. 1982).

Hanson and Smith used the Utah Population Database, which included individuals who were and were not exposed to severe food shortage in Utah in the mid-19th century. Their findings also showed sex differences, which seem largely in line with the findings from the Dutch studies described above. Men who had been exposed to poor nutritional circumstance for the most part of gestation had a reduced lifespan after 50 years of age compared to unexposed men. Exposed women also showed increased mortality after 50 years of age, but this increased mortality risk declined and showed a crossover with unexposed women at approximately 70 years of age (Hanson and Smith 2013).

A study of over 800.000 individuals who had or had not been exposed to the severe 1866–1868 famine in Finland did not demonstrate any evidence for associations between prenatal famine exposure and adult mortality (Kannisto et al. 1997). However, a re-analysis of these data taking cohort heterogeneity caused by selection sources into account, resulted in a different conclusion. Men prenatally exposed to the Great Finnish famine had a shorter life expectancy than unexposed men. For women the results were less conclusive (Doblhammer et al. 2013).

All in all, the combined animal and human data provide a good evidence basis for a negative effect of prenatal undernutrition on longevity.

10.7 Mechanisms

10.7.1 Direct Effects on Organ Development

A lack of nutrients during the prenatal period may directly affect the development of organs. These alterations may render the organs more vulnerable for effects of the ageing process. Evidence from animal experimental studies has shown such programming effects on a number of different organs and have also shown that changes lead to increased vulnerability for ageing and ageing associated diseases. There is also some evidence for direct effects of prenatal undernutrition on organ development in humans.

10.7.2 The Brain

Several rodent studies have shown that manipulation of the maternal diet during pregnancy induces changes in brain development with lasting effects on the brain and cognitive function in later life. Prenatal protein malnutrition in rats affected the normal development of hippocamapal CA3 pyramidal cells with changes still observable in old age (Diaz-Cintra et al. 1994). Gould et al. provided evidence in a mouse model that poor maternal nutrition shortly before conception is sufficient to cause abnormal brain development and adult memory loss (Gould et al. 2018).

Antonow-Schlorke et al. performed a detailed analysis of the fetal baboon brain after nutrient restriction from early to mid gestation and found a whole cascade of compromised processes at the brain cellular, genetic and transcriptional level (Antonow-Schlorke et al. 2011). That these adaptations have lifelong consequences for the brain was shown in a study by Franke et al. in which the brains of prenatally nutrient restricted baboons were shown to display premature ageing at a relatively young age (Franke et al. 2017). In a subsample study of the Dutch famine birth cohort, analyses of structural MRI scans demonstrated that men, but not women, exposed to undernutrition in early gestation had smaller intracranial volumes than unexposed men. Intracranial volume is a measure of the maximum brain size an individual has achieved, which thus seemed to be decreased in men who experienced undernutrition in early gestation (de Rooij et al. 2016). Cognitive and brain ageing and subsequent development of neurodegenerative diseases have been suggested to be influenced by the size of the brain. It has been postulated that size of the brain is an important determinant of brain and cognitive reserve capacity and large reserve capacity postpones the development of clinical symptoms of brain ageing (Mortimer et al. 2005; Stern 2002). Diminishing brain reserve capacity may thus be one of the ways in which prenatal undernutrition affects cognitive decline.

10.7.3 The Cardiovascular System

There have been many experimental studies in rodents on the effects of prenatal undernutrition on the cardiovascular system. Together they have provided clear evidence that prenatal undernutrition alters the structural development of the heart, vessels and their function. For example, protein restriction during gestation resulted in a lower weight of the heart in adult life, a decreased number of cardio myocytes and increased cardiac fibrosis (Amer et al. 2017). Nutrient restriction in pregnant rats led to deficient aortic development in the offspring followed by hypertrophic remodelling and larger aortic compliance in the perinatal period. It also led to a larger heart weight/body weight ratio in male offspring at birth, while in adulthood both males and females had a higher heart weight/body weight ratio and also a larger left ventricular mass and lower ejection fraction (Gutierrez-Arzapalo et al. 2017; Rodriguez-Rodriguez et al. 2017). In mice, negative effects of poor nutrition

in utero on adult offspring cardiac energy metabolism were found (Beauchamp et al. 2015). A low protein diet of female mice during the pre-implantation period induced hypertension and vascular dysfunction in the offspring in later life and also altered homeostasis of the renin-angiotensin-system (Watkins et al. 2010).

Direct effects of maternal undernutrition during gestation on development of the heart and vessels in humans is scarce. One study in the Dutch famine birth cohort investigated the intima media thickness of the aortic and femoral arteries and showed that this was smaller in participants who had been exposed to famine in prenatal life (Painter et al. 2007). This was un expected finding, as smaller intima media thickness is associated with a decreased risk for cardiovascular disease and could thus not explain the previously demonstrated higher heart disease risk among the famine exposed (Painter et al. 2006; Bots et al. 1997). More studies are needed to shed further light on potential direct effects of prenatal undernutrition on development of the cardiovascular system.

10.7.4 The Pancreas

In line with the cardiovascular system, evidence from experimental studies for the negative effects of prenatal undernutrition on the development of the pancreas and its function is wide. Several studies have shown that prenatal nutrient or protein restriction affects development of the pancreas and beta cells thereby inducing glucose intolerance and diabetes in later life. Already in 1990, Snoeck et al. showed that feeding pregnant rats a protein restricted diet led to a reduction in pancreatic beta cell proliferation and size of the islets in the head as well as the tail of the pancreas mass in the offspring (Snoeck et al. 1990). Berney et al. also applied a protein restricted diet in pregnant rats which resulted in more, but smaller pancreatic islets in the offspring with a reduction in the amount of beta cells (Berney et al. 1997). A study in male offspring of protein restricted mothers demonstrated particular effects with ageing. The insulin secretory response to glucose challenge in these offspring was impaired at all ages, with a clear effect of increasing age (Morimoto et al. 2012). Similar results have been obtained in a study investigating the consequences of prenatal exposure to the Dutch famine. Intravenous glucose tolerance tests were performed in a subsample from the Dutch famine birth cohort. Besides showing that prenatal famine exposure was associated with impaired glucose tolerance, it was also shown that those exposed to famine in early/mid gestation had impaired insulin secretion suggesting that the development of the beta cells had been impaired by exposure to poor nutritional circumstances in utero (de Rooij et al. 2006).

Direct negative effects of prenatal undernutrition on development and function of organs are highly likely to interact with different cellular and system processes that may also be programmed by prenatal undernutrition. Below we give a short description of a number of these mechanisms that may further explain how prenatal undernutrition exerts influence on ageing and longevity.

10.7.5 Telomeres

Telomeres are DNA repeat sequences that cap the ends of chromosomes. Telomeres decrease in length by a predictable amount with each cell division. When telomere length becomes critically short, the cell is no longer able to replicate and enters cellular senescence. Telomere length has been postulated as either a mechanism of or a marker for cellular ageing and longevity regulation (Calado and Young 2009). It has been associated with many diseases related to ageing as well as to lifespan itself. Experiments in rats showed that feeding rat mothers a protein restricted diet leads to reduced telomere length in the kidney, aortic tissue and pancreatic islet tissue in the offspring, possibly explaining the shortened lifespan in these animals (Jennings et al. 1999; Tarry-Adkins et al. 2008, 2009). One study in humans assessed the potential association between prenatal famine exposure and telomere length. At the age of 68 years, individuals who had been exposed to the Dutch famine in early gestation did not display shortened telomere length compared to unexposed individuals though (de Rooij et al. 2015). A potential explanation for this null finding is that telomere length was assessed in peripheral leukocytes, which is not strongly correlated with telomere length in other organs, such as the brain, heart, and kidney (Dlouha et al. 2017).

10.7.6 Oxidative Stress and Mitochondria

Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS), a natural by-product of the normal metabolism of oxygen in the body, and the ability of the body to neutralize ROS. Oxidative stress can result in oxidative damage to cells, tissues or organs and can cause telomere shortening independently of cell division. Oxidative stress has been implicated in ageing and many age-associated diseases, such as cancer, diabetes, cardiovascular disease and neuro-degenerative diseases. It has also been suggested as one of the causes of cellular ageing (Finkel and Holbrook 2000). Studies in the progeny of rats who received a protein restricted diet in utero showed an increased production of ROS and a decreased oxidative defence resulting in increased oxidative stress (Tarry-Adkins et al. 2008, 2009). Up to date, no studies have investigated oxidative stress related markers in human studies on prenatal undernutrition and ageing.

Closely related to oxidative stress is mitochondrial dysfunction. Mitochondrial dysfunction results in the generation of increased ROS and has been put forward as a central developmental programming pathway affecting many different tissues (Ozanne 2014). Prenatal protein restriction in rats followed by accelerated postnatal growth not only resulted in accelerated telomere shortening but also in an oxidative stress phenotype with mitochondrial dysfunction in the muscle (Tarry-Adkins et al. 2016). Here also, no studies have investigated mitochondrial dysfunction yet in human studies on prenatal undernutrition and ageing.

10.7.7 Inflammation

There is increasing evidence that chronic upregulation of pro-inflammatory mediators are implicated in the ageing process and diverse age-related diseases including cardiovascular disease, diabetes and dementia (Chung et al. 2009). Experimental evidence suggests that this chronic upregulation may be programmed by undernutrition in utero. Desai et al. showed that a 50% food restriction of the maternal diet of rats led to increased basal inflammation but decreased inflammation responses to inflammatory provoking stimuli in the offspring (Desai et al. 2009). Another rat study showed that malnutrition during the gestational period attenuated the severity of the acute inflammatory response as well as the chronic inflammatory response (Barreto et al. 2012; de Oliveira Assis et al. 2011). Neither basal inflammation nor inflammatory responses have been examined in humans exposed to undernutrition during gestation.

10.7.8 Epigenetic Mechanisms

An overarching mechanism that may underlie both structural and biological adaptations in response to undernutrition in utero is altered gene expression through epigenetic processes. Epigenetics refers to the reversible changes in DNA structure that control the amount of MRNA and protein production and therefore influence cell and tissue development. There are different epigenetic processes, of which DNA methylation is the most studied. Epigenetic alterations induced by prenatal undernutrition are a likely explanation for the findings in ageing-associated parameters in the famine studies. The Dutch Hunger Winter families study has been pivotal in establishing DNA methylation differences as a mechanism underlying clinical effects of prenatal exposure to famine. Within this cohort, a range of studies has been performed and all together provided consistent evidence for epigenetic changes after prenatal exposure to famine. A first study in 2008 was performed on DNA isolated from peripheral blood cells from 244 cohort members at 59 years of age and demonstrated less DNA methylation of the imprinted IGF2 gene in those with periconceptual exposure compared to their unexposed, same-sex siblings (Heijmans et al. 2008). Following this first study, the group went on showing that periconceptual famine exposure was associated with differential methylation of sites in genes along pathways that relate to growth and metabolism (Tobi et al. 2015). Taking a final crucial step, they demonstrated that the altered DNA methylation levels after prenatal famine exposure mediated the association between prenatal undernutrition and increased levels of BMI and serum triglycerides (Tobi et al. 2018).

A study by Waterland et al. examined potential effects of seasonal variation in nutrient availability during gestation on methylation levels of metastable epialleles in people from the Gambia. Methylation levels differed according to the season in which people were conceived (Waterland et al. 2010). These findings were partly

replicated in a study of individuals who were and were not prenatally exposed to a severe famine in Bangladesh between 1974 and 1975, showing significant differences in DNA methylation at seven metastable epialleles (Finer et al. 2016).

Prenatal nutritional circumstances are thus likely to exert their effects on ageing and longevity via DNA methylation.

10.8 Relevance and Implications

The number of elderly is growing rapidly worldwide. Although ageing is an inevitable biological process, the health with which old age is reached can be optimised, reducing societal costs as well as increasing the individual's quality of life. Optimisation of health in older age has mainly been tackled by aiming at prevention and intervention measures in middle to late life. However, evidence presented in this chapter demonstrates that suboptimal nutritional circumstances in the prenatal environment could be the starting point of an accelerated ageing process meaning that acting upon the ageing process has to start at a much earlier point than in middle to late life.

The findings presented here are of importance from a public health perspective at different levels. First, prenatal nutrition may be a modifiable factor affecting healthy ageing. Second, it may ultimately lead to the detection of people who are at high risk for developing ageing-associated diseases with the possibility of early intervention. These may also include others who have experienced a suboptimal start in life such as offspring of women suffering from pregnancy induced hypertension, placental insufficiency, excessive vomiting in pregnancy, those who are born pre-term and possibly those who are conceived through assisted reproduction techniques. Third, understanding the processes by which prenatal undernutrition leads to accelerated ageing may provide clues on how we can detect early ageing and implement interventional approaches when conditions are still reversible.

10.8.1 Pregnancy Intervention

If the present study hypothesis holds, one way to increase the number of healthy life years would be to improve the nutrition of pregnant women. Although severe malnutrition such as the shortages that occurred during the famine are uncommon in the Western world today, still many babies have a suboptimal nutritional start in life due to factors such as dieting of the mother (1 in 4 women of reproductive age diet at any given moment in time) and consuming an unbalanced diet in general. Worrying data from the UK suggested that only 3% of the women who get pregnant abide with the healthy diet guideline of less than 7 units of alcohol a week and taking enough folic acid, let alone taking fruits and vegetables daily (Inskip et al. 2009). Public health strategies should therefore be aimed at improving unbalanced and inadequate diets. It may seem like a long shot to achieve healthy ageing starting at conception,

but its impact may be much greater than trying to improve people's diet during their adult life as the experiments by Ozanne et al. suggest (Ozanne and Hales 2004). Furthermore, it may be more feasible to change the diet of women during pregnancy, which is only a short period of time and for the life-long good of their child than change the lifelong diet style of adults.

10.8.2 Detection and Intervention

Findings relating prenatal undernutrition and ageing are also relevant for the development of detection methods and intervention therapies by which we can delay the onset of typical diseases associated with older age. Analysis of the mechanisms underlying the potential link between the prenatal nutritional environment and ageing will expand our knowledge on ageing processes before disease has set in. This knowledge will be useful for future studies investigating potential detection and intervention strategies interfering in the ageing process before disease has developed.

10.8.3 Future Recognition of High Risk Groups

Placed in a broader perspective, a poor start in life may also be experienced by those whose mothers suffer from pre-eclampsia or hyperemesis gravidarum, those who are born pre-term and possibly those who are conceived by in vitro fertilization. Currently, we have little knowledge on the effects of poor circumstances early in life on the ageing process in humans. Future studies should shed light on these potential effects so that in the future we will have more knowledge on groups that are at high risk for developing ageing-associated diseases and premature ageing. Early detection of high risk groups provides the possibility of early intervention.

10.9 Conclusion

Prenatal undernutrition increases the risk for ageing-associated disorders, seems to accelerate the ageing process and decrease longevity. Given that moderate fetal undernutrition is widespread in both developing and developed countries, caused by poverty and natural disasters, but also by maternal dieting, placental insufficiency, or a multiple pregnancy, these findings are highly relevant for the human situation.

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Chapter 11
Influence of Maternal Obesity on the Long-Term Health of Offspring

Emma C. Johns, David Q. Stoye, Liu Yang and Rebecca M. Reynolds

Abstract Maternal obesity is a growing public health problem across the world. In many high-income countries, more than 1 in 5 pregnant women are now categorised as obese. Compared to offspring born to normal weight women, babies born to obese mothers have a greater risk of adverse health outcomes across their lifespan, including obesity, cardiovascular disease and premature mortality in adulthood. The mechanisms through which maternal obesity elicits this long-term influence on offspring health is believed to represent a 'programming' effect of the obesogenic in utero environment. Alterations in maternal glucose and insulin sensitivity and hypothalamic-pituitary-adrenal axis regulation have been described in association with maternal obesity and may contribute to fetal programming. In addition, epigenetic modifications in maternal adipose and feto-placental tissues have been described, although their clinical significance remains uncertain. Lifestyle and medical interventions have shown limited success in attenuating the impact of maternal obesity on offspring growth and body composition during infancy, although longer-term follow-up is required.

Keywords In utero environment · Fetal programming · Epigenetic modification · Maternal obesity · Long-term health outcome · Lifespan

E. C. Johns · D. Q. Stoye · R. M. Reynolds (✉)
MRC Centre for Reproductive Health, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK
e-mail: r.reynolds@ed.ac.uk

L. Yang · R. M. Reynolds
BHF/University Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK

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11.1 The Rising Challenge of Maternal Obesity

The obesity epidemic is one of the greatest global public health challenges of the 21st century. Defined as a body mass index (BMI) ≥ 30 kg/m^2, obesity is now recognised as a distinct disease process with a high burden of associated morbidity and mortality. The worldwide prevalence of obesity almost tripled between 1975 and 2016 (World Health Organization 2016). In this time period, the number of obese adults increased from approximately 100 million to 650 million, equating to 13% of the world's adult population (World Health Organization 2016; NCD Risk Factor Collaboration (NCD-RisC) 2017). The burden of obesity has increased dramatically in both high-income and low- and middle- income countries (Ford et al. 2017). Between 1980 and 2015, the prevalence of obesity doubled in more than 70 countries, with an ongoing increase observed in most other countries (The GBD 2015 Obesity Collaborators 2017). Similarly concerning trends are evident amongst children and adolescents, with the worldwide prevalence of obesity amongst 5–19 year olds increasing from 1% in 1975 to 6% of girls and 8% of boys in 2016 (World Health Organization 2016). In the United States (US), 16.9% of children and adolescents were obese in 2009–10 (Ogden et al. 2012).

In this context, it is unsurprising that obesity during pregnancy is an emerging crisis. In the United Kingdom (UK), the estimated prevalence of maternal obesity has increased from 7–10% in 1990 to 15–19% in the 2000s (Heslehurst et al. 2007, 2010; Kanagalingam et al. 2005). In 2016, data from 20 European countries estimated the prevalence of pre-pregnancy obesity (or obesity in women aged 20 years and older from 2009 World Health Organization (WHO) data where pre-pregnancy data was unavailable) was greater than 20% in the UK, Ireland, Spain and Hungary, and was greater than 10% in 17 of the 20 countries (Devlieger et al. 2016). In the US, the prevalence of obesity in women of reproductive age was approximately 31.8% in 2011–12 (Ogden et al. 2014). The issue of maternal obesity is not limited to high-income countries. Indeed, in the 10-year period between 2005 and 2014, the estimated number of obese pregnant women increased most markedly in lower-middle-income countries (Chen et al. 2018). For example, increases of 69.1% in Pakistan, 72.7%% in Indonesia and 96.9% in Nigeria were identified in analyses using WHO data (Chen et al. 2018). In other middle-income and high-income countries with a high prevalence of obesity, for example the US and Mexico, more modest increases were noted (11.3% and 15.7% respectively). Whilst the absolute number of obese pregnant women in low income countries is considerably lower than countries from other income groups, increases have also been observed in these areas. For example, increases of 111.6% in the United Republic of Tanzania and 102.2% in the Democratic Republic of Congo were noted between 2004 and 2015.

Obesity is the consequence of multiple, complex interacting aetiological factors. The increased consumption of energy-dense foods, reduced physical activity and adoption of sedentary behaviours are key drivers leading to the accumulation of excess body fat in populations. The adoption of these lifestyle changes in high-income countries, and more recently in low- and middle-income countries in parallel with

social and economic globalisation, have been instrumental in the development of the global obesity epidemic (Costa-Font and Mas 2016; Popkin et al. 2012). Aside from environmental influences, a diverse range of factors and traits have received attention for their role in determining susceptibility to or propagation of obesity in adults (Ghosh and Bouchard 2017). These include inflammation, ethnicity, adipose tissue dysfunction, hormonal abnormalities, variation in the central regulation of appetite and energy balance, and alterations in the gut microbiome (Ghosh and Bouchard 2017). Obesity is heritable within families, suggesting genetic factors also play a role in determining propensity to this disease (Harris and North 2010). However, whilst more than 100 genetic loci have been identified in association with obesity, these are typically characterised by small effect sizes when considered individually (Ghosh and Bouchard 2017; van Dijk et al. 2015). Epigenetic signals, referring to alterations in gene expression in response to environmental stimuli which do not reflect changes in the underlying DNA sequence, can be transmitted between generations and are also thought to modulate susceptibility to obesity (Ghosh and Bouchard 2017; van Dijk et al. 2015).

11.2 Implications of Maternal Obesity on Long-Term Offspring Health

Maternal obesity is known to increase the risk of pre- and post-natal pregnancy complications including miscarriage, macrosomia (birth weight over 4 kg), stillbirth and congenital malformations (Sebire et al. 2001; Owens et al. 2010). However, the offspring of obese women also demonstrate an increased risk of morbidity and mortality in later life. Compared to offspring born to lean women, those born to obese women are more likely to be obese in childhood and adulthood (Gaillard et al. 2014; Yu et al. 2013; Eriksson et al. 2003). Elevated maternal BMI is also associated with an increased risk of cardiovascular disease, stroke, type 2 diabetes mellitus (statistically significant in females only) and premature all-cause mortality in adult offspring (Forsén et al. 1997; Eriksson et al. 2014; Reynolds et al. 2013). An increased risk of death from coronary heart disease was also demonstrated in a Finnish cohort study, limited to offspring born to mothers of below average stature (Forsén et al. 1997). Furthermore, maternal obesity has been associated with increased risk of childhood asthma and onset of type 1 diabetes mellitus (in the absence of history of parental diabetes) in offspring (Forno et al. 2014; Hussen et al. 2015). Finally, impaired cognitive performance and neurodevelopment have been reported in the offspring of obese women, however data are conflicting and these relationships are not firmly established (Contu and Hawkes 2017; Godfrey et al. 2017).

Whilst the mechanisms through which maternal obesity mediates its impact on offspring health are not fully understood, both pre- and postnatal factors are implicated, as well as shared genes. The concept of early life ‘programming’ describes the adaptive changes which occur in the fetus, in response to in utero exposures,

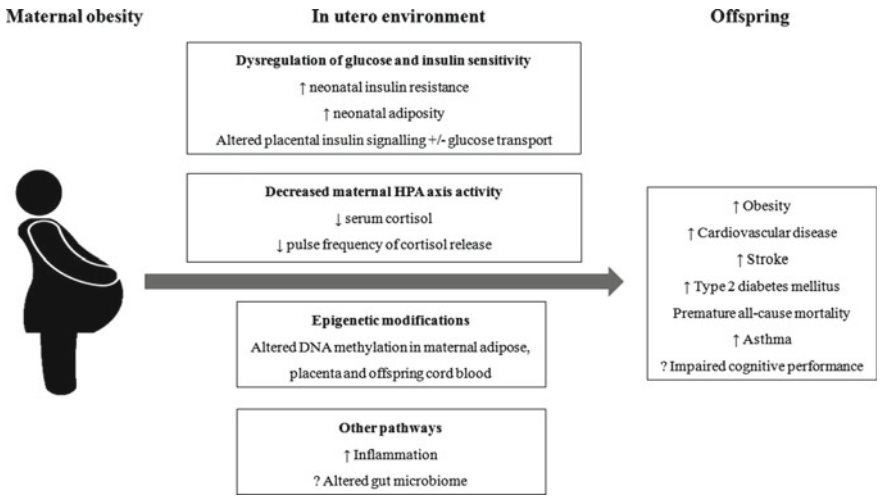

Fig. 11.1 Proposed mechanisms leading to adverse long-term health outcomes in the offspring of obese women

which determine the propensity to disease in adulthood (Barker 2004). Maternal obesity, therefore, appears to programme offspring for an adverse long-term health trajectory. The metabolic environment that the developing fetus is exposed to in an obese mother compared to a lean mother includes altered nutrient supply of glucose, lipids and essential fatty acids, dysregulation of hormonal axes including the hypothalamic-pituitary-adrenal (HPA) axis, dysregulation of glucose and insulin sensitivity, inflammatory cytokines, microbiome and epigenetic pathways in response to obesity, offering potential insights into the prenatal mechanisms leading to adverse health outcomes in the offspring. Following birth, the offspring of obese mothers are more likely to be exposed to an obesity promoting or 'obesogenic' postnatal environment, potentially contributing to an elevated future risk of obesity and metabolic disease. The potential for the postnatal environment to determine offspring risk of obesity was demonstrated in rats, where obesity-prone pups cross-fostered to obesity-resistant dams improved their insulin sensitivity in adulthood, whereas obesity-resistant pups cross-fostered to genetically obese dams developed increased adiposity, reduced insulin sensitivity and altered expression of hypothalamic receptors involved in the regulation of energy balance (Gorski 2006).

This chapter will discuss the regulation of glucose and insulin, the HPA axis, and epigenetic pathways in obese pregnant women, and consider the potential role of these pathways in the developmental programming of maternal obesity on the offspring (Fig. 11.1). Consideration will also be given to interventions which may curtail the burden of maternal obesity, potentially benefiting the health of subsequent generations.

11.3 Glucose and Insulin

11.3.1 Glucose and Insulin Regulation in Normal Pregnancy

Normal pregnancy is characterised by several changes in maternal glucose and insulin regulation in order to optimise nutrient supply to the developing fetus. From pre-pregnancy to the third trimester, there is an approximate 50% reduction in peripheral insulin sensitivity and a 30% increase in hepatic glucose production (Catalano et al. 1991, 1992). Pancreatic beta islet cells adapt to these changes by producing increased amounts of insulin, allowing the maintenance of normal, or perhaps slightly lower than pre-pregnancy, maternal blood glucose concentrations (Sorenson and Brelje 2009). This response is mediated, at least in part, by placental hormones including prolactin and placental lactogens, which have been shown to promote growth and increase secretory activity of the beta islet cells (Sorenson and Brelje 2009; Brelje et al. 1993). The insulin resistance associated with pregnancy appears to resolve within days of delivery (Ryan et al. 1985).

Glucose is the primary energy substrate for the fetus and placenta and is essential for normal fetal growth and development. As the fetus produces negligible endogenous glucose, it is reliant on the supply from the maternal circulation. The placental syncytiotrophoblast is a multinucleated cell layer which forms a barrier regulating nutrient transfer (Lager and Powell 2012). Glucose is transported across the syncytium, down its concentration gradient, by glucose transporter proteins (GLUTs) on the maternal-facing microvillous membrane (MVM) and fetal-facing basal membrane (BM). A range of GLUT isoforms are expressed in the placenta, including GLUT-1, GLUT-3, GLUT-4, GLUT-8, GLUT-9 and GLUT-10 (Lager and Powell 2012). GLUT-1 is the principal placental isoform and is present in abundance from early pregnancy, with greatest expression at term (Lager and Powell 2012; Illsley 2000). GLUT-4, an insulin-sensitive transporter found primarily in adipose tissue and skeletal muscle, is expressed most highly in the placenta during the first trimester (Ericsson et al. 2005).

11.3.2 The Impact of Maternal Obesity on Fetoplacental Glucose and Insulin Regulation

The offspring of obese women demonstrate alterations in glucose and insulin regulation at birth. In a study of 32 overweight/obese women and 20 lean controls with normal glucose tolerance and healthy term pregnancy, umbilical vein plasma glucose level (a surrogate of fetal plasma glucose level) was positively correlated with maternal BMI (Acosta et al. 2015). Notably, there was no association between maternal fasting plasma glucose level and umbilical vein plasma glucose level. In this prospective cohort study, increasing birthweight was positively associated with maternal BMI ($r^2 = 0.16$, $p = 0.03$), umbilical vein plasma glucose ($r^2 = 0.24$, $p =$

0.008), umbilical vein plasma insulin (r^2 0.18, $p = 0.04$), and placental weight ($r^2 = 0.34$, $p = 0.001$).

Neonatal metabolic phenotype was also assessed in a study comparing the offspring of 68 obese and 53 lean women with normal glucose tolerance following elective caesarean section (Catalano et al. 2009). The offspring of obese women had significantly greater fat mass, percent body fat and ponderal index (a ratio of weight to length) than offspring of lean women, although there was no difference in weight or lean body mass. Newborn insulin resistance was quantified using the homeostatic model assessment of insulin resistance (HOMA-IR), a metric calculated using umbilical cord plasma glucose and insulin concentrations. Insulin resistance was significantly greater in the offspring of obese mothers compared to the offspring of lean mothers. There was a positive relationship between maternal pre-pregnancy BMI and neonatal insulin resistance ($r = 0.31$, $p = 0.007$), which remained significant after adjustment for maternal confounders and neonatal fat mass or percent body fat ($r = 0.24$, 0.003). A weakly positive correlation was identified between maternal and neonatal insulin resistance ($r = 0.35$, $p = 0.0002$). Furthermore, neonatal insulin resistance was positively associated with neonatal adiposity ($r = 0.32$, $p = 0.0008$).

These results suggest that maternal obesity is associated with the development of fetal metabolic compromise in utero. Whether the observed neonatal hyperinsulinemia and insulin resistance is a precursor of, or response to, increased fetal fat mass is unknown. Whilst insulin promotes lipogenesis in the non-pregnant state, maternal insulin resistance during pregnancy enhances lipolysis, thereby increasing the essential supply of free fatty acids available for fetal adipogenesis and organ development (Catalano et al. 2009). Exposure to hyperinsulinaemia during the final third of pregnancy, in the absence of hyperglycaemia, led to fetal overgrowth and increased adipose tissue depots in the fetal rhesus monkey, demonstrating the anabolic capacity of insulin in the fetus (Susa 1984). On the other hand, excess adipose tissue is a key component of the metabolic syndrome in obese adults, where adipocytes demonstrate resistance to insulin-stimulated glucose transport and metabolism (Kahn and Flier 2000). As the association between maternal BMI and neonatal insulin resistance remained significant despite adjustment for neonatal fat mass or percentage body fat (Catalano et al. 2009), the role of alternative mediators, for example genetic and epigenetic factors, must be considered in the development of fetal insulin resistance. Whilst these pathways remain incompletely understood, these findings certainly suggest that maternal obesity leads to modified energy homeostasis in the developing fetus, presenting a potential route through which maternal obesity may increase the long-term risk of metabolic disease in the offspring.

Relatively little is known about the impact of maternal obesity on placental glucose transport and insulin signalling. In the previously discussed study by Acosta et al, placental GLUT expression at term was examined in a subgroup of 33 overweight/obese women and lean controls. A positive correlation was identified between infant birthweight and BM GLUT-1 protein levels (Acosta et al. 2015). However, there was no corresponding association between birthweight and glucose transport activity. In another study of 6 obese and 6 non-obese women, obesity was associated with significantly reduced GLUT-4 mRNA expression in term placental samples (Colomiere

et al. 2009). However, no difference in GLUT-4 protein, GLUT-1 mRNA or GLUT-1 protein levels were observed. Evidence of altered insulin signalling protein levels in the obese placental samples were also identified: insulin receptor substrate (IRS)-2 protein level was increased whilst PI3 p85α (a downstream intracellular mediator of insulin signalling) mRNA and protein levels were decreased, in comparison to lean controls. No difference in protein and mRNA levels of IRS-1 and insulin receptor-β were observed comparing obese and lean groups. Further investigations in larger sample sizes and from samples collected earlier in pregnancy are required to help advance understanding of the impact of obesity on glucose regulation and insulin signalling at the placental level.

11.3.3 Obesity and Gestational Diabetes

Gestational diabetes (GDM) is traditionally defined as 'carbohydrate intolerance of variable severity with onset or first detection during pregnancy', and is characterised by varying levels of hyperglycaemia in the second and third trimesters (World Health Organization 1999). GDM develops when the pancreatic beta cells are unable to adapt sufficiently to overcome the insulin resistance of pregnancy. Mechanistic studies have identified that GDM occurs in women with impaired insulin sensitivity, which is typically unrecognised, prior to pregnancy (Catalano 2014). The prevalence of GDM has increased rapidly in recent decades, with 1 in 7 births globally estimated to be affected in 2017 (Ferrara 2007a; International Diabetes Federation 2017). Obesity is an established risk factor for GDM, with the likelihood of GDM diagnosis increasing with rising maternal BMI (Ferrara 2007b). Obese pregnant women have a nearly four-fold increased risk of developing GDM compared to lean pregnant women, rising to a greater than eight-fold increased risk in the severely obese (Chu et al. 2007). Compared to 2% prevalence of GDM in those with normal BMI, the prevalence of GDM in obese and severely obese women is approximately 5.5% and 11.5% respectively (Kim et al. 2010).

The rising burden of GDM has been implicated as a potential contributor to the obesity epidemic because of the impact for the offspring of being exposed to hyperglycaemia in utero. Offspring exposed to GDM during fetal development have increased childhood adiposity compared to the offspring of women without diabetes and higher BMI in adolescence compared to the background population (Krishnaveni et al. 2010; Hammoud et al. 2018). Exposure to diet-controlled GDM in utero was also associated with reduced insulin sensitivity and increased risk of pre-diabetes/diabetes and metabolic syndrome, compared to the background population, in a cohort of 597 Danish offspring aged 18–27 years (Kelstrup et al. 2013; Clausen et al. 2008, 2009). The increased risk of obesity and metabolic disease in the offspring of women with obesity or GDM raises the possibility that these conditions may influence fetal programming through similar mechanisms.

The impact of maternal obesity, with and without GDM, on the metabolic phenotype and body composition of offspring was assessed in a pilot study conducted

in Germany (Uebel et al. 2014). Umbilical cord plasma metabolic parameters were collected at birth, and anthropometric data collected at timepoints between 1 week to 1 year of age, from the offspring of obese women with GDM (n = 16), normoglycaemic obese women (n = 13) and normoglycaemic lean women (n = 15). Umbilical cord plasma insulin levels and insulin resistance (HOMA-IR) were significantly higher in the offspring of obese women with GDM compared to offspring of normoglycaemic obese and lean women. There was no significant difference observed between groups in any other umbilical cord plasma parameter measured including glucose, leptin, adiponectin and lipid profiles, although the study was not powered to look at these outcomes. The offspring of obese women with GDM demonstrated significantly increased skin fold thickness and fat mass (estimated using a predictive skinfold thickness equation) compared to offspring of normoglycaemic obese and lean women at 1 and 6 weeks of age, with no significant difference observed thereafter. Abdominal preperitoneal adipose tissue (PPA), a surrogate for visceral fat measured using ultrasound (Mook-Kanamori et al. 2009), was significantly increased in the offspring of obese women with GDM compared to normoglycaemic obese and lean women at 1 week of age. Abdominal subcutaneous adipose tissue (SCA), also measured using ultrasound, was significantly increased in offspring of obese women with GDM at 1 week of age in comparison to the lean group only. A significant positive relationship was identified between umbilical cord plasma insulin levels with infant abdominal SCA and PPA at 1 week postpartum. In adjusted linear regression analyses, abdominal PPA at 1 week postpartum was found to independently predict PPA at 1 year. A significant positive relationship between third trimester maternal c-peptide and infant preperitoneal adipose tissue at 1 week, and significant inverse relationship between third trimester high molecular weight adiponectin levels and infant preperitoneal adipose tissue at 1 week, were also identified.

In summary, this study reported that maternal obesity in combination with GDM is associated with offspring hyperinsulinemia at birth and increased fat mass until 6 weeks of age, relative to maternal obesity without GDM. Also of note is the increase in offspring PPA at 1 week of infancy, which was also was found to predict PPA development at 1 year, in offspring of obese women with GDM. PPA and SCA have previously been shown to relate to insulin levels in children, and levels of visceral fat are known to inversely correlate with insulin sensitivity (Tamura et al. 2000; Cnop et al. 2002). Furthermore, visceral fat accumulation has been implicated as a predictor of cardiovascular risk in obese children and lean adults (Polat et al. 2008; Tadokoro et al. 2000; Liu et al. 2003). The similarity in neonatal insulin levels observed in the offspring of normoglycaemic obese and lean women in this study is in contrast to the previously discussed findings by Catalano et al. (Catalano et al. 2009). Differences in the ethnicity of study participants (Caucasian vs. ethnically diverse) and severity of obesity (median maternal BMI of 36.1 vs. 38.4 in obese groups) may contribute to the discrepancy in this finding.

Neonatal cord blood c-peptide level and adiposity were shown to positively correlate with maternal glycaemia in the landmark Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study (The HAPO Study Cooperative Research Group 2008). Recently published follow-up data on 4832 offspring from this cohort showed

that untreated maternal GDM, compared to no maternal GDM, was associated with a significantly increased odds of obesity at 10–14 years of age (odds ratio [OR] 1.58, 95% confidence interval [95% CI] 1.24–2.01, $p < 0.001$), when adjusted for maternal BMI at the time of oral glucose tolerance test (Lowe et al. 2018). There was no significant difference between children of mothers with or without GDM in the likelihood of overweight and obesity, when considered as a composite outcome (OR 1.21, 95% CI 1.00–1.46, $p = 0.74$). Compared to the offspring of women without GDM, GDM offspring were more likely to display sum of skinfolds > 85th percentile (OR 1.57, 95% CI 1.27–1.95, $p < 0.001$), body fat percentage > 85th percentile (OR 1.35, 95% CI 1.08–1.68, $p = 0.007$) and waist circumference > 85th percentile (OR 1.34, 95% CI 1.08–1.67).

Overall, it is possible that alterations in fetal adipose growth and distribution, in response to the hyperglycaemic and hyperinsulinaemic environment of GDM, programme an increased lifelong risk of obesity and cardiometabolic disease in the offspring. Ongoing follow-up of large cohorts, including HAPO offspring, may provide further insights into the long-term consequences of in utero exposure to GDM in later life, for example potential implications on cardiovascular outcomes and mortality.

11.4 The Hypothalamic-Pituitary-Adrenal (HPA) Axis

During pregnancy glucocorticoids play a crucial role in directing fetal maturation and growth. Variation in the type, dose and timing of glucocorticoid exposure can influence offspring health across the life course (Reynolds 2013). Obesity is associated with changes to the maternal HPA axis, and there is preliminary evidence linking these changes with neonatal outcomes (Stirrat et al. 2016). As glucocorticoids directly influence fetal development, alterations in the maternal HPA axis associated with obesity, may hold life-long consequences for offspring.

11.4.1 Glucocorticoid Actions and HPA Axis Regulation Across Pregnancy

Across mammalian species circulating fetal glucocorticoid levels rise towards the end of gestation (Moisiadis and Matthews 2014). Glucocorticoid exposure to developing tissues contributes to a change in structure and function in organs including the heart, liver, brain, and is part of the priming process that is essential for transition to life outside the womb (Fowden et al. 1998). This maturation effect is therapeutically exploited in infants at risk of being delivered preterm. Synthetic glucocorticoids trigger surfactant production in the lungs, and reduces neonatal morbidity and mortality in infants born preterm (Sloboda et al. 2005). However inappropriate exposure to

glucocorticoids may change the typical developmental path of an organ influencing its function in later life.

Outside of pregnancy the secretion of cortisol, the primary glucocorticoid in humans, is tightly regulated by a negative feedback loop involving the HPA axis. Cortisol is released from the adrenal gland in pulses, forming an ultradian rhythm, and release is highest in the morning, forming a diurnal rhythm. Glucocorticoids exert physiological effects by activating glucocorticoid and mineralocorticoid receptors. It has recently been discovered that the pattern as well as concentration of cortisol tissue exposure is important in determining glucocorticoids' actions, altering gene expression, hormonal stress responses and human cognitive function (Kalafatakis et al. 2018; Oster et al. 2017).

During pregnancy the maternal HPA axis undergoes dramatic changes, becoming integrated with the placenta and fetus into one endocrine unit (Lindsay and Nieman 2005). Maternal cortisol levels rise approximately threefold towards the end of pregnancy (Jung et al. 2011). The placenta has a stimulatory effect on the maternal HPA axis, actively secreting corticotropin releasing hormone (CRH), leading to increased maternal Adrenocorticotropic hormone (ACTH) and cortisol release (Goland et al. 1994). Additionally, rising oestrogen levels contribute indirectly to this rise in cortisol by stimulating cortisol binding globulin (CBG) production (Qureshi et al. 2007).

The concentration of cortisol in maternal blood is an important determinant of fetal cortisol exposure. This is supported by studies that have found correlations between cortisol measured in paired measurements of cortisol in maternal blood, and fetal blood or amniotic fluid (Baibazarova et al. 2013; Gitau et al. 1998; Sarkar et al. 2007). Additionally, the placenta plays a key role in controlling the amount of cortisol that is transferred between mother and fetus (Konstantakou et al. 2017). It contains 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2), an enzyme that metabolises cortisol to the less biologically active derivative cortisone (Cottrell et al. 2014).

Regulation of the maternal HPA axis may change according to a diverse range of environmental, maternal and even fetal factors. These include maternal age, ethnicity, parity and psychosocial stress (Bleker et al. 2017; Talge et al. 2007). Drugs can also change cortisol regulation. For instance, liquorice inhibits 11β-HSD2 activity likely resulting in the greater transfer of cortisol across the placenta (Benediktsson et al. 1997). Intriguingly fetal sex may also influence maternal cortisol levels, highlighting the integrated nature of the hormonal stress response system during pregnancy (DiPietro et al. 2011).

11.4.2 Glucocorticoid Exposure, the HPA Axis and Offspring Outcomes

There is a growing body of literature from animal models and human observational studies that supports the hypothesis that fetal glucocorticoid exposure influences health across the life course (Cottrell and Seckl 2009). As more studies have emerged

it has also become evident that the relationship between glucocorticoid exposure and fetal outcomes is not a simple linear relationship with increased glucocorticoid leading to negative health consequences. Instead the timing and type of exposure appears critical in altering offspring health (Singh et al. 2012). Additionally, fetuses appear to have a different susceptibility to cortisol exposure dependent on their sex (Gifford and Reynolds 2017).

Glucocorticoid exposure influences fetal growth and gestation length. Antenatal corticosteroid administration is associated with reduced infant birth weight. Within the ABCD study, a large cohort consisting of over 3000 women, maternal serum cortisol measured in the morning during the 2nd trimester was negatively associated with offspring birthweight (Goedhart et al. 2010). In a metanalysis involving 9 studies and over 1600 participants maternal saliva cortisol was negatively associated with infant birthweight (Cherak et al. 2018). Cortisol measured in a spot urine during mid-morning at 16 weeks' gestation was also negatively associated with fetal growth (Diego et al. 2009). Additionally, maternal cortisol levels may also influence the length of pregnancy, with higher maternal plasma cortisol measured at 15 weeks' gestation being associated with preterm delivery (Sandman et al. 2006).

Antenatal corticosteroid administration and high maternal cortisol are also associated with adverse metabolic phenotypes across the life course. Administration of antenatal steroids have been associated with higher blood pressure at 14 years of age (Doyle et al. 2000), and insulin resistance at age 30 years (Dalziel et al. 2005). High maternal cortisol measured in maternal serum during the third trimester of pregnancy was linked to increased cardiovascular risk in female offspring at 42 years of age, but not for male offspring (Stinson et al. 2015).

Changes in the maternal HPA axis are associated with both offspring cognition and neurobehaviour, and brain structure represented by MRI. The amygdala, a region of the brain important for emotional processing, appears especially susceptible to alterations in glucocorticoid exposure (Tottenham 2009). Increased maternal cortisol measured in saliva during pregnancy has been associated with increased internalizing symptoms, along with increased neural communication between the amygdala and other brain regions important for emotional processing at 2 years (Graham 2018), and amygdala volume at 7 years (Buss et al. 2012), in female offspring. Not all studies have found a positive association between high maternal cortisol levels and adverse infant neurodevelopment. In a cohort where maternal cortisol was measured in saliva at multiple time-points during pregnancy, infant cognitive scores at 1 year where negatively associated with high maternal cortisol at 15 weeks, and were positively associated with maternal cortisol at 31 weeks. This suggests that the timing of cortisol exposure influences infants cognition differently, and that high maternal cortisol levels towards the end of pregnancy may be advantageous to fetal neurodevelopment (Davis and Sandman 2010).

11.4.3 The HPA Axis as a Link Between Obese Pregnancy and Adverse Offspring Outcomes

Obesity in non-pregnancy is recognised to be associated with dysregulation of the HPA axis (Incollingo Rodriguez 2015). There is a small but growing literature that the maternal HPA axis also differs in the context of obese compared to lean pregnancy. This includes differences in absolute cortisol levels and the pulsatile release.

Increased maternal BMI or measures of adiposity have been associated with lower levels of maternal blood cortisol in four recent studies. Within the ABCD cohort, there was an inverse relationship between maternal BMI and serum cortisol measured during the 2nd trimester (Bleker et al. 2017). In the PREOBE study, which followed 331 women across pregnancy, obese participants with a body mass index (BMI) greater than 30 kg/m^2 had a lower serum cortisol at 24 weeks gestation and at delivery, but not at 34 weeks, compared to lean participants (Berglund et al. 2016). A study of 25 African American women found that markers of maternal adiposity was inversely associated with plasma cortisol measured between 6 and 16 weeks (Luiza et al. 2015). In a longitudinal cohort carried out by our group in Edinburgh, fasting morning serum cortisol was lower in an obese group, including 276 participants with a BMI greater than 40 kg/m^2, compared to 137 lean participants, measured at 16, 28 and 36 weeks' gestation (Stirrat et al. 2016). CRH was also measured in a subgroup of participants, and found to be lower in the obese group at 28 weeks and 36 weeks' gestation. Placental CRH forms a positive feedback loop with cortisol and so this reduced CRH could feasibly be a driver or consequence of the reduced blood cortisol (King et al. 2001).

How these lower blood cortisol levels seen in the context of obese pregnancy translate into fetal exposure of cortisol, and offspring outcomes, is yet to be established. In two studies there was no significant difference in the level of cortisol measured in cord blood at delivery between obese and non-obese mothers (Berglund et al. 2016; Stirrat et al. 2017). However, cord blood cortisol is confounded by the stressful conditions at delivery, and is unlikely to accurately represent fetal cortisol levels at other stages of pregnancy. Low blood cortisol seen in the context of obese pregnancy may lead to reduced fetal glucocorticoid exposure during pregnancy. Just as increased cortisol exposure is associated with low birth weight and shorter birth gestation low maternal cortisol may contribute to macrosomia and prolonged gestations, both known complications of obese pregnancy. Supporting this hypothesis blood CRH levels measured at 28 weeks has been negatively associated with the gestational length of pregnancy ($r = -0.49$ $p = 0.04$), in obese pregnancy (Stirrat et al. 2016). Additionally, there was a negative trend between cortisol and birthweight in an obese group ($r = -0.13$, $p = 0.066$).

There is also emerging evidence that the pulsatility of cortisol release changes in obese pregnancy. Obesity has been associated with a lower morning rise in cortisol (Stirrat et al. 2016), and high evening cortisol, measured in saliva (Aubuchon-Endsley et al. 2014), suggesting potential alterations in the diurnal rhythm. Additionally, in the first study to assess cortisol ultradian rhythms in human pregnancy the pulse fre-

quency of cortisol measured in interstitial fluid significantly reduced with advancing gestation in obese but not lean pregnancies (Stirrat et al. 2018). As the pulsatility of glucocorticoid exposure influences glucocorticoid mediated gene expression, this alteration in the HPA axis rhythm associated with obesity may also influence fetal programming. This could be mediated by either the direct actions of glucocorticoids on the fetus, or indirectly by changing placental gene expression and function. Further work is needed to understand the complex changes of the regulation of glucocorticoid action in the maternal-placental-fetal unit, and the consequences for offspring development, in obese pregnancy.

11.5 Epigenetics

11.5.1 Epigenetic Modifications

Epigenetic modifications are known to be a key pathway regulating gene expression. The definition of "epigenetic" changes was first described by Waddington (Waddington 1956), and later has been defined as 'the inheritable changes in gene expression due to the influence of environmental exposures and without changes of DNA sequence (Jablonka and Lamb 2006).

The main mechanisms of epigenetic modifications include DNA methylation, histone modification and non-coding RNAs. DNA methylation is one of the common epigenetic mechanisms and has been most studied in the context of fetal developmental programming (Waterland et al. 2004; Gentilini et al. 2013). The process of DNA methylation (addition of a methyl group to the 5′ carbon of cytosines) is catalysed by the DNA methyltransferases (DNMTs), which usually results in the repression of gene transcription. Groups of unmethylated CpGs are termed 'CpG islands', and methylation in the 'CpG islands' is thought to be highly relevant to gene inactivity (Godfrey et al. 2015). DNA methylation is observed in most mammals, including human, mouse and sheep (Santos et al. 2002; Beaujean et al. 2004; Joubert et al. 2012). DNA methylation also occurs in specific tissues, for example, embryonic stem cells, germ cells and trophoblast stem cells, with their own unique DNA methylation patterns (Ohgane et al. 2008). DNA methylation is also associated with imprinted gene and X chromosome inactivation (Jones and Takai 2001).

Histone modification includes methylation, phosphorylation, acetylation, and ubiquitylation (Tessarz and Kouzarides 2014). This happens on the histone proteins, and can regulate chromatin structure and thus influence silencing or activation of gene expression. In general, active and silence chromatin is associated with specific modifications on the histones. For example, the lysine acetylation on the histone tails H3 and H4 is associated with active genes, and the trimethylation of lysine 27 is relevant to gene repression (Zhang et al. 2015).

Non-coding RNA is another process of epigenetic modification. MicroRNAs (miRNAs) are one of the common, short, noncoding RNA (21–24 nucleotides in

length), which can repress gene expression by mRNA degradation and/or protein translation repression (Cora' et al. 2017). MiRNAs can regulate gene expression by binding to a repeat sequence in the 3′-UTR of the target gene mRNAs. A single miRNA can target hundreds of genes, and contrariwise, a single mRNA transcript might contain cooperative binding sites for multiple miRNAs (Brennecke et al. 2005).

11.5.2 Epigenetic Modification in Obese Pregnancy

Whether maternal obesity is associated with epigenetic modifications has been tested in various tissues including maternal and cord blood, umbilical cord, visceral and abdominal fat and placenta. Criticisms of the studies include that there is uncertainty about the relevance of DNA methylation changes in these peripheral tissues and how these relate to fetal development. In addition, in several studies the observed effect sizes are small and so the clinical relevance is unclear. Nevertheless, a number of studies have reported associations between DNA methylation changes either in candidate genes thought to be relevant to maternal obesity and/or global DNA methylation changes in these tissues which are linked to maternal BMI.

The majority of studies have used umbilical cord blood to investigate differences in individual genes' methylation with maternal obesity. For example, insulin-like growth factor 2 (IGF-2, which plays an essential role in growth and development before birth) DNA methylation was reported as decreased in obese cord blood (Hoyo et al. 2012), whereas aryl-hydrocarbon receptor repressor (AHRR, involved in regulation of cell growth and differentiation) methylation was positively associated with maternal BMI and increased in cord blood of offspring born to obese pregnant women (Burris et al. 2015). Promoter methylation of the proliferator-activated receptor-γ coactivator 1α gene (PPARGC1A), which is involved in gluconeogenesis, was found to be positively associated with maternal BMI (Gemma 2009). Global DNA methylation in cord blood from obese pregnant women was not associated with gestational weight gain (GWG), but there was some evidence that associations of maternal obesity with greater offspring adiposity may be mediated via increased DNA methylation. CpG sites that were hypermethylated in association with maternal obesity tended to be positively associated with offspring adiposity, and sites that were hypomethylated in association with maternal obesity tended to be inversely associated with offspring adiposity (Sharp et al. 2015). Further, the associations of maternal obesity with offspring methylation were stronger than associations of paternal obesity, supporting an intrauterine mechanism.

Visceral, abdominal fat and placenta tissues have also been used to investigate whether there are differences in DNA methylation in these tissues in obese pregnant women. DNA methylation of indolethylamine N-methyltransferase (INMT, protein coding gene which is related to metabolism) and Ephrin type-B receptor 6 (EPHB6, involved in cell adhesion and migration) in abdominal fat samples was reported to be lower in obese ($n = 4$) compared with lean ($n = 4$) pregnant women (Bashiri et al. 2014). Another study using placenta samples demonstrated that PPARGC1A DNA

methylation levels were positively associated with maternal glucose and cord blood leptin levels (Côté et al. 2016).

In the most recent human obese epigenome wide association study (EWAS) with a large sample size (n = 10,261), increased body mass index (BMI) was associated with widespread changes in DNA methylation in whole blood samples, with 187 identified loci found to be associated with BMI. The methylation loci identified genes that were involved in various pathways that could impact on offspring growth and development. For example, Mitogen-activated protein kinase 2 (MAP3K2), is involved in the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB, immune response pathway) (Karin and Ben-Neriah 2000); Interleukin 5 receptor, alpha (IL5RA) is involved in the development of immune cells and linking to asthma and cardiovascular disease (Brightling et al. 2014); ATP-binding cassette sub-family G member 1 (ABCG1) is involved in regulation of insulin secretion (Hidalgo et al. 2014). There were 62 of the 187 identified loci that were found to be associated with type-2 diabetes (T2DM), and a weighted methylation risk score was calculated across each loci showed a strong association of T2D risk in the future (Bianco-Miotto et al. 2017; Wahl et al. 2017). However, this study suggested that the alterations in methylation were more likely to be the consequence of the obesity rather than the cause as the predicted effects of a BMI genetic risk score was strongly correlated with the observed effects on methylation (Aron-Wisnewsky et al. 2011; Johansson et al. 2012). Even if such changes represent the consequences of obesity, further work is needed to understand the clinical relevance and impact on fetal growth and development.

11.6 Interventions in Maternal Obesity

The potential for lifestyle, medical and surgical interventions to attenuate the adverse impact of obesity on maternal and offspring outcomes have been examined in a variety of settings. A meta-analysis of individual participant data from 36 randomised trials involving more than 12,000 women examined the impact of diet and/or physical activity based interventions during pregnancy on gestational weight gain and short-term maternal and offspring outcomes (The International Weight Management in Pregnancy (i-WIP) Collaborative Group 2017). Intervention was associated with a modest reduction in gestational weight gain (mean difference −0.70 kg, 95% CI −0.92 to −0.48 kg) and odds of caesarean section compared to control (OR 0.91, 95% CI 0.83–0.99). However, there was no evidence that intervention was associated with a reduction in any adverse offspring outcome, including stillbirth, small for gestational age, large for gestational age or neonatal unit admission. Additionally, there was no significant reduction in the odds of adverse maternal and offspring composite outcomes between the intervention and control groups. Whilst these results appear 'negative' in terms of the key offspring outcomes of reducing excess birthweight, it is possible that the lifestyle interventions delivered in pregnancy may have a more sustained effect on lifestyle choices in the postpartum period and that this might impact

on the nutrition of the child and also the health of the woman entering her next pregnancy. Several follow-up studies of infants born to women who participated in trials included in the meta-analysis have now been reported and provide early insights into the consequences of lifestyle intervention on offspring body composition (Patel et al. 2017; Dodd et al. 2018). The UPBEAT and LIMIT trials randomised obese (±overweight) pregnant women to receive dietary and lifestyle advice or standard care and found no difference between groups in the primary outcomes of risk of large for gestational age infant (both) and incidence of GDM (primary outcome in UPBEAT only) (Poston et al. 2015; Dodd 2014). At a mean age of 5.92 months, 342 infants from the UPBEAT trial whose mothers were exposed to the intervention had a lower subscapular skinfold thickness z-score compared with 356 infants whose mothers received standard care (−0.26 SD, 95% CI −0.49 to −0.02, p = 0.03) (Patel et al. 2017). However, there was no difference in triceps skinfold thickness z-score between groups (−0.14 SD, −0.38 to 0.10, p = 0.246). There was some evidence of improved maternal diet in the intervention group, with reduced maternal dietary glycemic load and saturated fat intake reported in comparison with the control group. Follow-up of the LIMIT trial, involving 1754 infants assessed at age 6 months, found no significant difference between treatment groups in any measured index of infant growth or adiposity (Dodd et al. 2018). Follow-up studies of these and other intervention trials are ongoing and may give insights into the consequences of antenatal lifestyle intervention on offspring phenotypes in childhood and later life.

The potential for metformin, an insulin sensitising agent commonly used in the treatment of T2DM and GDM, to improve adverse outcomes in obese pregnant women without diabetes has been examined in two randomised, double-blind, placebo-controlled trials (Chiswick et al. 2015; Syngelaki et al. 2016). The EMPOWaR trial, which included 434 women of BMI ≥ 30 kg/m^2, and the MOP trial, involving 400 women of BMI ≥ 35 kg/m^2, both identified no significant difference in mean birthweight percentile in the offspring born to women treated with metformin or placebo (Chiswick et al. 2015; Syngelaki et al. 2016). Whilst the MOP trial reported treatment with metformin compared to placebo was associated with less maternal weight gain (median 4.6 kg [interquartile range 1.3 to 7.2] vs. 6.3 kg [2.9 to 9.2], p < 0.001) and reduced incidence of pre-eclampsia (OR 0.24, 95% CI 0.10–0.61, p = 0.001), no significant between group differences in these outcomes were identified in the EMPOWaR trial. Participants in the MOP trial were older and used a higher dose of metformin than EMPOWaR (3.0 g vs. 2.5 g daily), differences which may contribute to these discordant findings. Offspring follow-up to 9 years of age is available from the MiG trial, which allocated 751 women with GDM and uncontrolled hyperglycaemia to open-label treatment with metformin or insulin (Rowan et al. 2008, 2011, 2018). Obesity was common amongst the GDM population (mean BMI 32.2 ± 8.2 kg/m^2 in metformin group, 31.9 ± 7.6 kg/m^2 in insulin group). Amongst 318 children reviewed at 2 years old, children exposed to metformin had larger upper-arm circumferences and subscapular and biceps skinfolds compared to children exposed to insulin (Rowan et al. 2011). There was no difference in waist-to-hip ratios, total fat mass and percentage body fat between groups. The clinical relevance of these findings is unknown though the authors sug-

gested metformin exposure may be associated with a more favourable adipose tissue distribution in the offspring. Further follow-up of 99 children at age 9 years showed ongoing differences in body composition with a mean higher weight (37.0 ± 12.6 vs. 32.7 ± 7.7 kg, p = 0.049), upper-arm circumference (23.0 ± 4.3 cm vs. 21.2 ± 2.9, p = 0.02) and waist circumference (69.1. ± 12.2 vs. 64.2 ± 8.4 cm, p = 0.04) observed in offspring of the metformin group compared to the insulin group (Rowan et al. 2018). However, there was no significant difference in total fat mass, total fat percentage or any measure of fat distribution including measures of abdominal visceral fat using MRI. Whilst these data provide some reassurance regarding the safety of metformin use during pregnancy, there is no clear evidence that exposure to an insulin sensitising agent has lasting favourable effects on body composition in the offspring of obese women. Long-term follow-up of infants born to mothers in the EMPOWaR and MOP trials will further inform our knowledge of the long-term sequelae in the offspring of metformin treatment during obese pregnancy, and whether this treatment has the capacity to reduce the burden of obesity and metabolic disease across generations.

Finally, maternal and offspring outcomes were examined in a group of 596 pregnant women who had previously undergone bariatric surgery, and 2356 control pregnancies matched to the mother's pre-surgery BMI (Johansson et al. 2015). Pregnancies after bariatric surgery, as compared to matched control pregnancies, were associated with a lower risk of GDM (8.6% vs. 22.4%, OR 0.25, 95% CI 0.13–0.47, p < 0.001) and large for gestational age infants (8.6% vs. 22.4%, OR 0.33, 95% CI 0.24–0.44, p < 0.001). However, they were also associated with an increased risk of small for gestational age infants (15.6% vs. 7.6%, OR 2.20, 95% CI 1.64–2.95, p < 0.001) and shorter gestation (273.0 vs. 277.5 days, mean difference −4.5 days, 95% CI −2.9 to −6.0, p < 0.001), although the risk of preterm birth was similar between groups. The risk of stillbirth or neonatal death was numerically increased in the bariatric surgery group, although this was not statistically significant (OR 2.39, 95% CI 0.98–5.85, p = 0.06). Whilst these data highlight the potential for beneficial maternal and fetal outcomes resulting from bariatric intervention, women who are pregnant in this setting should have specialised antenatal care to ensure nutrition is optimised and fetal growth is closely monitored.

In conclusion, increasing evidence supports a link between maternal obesity and adverse health outcomes in the offspring. With the rise in prevalence of obesity among women of reproductive age in both developed and developing countries, this is a concern. Underlying mechanisms are poorly understood but studies indicated a role for dysregulation of key hormonal axes including glucose, insulin and the HPA axis. A handful of studies have implicated epigenetic modifications, particularly in DNA methylation as a candidate mechanistic pathway, but whether these changes represent the cause or the consequence of obesity is not known. To date, intervention studies conducted in pregnancy which have targeted limiting gestational weight gain and/or improving insulin sensitivity have had little impact on modifying birthweight though longer term follow-up studies of the children are needed.

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Chapter 12
Prenatal Exposure to Famine and Ageing

Tessa J. Roseboom

Abstract Chronic mild caloric restriction delays the aging process and increases lifespan. But poor nutrition during critical periods of early human development has lasting negative consequences for growth, development and health. Studies of men and women born around the time of the Dutch famine of 1944–1945 have shown that undernutrition during critical periods of development increase the risk of chronic degenerative diseases in later life and may accelerate the aging process. The Dutch famine was an acute period of undernutrition that was clearly circumscribed in time and place, it had an abrupt beginning and end and struck a population that was previously and subsequently well nourished. Also, the administration was well organised and records were kept allowing researchers to investigate the consequences of starvation in the decades that followed. All these characteristics make the Dutch famine uniquely suited for such studies, and allow researchers to take a quasi-experimental design to address a question that would otherwise be impossible to answer in a human setting. The effects of undernutrition depended on its timing during gestation, and the organs and tissues undergoing critical periods of development at that time. Early gestation appeared to be the most vulnerable period. The effects of famine exposure were widespread and affected the structure and function of many organs and tissues, resulted in altered behaviour, accelerated aging and increased risks of chronic degenerative diseases, which in turn led to reduced participation in the labour market and increased mortality. Studies in other settings also show that those faced with undernutrition during the critical earliest stages of development have increased rates of chronic generative diseases in adult life. This suggests that these findings reflect biologically fundamental processes that describe human plasticity. Proper nutrition

T. J. Roseboom (✉)
Department of Obstetrics and Gynaecology, University of Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands
e-mail: t.j.roseboom@amc.uva.nl

Department of Clinical Epidemiology, Biostatistics and Bioinformatics, University of Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands

Amsterdam Reproduction and Development, Amsterdam, The Netherlands

Amsterdam Public Health Research Institute, Amsterdam, The Netherlands

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from the earliest stages of life will allow future generations to reach their full potential and lead healthier and more productive lives, ultimately leading to a healthier future.

Keywords Dutch famine · Prenatal famine exposure · Quasi-experimental design · Critical period of development · Chronic degenerative disease · Ageing

Good nutrition is fundamentally important for growth, development, reproduction and health. Poor diets, due to insufficient, imbalanced or excessive intakes of nutrients, can impair growth and development and induce disease. Although chronic mild caloric restriction is one of the most effective ways of delaying the aging process and increasing lifespan (Fontana and Partridge 2010) undernutrition before birth has negative effects on health and reduces lifespan (Gluckman et al. 2008).

This chapter describes the evidence in humans that undernutrition before birth profoundly affects growth development and health. The consequences are apparent throughout the life-course and include altered structure and function of organs and tissues, resulting in increased rates of chronic degenerative diseases and accelerated aging.

12.1 The Long Term Consequences of Poor Diets in Early Life

Studies across the world have consistently shown that babies who were small at birth have increased rates of chronic degenerative diseases (Gluckman et al. 2008). These associations cannot be explained by prematurity, but rather reflect variations in early growth to be associated with later disease risk. This led to the hypothesis that a limited supply of nutrients to the developing fetus induce adaptations that increase its chances of survival in the short term but also increase its risk of disease in later life (Hales and Barker 1992; de Boo and Harding 2006). This is thought to reflect developmental programming: early environmental cues induce anatomical and physiological changes that have lasting consequences for the function of organs and tissues and permanently affect the physiology.

12.2 The Dutch Famine as a Model

While famine is sadly not uncommon in many parts of the world, studying effects of undernutrition during pregnancy in humans is hampered by the fact that undernutrition is usually not restricted to pregnancy alone, and effects of chronic undernutrition and accompanying problems of infection complicate the situation. The tragic circumstances of the Dutch famine of 1944–45 created a unique opportunity to assess the

effects of prenatal famine exposure on health in later life. The Dutch famine has been used by various investigators as an equivalent to an experimental set-up to investigate the effects of prenatal undernutrition in humans. What is unusual about the Dutch famine is; that the famine was imposed on a previously well-nourished population; there was a sudden onset and relief from the famine; and, despite the adversities of the war, midwives and doctors continued to offer professional obstetric care and kept detailed records of the course of pregnancy, the delivery and the size and health of the baby at birth. Furthermore, detailed information is available on the weekly rations provided during the famine, and in several inflicted cities birth records were kept which allowed researchers to trace those born around the time of the famine and thus to study the long-term effects of prenatal famine exposure.

12.2.1 The Historical Course of Events that Led to the Dutch Famine 1944–45

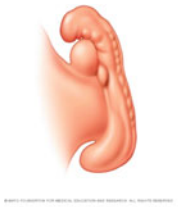
When the Allied forces invaded France on the 6th of June 1944, a few weeks of heavy fights pursued. But finally, the Allied forces broke through German lines and quickly took possession of France, Luxembourg and Belgium. Early September 1944, the Allied forces had the strategic city of Antwerp in their hands, and on the 14th the Allies entered the Netherlands. The Dutch expected that the German occupation would soon be over, and so did the commanders of the Allied forces. In order to capture strategic bridges across the river Rhine to open a pathway for rapid invasion into Germany, the Allied forces launched a parachute attack behind the Nazi forces near the city of Arnhem. However, the operation (Market Garden) failed with major losses. Subsequently, the Dutch government called for a strike of the Dutch railways in order to support the Allied offensive. As a reprisal, the Germans banned all food transports. The food situation in the western part of the Netherlands worsened dramatically. Food stocks ran out rapidly, and soon rations for adults dropped to below 1000 calories a day. The embargo on food transports was lifted in early November 1944, when food transport across water was permitted again. But because most canals and waterways were frozen due to the early and extremely severe winter, it had become impossible to bring in food from the rural east to the urban west of the Netherlands. Food rations declined to extremely low levels between February and May 1945, with daily rations varying between 400 and 800 calories a day. A typical ration would consist of two potatoes, two slices of bread and half a sugar-beet. During the famine, infants were relatively protected, because their official daily rations never fell below 1000 calories. Pregnant and lactating women were entitled to an extra amount of food, but at the peak of the famine these extra supplies could not be provided anymore. Also, extra food came from the black market, central kitchens, church organisations and foraging trips to the countryside. The period of famine ceased in early May 1945 immediately after the final surrender of the Germans. The food situation quickly improved and within a month rations were above 2000 calories.

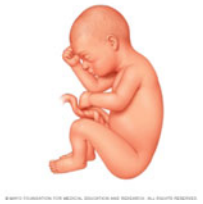
In addition to the immediate provision of food after the war, medical aid was a top priority for the Netherlands. The famine had a profound effect on the general health of the population. In Amsterdam, the mortality rate in 1945 had more than doubled compared to 1939, and it is very likely that most of this increase in mortality was attributable to undernutrition. Doctors from the UK and US were sent to survey medical needs. Clement Smith from Harvard Medical School was among the first to witness the effects of the famine on the health of the Dutch population. He immediately saw the opportunity to obtain information that would help resolve important questions on how poor maternal nutrition affects pregnancy and the development of the fetus before birth. Using obstetric records from Rotterdam and The Hague, he studied effects of prenatal exposure to famine on pregnancy and the fetus which he described in his paper: *The effect of famine on pregnancy and its product* (Smith 1947).

Since the Dutch famine lasted 5–6 months (from late November 1944 until early May 1945) investigators have been able to not only assess effects of prenatal undernutrition per se, but also to differentiate between effects of undernutrition according to its timing during gestation and the organs and tissues developing at that time gestation (Fig. 12.1). Although the exact definitions differ between studies, all studies assessing effects of prenatal famine exposure have differentiated between effects of famine in early, mid or late gestation. In contrast to the effects on size at birth, which were most pronounced among those exposed to famine in late gestation, those born during or just after the famine, the effects on later health were most pronounced among those exposed to famine in early gestation. This may not be surprising considering the fact that all organs are laid down in early gestation and insufficient food supply during the formation of the organs can interfere most with physiology.

12.3 Chronic Degenerative Disease Risk After Prenatal Exposure to the Dutch Famine

Studies of adult men and women who were born around the time of the Dutch famine have provided the first evidence in humans to suggest that prenatal undernutrition increases the risk of chronic degenerative diseases. Men and women who had been undernourished before birth have increased rates of type 2 diabetes (Ravelli et al. 1998; Lumey et al. 2009a; de Rooij et al. 2006) cardiovascular disease (Roseboom et al. 2000a), breast cancer (Painter et al. 2006a), chronic obstructive airways disease (Lopuhaä et al. 2000), and mental health issues including schizophrenia, anti-social personality disorder, affective psychoses and depression (Neugebauer et al. 1999; Hoek et al. 1996; Franzek et al. 2008; Stein et al. 2009; de Rooij et al. 2011). Also, the levels of biological risk factors for these diseases were elevated. For instance, those exposed to famine in early gestation were more obese as adults (Ravelli et al. 1976, 1999; Stein et al. 2007), and had a more atherogenic lipid profile (Roseboom et al. 2000b; Lumey et al. 2009b), altered blood coagulation (Roseboom et al. 2000c), and increased stress responsiveness (Painter et al. 2006b). They furthermore had





early	mid	late
glucose tolerance	glucose tolerance	glucose tolerance
cardiovascular disease	obstructive airways disease	
breast cancer	microalbuminurea	
depression		
schizophrenia		
stress responsiveness		
cognition		
addiction		
food preference		
fertility		
participation labour market		
mortality		

Fig. 12.1 The effects of prenatal famine exposure depend on its timing during gestation

poor physical function in later life, as evidenced by reduced hand grip strength, reduced walking speed, lower physical activity and a lower physical performance score (Bleker et al. 2016). As impaired physical function is an important marker of aging, these findings may suggest that those undernourished during critical periods of early development age more quickly.

Several findings indeed support this notion. Not only do those exposed to famine in early gestation have increased rates of cardiovascular disease (Roseboom et al. 2000a), but the disease also occurred at a younger age (Painter et al. 2006c). Another line of evidence suggests that people who had been exposed to undernutrition during early gestation performed worse on a selective attention (Stroop) task (de Rooij et al. 2010), which is a cognitive ability that usually declines with increasing age. Performance on this task, has been shown to be a strong predictor for conversion to Alzheimer's disease even before memory deficits are present. Imaging studies of the brains have shown lasting effects of famine exposure on brain size and structure (Rooij et al. 2016a, b). Men who had been exposed to famine in early gestation had smaller intracortical volumes and total brain volumes than unexposed men. They also had smaller volumes of total cortical grey matter, white matter cerebellar

grey matter, thalamus, caudate nuclear and accumbens area and a large number of more specific cortical white and grey matter areas. The overall reduction in brain size after prenatal famine exposure was ~5%. A decreased intra-cortical volume was also reported in a smaller study of schizophrenic patients (Hulshoff Pol et al. 2000), which suggests that prenatal undernutrition has lasting effects on brain size and structure. A study implementing an innovative biomarker for individual brain aging, using structural neuroimaging, showed that undernutrition in early gestation was associated with a status of premature brain aging during late adulthood in men (Franke et al. 2018). Interestingly, the status of premature brain aging in participants exposed to the Dutch famine during early gestation occurred in the absence of fetal growth restriction at birth as well as vascular pathology in late-life. Effects of prenatal exposure to the Dutch famine on selective attention at age 58, intracranial volume at age 68 years, and BrainAGE at age 68 years are presented in the Fig. 12.2.

The effects of famine exposure in early gestation are not limited to health but appear to have economic consequences too. The most striking finding was that the probability of being employed was significantly lower among those who had been exposed to famine in early gestation (Scholte et al. 2015). This result fits with findings of poorer performance on cognitive tasks in men who had been exposed to famine in early gestation. It seems that the effects of famine on employment are at least partly explained by effects on cognition. Mental disorders such as schizophrenia and anti-social personality disorders which were more common after exposure to famine in early gestation may contribute to this, as well as the physical health. It could be argued that the effects of famine exposure on health reduced individual productivity and hence employability. Finally, prenatal exposure to famine has been linked with increased rates of mortality (Van Abeelen et al. 2012; Ekamper et al. 2014).

12.4 Critical Periods

The hypothesis that the organs and tissues growing most rapidly are more susceptible to variations in diet, is supported by several observations from famine studies. For instance, exposure to famine in mid gestation was linked to an increase in occurrence of micro-albuminurea in adulthood and a decrease in creatinine clearance (Painter et al. 2005). It may be that mid gestational exposure to famine—the period of rapid increase in nephron number-may prevent formation of sufficient glomeruli and thus increase the risk for micro-albuminurea and deteriorated renal function in adulthood. This supports the concept that intrauterine conditions during distinct, organ-specific periods of sensitivity may permanently determine health outcome in later life. Another example of this phenomenon is the finding in the same study that people who had been exposed to famine in mid gestation had an increased prevalence of obstructive airways disease (Lopuhaä et al. 2000). These observations were not paralleled by reduced lung function or increased serum concentrations of IgE. This suggests that the increased prevalence of symptoms and disease may be attributable to increased bronchial reactivity rather than to irreversible airflow obstruction or atopic

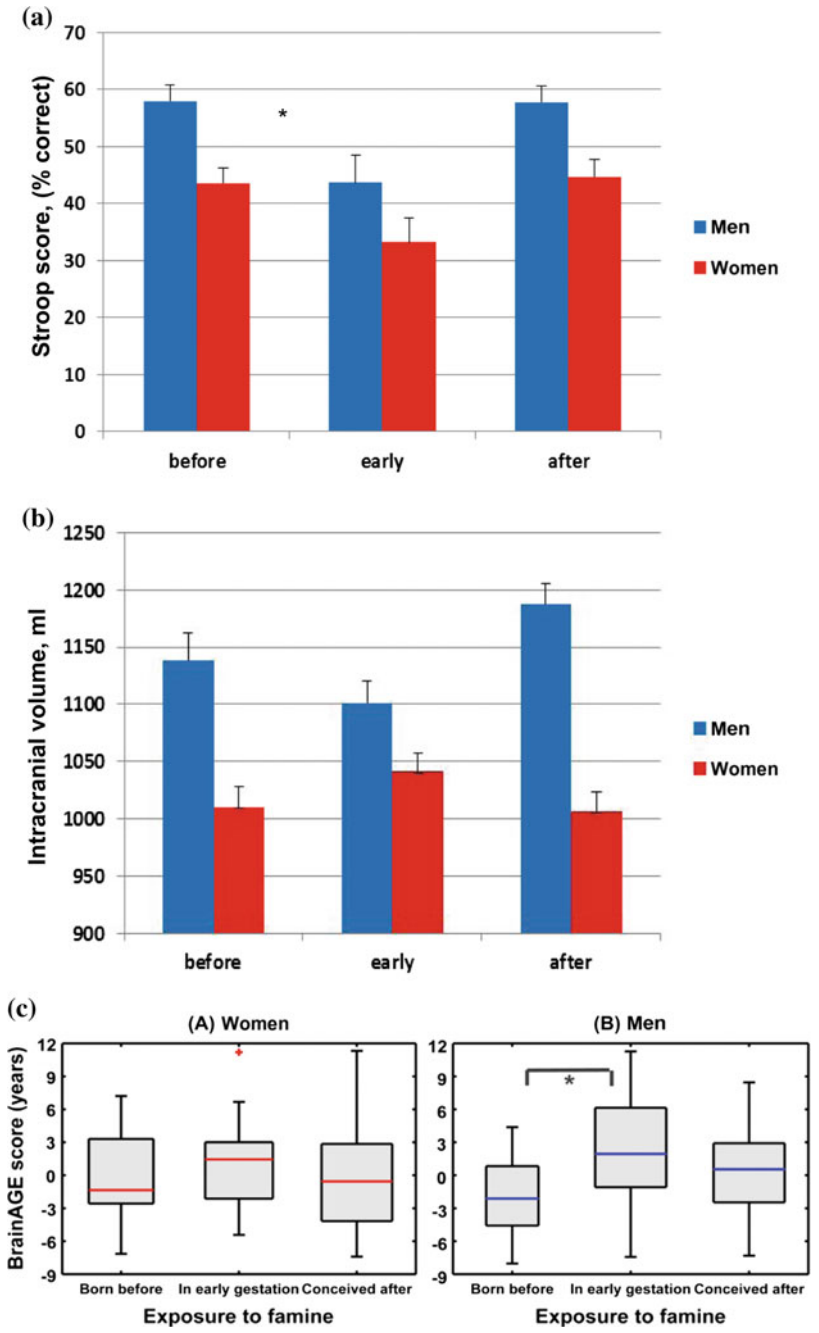


Fig. 12.2 Effects of prenatal exposure to the Dutch famine on: **a** selective attention at age 58, **b** intracranial volume at age 68 years, **c** BrainAGE at age 68 years

disease. Because the bronchial tree grows most rapidly in mid gestation, these findings support the hypothesis that fetal undernutrition permanently affects the structure and physiology of the airways during 'critical periods' of development that coincide with periods of rapid growth.

12.5 Similar Findings in Different Settings

The findings from the studies of the long term consequences of the Dutch famine have now been replicated in other settings in which the effects of famines have been examined. Studies in other settings, of famines with different durations and severity affecting different populations support these findings and suggest that the results of studies on the Dutch famine are not uniquely linked to the characteristics and setting of the Dutch famine, but rather reflect biologically fundamental processes that describe human plasticity (Stearns 1989).

A study in Nigeria showed that prenatal undernutrition also affects later health in African populations (Hult et al. 2010). People who had been exposed to the Biafran famine during the Nigerian civil war (1967–1970) in utero were found that have increased rates of hypertension and type 2 diabetes at the age of 40 compared to those who had not been exposed to the Biafran famine in utero. Similarly, studies of people exposed to the Great Leap Forward famine in China have shown similar effects of prenatal famine exposure in later life risk of diabetes, hypertension and schizophrenia (Meng et al. 2018; Li et al. 2017; Chen and Zhou 2007). A unique Austrian study among showed excess risk of diabetes among people born around the time of the three periods of famine that struck the country in 1918–1919, 1938 and 1946–1947 (Thurner et al. 2013). Similar effects were found in a study of the long term consequences of the Ukrainian famine, and the Greek famine (Lumey et al. 2015; Neelsen and Stratmann 2011). In a cross sectional study of rural Bangladeshi, people prenatally exposed to the 1974–1975 famine induced by a severe monsoon that destroyed the majority of the annual rice crop had higher rates of diabetes (Fine et al. 2016). The study showed that famine exposure programmed Bangladeshis towards diabetes and obesity in adulthood through epigenetic processes. Similarly, in The Gambia—where food availability varies greatly throughout the season have shown that effects of variations in periconceptional nutrient availability affect health and longevity through epigenetic processes (Waterland et al. 2010), just like in the Dutch famine (Tobi et al. 2009; Heijmans et al. 2008).

The only study of prenatal famine exposure that did not detect any difference in health between men and women who had or had not been exposed to famine was a study among men and women born around the time of the Siege of Leningrad (Stanner et al. 1997). People in Leningrad were already undernourished before the siege and the standard of living remained relatively poor after the siege, which may suggest that the contrast of the pre- and postnatal environment may be important in programming negative consequences.

12.6 Differentiating Famine Nutrition Effects from Cold and Infection

In all the famine studies mentioned, the hypothesized factor affecting adult health was prenatal nutrition due to maternal exposure to food shortage. Although in all instances the famine was characterized by severe food shortage, the availability of food was not the only aspect that varied with the famine. The famine in the Netherlands coincided with a very cold winter during which infections were widespread. Also, the stress experienced by pregnant women due to lack of food, the war and the absence of their spouses will have been more extreme than those of women pregnant before or after the famine. We therefore cannot rule out effects of prenatal exposure to stress as a possible cause of the long term effects. Indeed, there are indications that prenatal stress alone has programming effects that are similar to those of famine (Alastalo 2009; Brand et al. 2006). It seems unlikely, however, that stress is the sole cause of the effects of prenatal famine exposure since there were no differences in health between people who were born before the famine and those conceived after the famine whereas one would expect difference in the levels of exposure to stress between these two groups. Moreover, effects of prenatal exposure to famine on health were predominantly among offspring of women exposed to famine in early gestation. One would expect at least the same or even higher levels of stress in pregnant women exposed to famine in later of mid gestation.

Still, from the famine studies it is not possible to differentiate between effects of undernutrition from those caused by the stress of war and infection and other phenomena that accompany periods of famine. There are certainly indications that stress due to war has negative programming effects in the absence of food scarcity (Alastalo 2009; Brand et al. 2006) and there are also indications that prenatal exposure to infection (such as it occurred in the 1918–1919 flu pandemic) had negative consequences for the men and women who were exposed to these stressors prenatally (Mazumder et al. 2010). Also, such stressors have been shown to have negative effects for health if they occur during the early postnatal years. For instance, studies of war evacuees from Finland have shown that separation from biological parents during the war left lasting consequences for these children: they had increased rates of type 2 diabetes and other chronic degenerative diseases in later life and the effects were most pronounced if they were young when they were evacuated and if the evacuation period lasted longer (Alastalo 2009).

12.7 To What Extent Might All These Finding Be Due to Selection Rather Than Programming Effects?

By comparing the health of people born at different times in relation to famine, many researchers have attempted to mimic an experimental setting. However, the analogy with an experiment is violated to some extent because the famine affected

fertility and early mortality. Selective fertility did not seem to explain the findings as adjustments for maternal characteristics that might be proxies for fertility (age, parity, socioeconomic status, weight) hardly altered the results. Nor is it likely that early mortality caused differences in adult health, as early mortality differed most between those born before the famine and those conceived after it, while their adult health was not different. Yet, this not exclude the possibility of selection completely. Indeed, a recent study suggests that there may be indications that selection explains some of the findings in famine studies (Tobi et al. 2018).

12.8 Conclusions

The studies of people born around the time of famines across the globe underline the importance of ensuring sufficient nutrition during the critical periods of growth and development in early life. The effects of undernutrition seem to be large and depend on the timing during and the organs and tissues developing at that time. Also, the effects may occur without affecting the size of the baby at birth. This implies that adaptations that enable the fetus to continue to grow may nevertheless have adverse consequences for health in later life. Proper nutrition from the earliest stages of life will allow future generations to reach their full potential and lead healthier, more productive and longer lives.

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Chapter 13
Why Is Parental Lifespan Linked to Children's Chances of Reaching a High Age? A Transgenerational Hypothesis

Denny Vågerö, Vanda Aronsson and Bitte Modin

Abstract Transgenerational determinants of longevity are poorly understood. We studied four linked generations (G0, G1, G2 and G3) of the Uppsala Birth Cohort Multigeneration Study to address this issue. Mortality in G1 (N = 9,565) was followed 1961–2015 and analysed by their parents' (G0) age-at-death using Cox regression. For an almost entirely deceased segment of G1 (n = 1,149), born 1915–1917, we compared exact age-at-death with G0 parents' age-at-death. Finally, we explored 'resilience' as a potential mechanism for intergenerational transmission of longevity, using conscript information from psychological interviews of G2 and G3 men. G0 men's and women's ages-at-death were independently associated with G1 midlife and old age mortality. We observed an increased lifespan in all social groups. Median difference in age-at-death for sons compared to fathers was +3.9 years, and +6.9 years for daughters compared to mothers. Parents' and maternal grandmother's longevity were associated with resilience in subsequent generations. Resilience scores of G2 men were also associated with those of their G3 sons and with their own mortality in midlife. We conclude that chances of reaching a high age are transmitted from parents to children in a modest, but robust way. Longevity inheritance is paralleled by the inheritance of individual resilience. Individual resilience, we propose, develops in the first part of life as a response to adversity and early experience in general. This transgenerational pathway is distinct from social class trajectories. A theory of longevity inheritance should bring together previous thinking around general susceptibility, frailty and resilience with new insights from epigenetics and social epidemiology.

Keywords Uppsala multigeneration study · Parental lifespan · Transgenerational hypothesis · Age-at-death · Intergenerational transmission of longevity

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D. Vågerö (✉) · V. Aronsson · B. Modin
CHESS, Centre for Health Equity Studies, Department of Public Health Sciences, Stockholm University/Karolinska Institutet, SE-106 91 Stockholm, Sweden
e-mail: denny.vagero@su.se

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13.1 Introduction

Mortality, life expectancy and age-at-death are all strongly socially structured. Despite economic growth, welfare state provisions, modern medicine and a fundamental change in disease panorama, we find a negative social gradient in mortality generation after generation. We know from sociological studies that "the long shadow of the past" influences occupational and educational careers in successive generations, creating continuity in social (dis)advantage across generations. Because education, occupation and income all predict health and survival we should also expect such characteristics in the parental generation to predict the next generation's health prospects, resulting in "inheritance of longevity". It is possible, however, that this influence from previous generations is considerably broader than that working through the children's own education, occupation and income. Variation in mortality risk within social groups is great. To understand "inheritance of longevity" we need a conceptual framework that also identifies those within-class influences.

Already in 1934 Kermack et al. (reprinted 2001) suggested that the first 15 years of life could determine your mortality risk during the entire lifecourse. Similarly, the so-called DOHaD (Developmental Origins of Health and Disease) theory suggests that early life experiences is an important determinant of adult health and disease (Gluckman et al. 2008). DOHaD theory has focused on specific aetiologies and influences, such as that of foetal growth restriction on blood pressure and circulatory disease.

Another, earlier school of thinking, represented by epidemiologists Syme and Berkman (1976) and Cassel (1974), argued for more general disease-causing mechanisms. Demographers Vaupel et al. (1979) noted the considerable individual heterogeneity in mortality risk. Concepts like *frailty* (Vaupel et al. 1979; Sternberg et al. 2011), *general susceptibility* (Cassel 1976; Syme and Berkman 1976) or *differential vulnerability* (Nordahl et al. 2014) refer to individual differences in the ability to survive hardship. Cassel's concept of *host resistance* (1976) forebodes the recent psychological discourse on *resilience*, defined as the capacity of a human being to "bounce back" in the face of adversity (Windle 2011; Rutter 2006). *Weathering* (Simons et al. 2016) and *scarring* (Heckman and Borjas 1980; Stewart 2001), are other related, but not identical, terms widely used in the economic literature to describe long-term change of individual characteristics in response to adversity.

Demographic concepts like frailty, epidemiological ones like general susceptibility and psychological ones like resilience all refer to the same real-life-phenomenon: a general rather than specific vulnerability to disease. Syme and Berkman (1976) and Cassel (1976) stressed its social roots, while Vaupel et al. (1979) perhaps assumed it to have a more genetic basis. Resilience, in turn, may be related to both views (Rutter 2006). It could be thought of as the opposite extreme to susceptibility/frailty on the same underlying dimension. In this study, we argue that resilience is acquired early and maintained throughout life. Resilience should therefore influence the ability to survive up to a high age and be linked to longevity, as a number of studies indeed suggest (Shen and Zeng 2010; Zeng and Shen 2010; Charney 2004).

"Inheritance of longevity" has been discussed at length in the literature. Its precise nature is somewhat elusive (Vaupel et al. 1998; Christensen et al. 2006; Pal and Tyler 2016; Piraino et al. 2014). Gudmundsson et al. (2000), studying the entire Icelandic population, concluded that longevity was inherited within families, in their view probably because of shared genes. Hjelmborg et al. (2006), looking at twin data, concluded that genetic influences on the lifespan were minimal before age 60 and only increase after that age. Kowald and Kirkwood (2016), on the other hand, rejected any idea that mortality in old age is genetically programmed. Consistent with that view, a Swedish study of men born in 1913, found that a number of social and behavioural factors measured at age 50, but not their parents' survival, predicted longevity (Wilhelmsen et al. 2011).

Evolutionary theorists have debated whether there is any evolutionary pressure to promote survival into old age (Williams 1957). Nevertheless, we observe a steady lifespan extension in modern societies, especially among women, partly based on falling mortality rates across their long post-reproductive period. That children tend to live longer than their parents is likely to be determined both by what experience parents brings to the next generation, and by the improved life circumstances of the children themselves in their childhood and adult life. The importance of genetic factors for longevity, we suggest, may lie in their interaction with other factors, perhaps especially if this interaction takes place at an early age.

13.2 Theoretical Proposals

We make these theoretical proposals: The ability to survive into old age is transmitted across generations. This *inheritance* cannot be reduced to the influence of parents' social class or marital status at the time of the birth of the child or to the birth order of the new individual or to shared genes. In all social classes and family types there is considerable individual heterogeneity in the ability to reach a high age. We propose that this heterogeneity to some extent mirrors a person's very early experience, such as her history of coping with challenging and adverse experience early in life. This would constitute a fundamental learning process, engaging the whole individual, mentally and physiologically, including the hypothalamus-pituitary-adrenal (HPA) axis, regulating neuroendocrine stress responses. How the individual handles early experiences, and whether or not she can rely on support from family and friends in this, may be crucial for the differential adaption to adversity. Small initial differences in trajectories between children in similar family circumstances, even between siblings, may be reinforced and greatly magnified during development, along a resilience/susceptibility dimension.

We may think of this process, determining resilience/susceptibility as a (potentially) adaptive "switch", turned on early in life. The switch may involve epigenetic changes across large parts of the genome. If resilience is transmitted across generations, it would contribute to inheritance of longevity, beyond its link to social class. Three intergenerational pathways of resilience transmittance should be considered.

Firstly, parental care and understanding how to cope with success and adversity (Meaney 2001). Secondly, specific "longevity genes", which promote resilience and a long life could be inherited in families (Gudmundsson et al. 2000). More intriguingly, thirdly, is the possibility that resilience may be fixed in the germline epigenome early in life as has been suggested by several researchers (Franklin et al. 2010; Vaiserman 2012; Rando 2016; Marsland 2017; Sharma 2017).

Our theoretical ideas about longevity inheritance, and the role of resilience in this, led to a set of prior hypotheses, which we wanted to test. Thus, we examined length of lifespan and/or survival into old age in two consecutive generations: parents (G0) and their children (G1). In the next two generations, we compared fathers (G2) and sons (G3), with regard to a resilience measure, based on a psychological interview at military conscription at age 18. Finally, we explored the association between resilience and mortality, within and across generations.

We were able to address these questions empirically:

(1) Does age-at-death of parents (G0) predict offspring's (G1) mortality risk in midlife and old age?
(2) If so, is this because parents (G0) who live longer also tend to promote a more advantageous social class trajectory for their children (G1)?
(3) How do parents' (G0) and their children's (G1) lifespans compare?
(4) Is resilience a characteristic which

   (a) predicts later mortality (in G2)?
   (b) is transmitted across generations (from G2 fathers to G3 sons)?
   (c) is predicted by longevity in previous family generations (from G0 and G1 men and women to G2 and G3 men)?

13.3 A Study of Four Generations

13.3.1 Uppsala Multigeneration Study (UBCoS Multigen)

Four successive generations were linked by combining existing data on a cohort of all 14,193 men and women born alive at Uppsala Academic Hospital in 1915–1929 (Uppsala Birth Cohort Study: UBCoS) with information from Statistic Sweden's Multigeneration Register through their personal identity numbers, to create UBCoS Multigen (Fig. 13.1). UBCoS individuals who were alive and resident in Sweden in 1947 (when PIN-numbers were introduced in Sweden) constitute generation 1 (G1: N = 12,168) in UBCoS Multigen (Fig. 13.2). This cohort and its successive generations have been extensively studied and presented previously (Modin 2002; Modin et al. 2008, 2009; de Stavola et al. 2011; Fors et al. 2012; Juarez et al. 2016; Vågerö et al. 2018a, b).

For this study we traced the parents of G1, with full names and birth date, through hospital records and parish registers. Members of this generation (G0: N = 15,706),

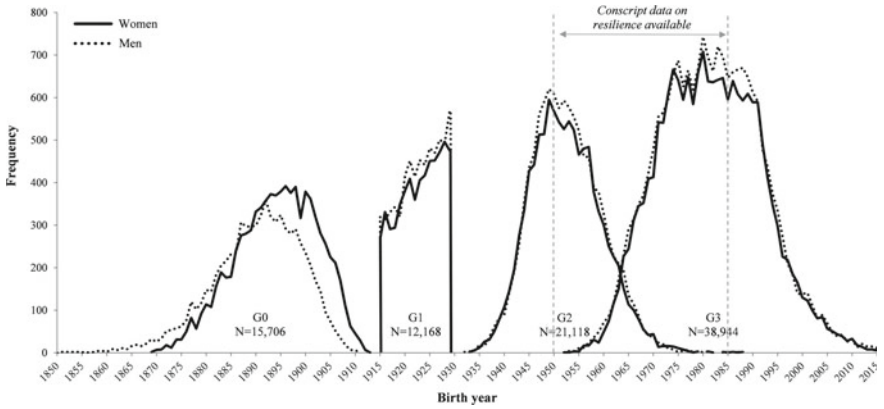

Fig. 13.1 Birth year distribution of G0, G1, G2 and G3 by gender

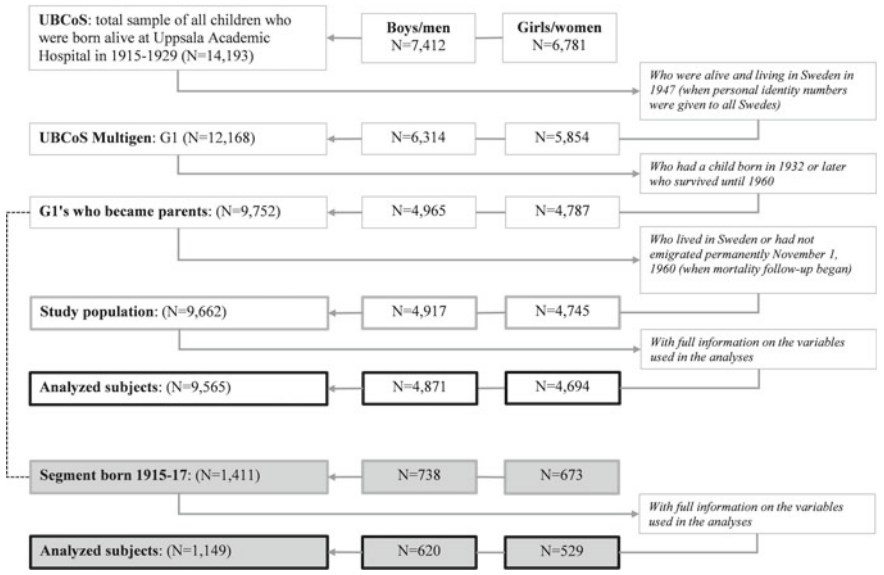

Fig. 13.2 UBCoS generation 1. N = 14,193 live-born births (7412 men and 6781 women) in 1915–1929, at Akademiska Hospital, Uppsala, Sweden. Study samples in bold face

are now dead; their date-of-death were traced through the Swedish Death Index (6th edition), published by Statistics Sweden and the Swedish Genealogical Society. This includes all recorded deaths in Sweden 1901–2013.

To increase comparability between G0 and G1, parenthood was an inclusion criterion also in G1. Details regarding inclusion of study subjects for analyses of G0 and G1 can be found in Fig. 13.2.

For analyses of resilience as a determinant or as an outcome. G1 partners (the other parent to G2) were included in analysis of how longevity predict resilience in G2 and G3. See Modin et al. (2009) for a detailed description of inclusion of partners.

13.3.2 Analyses and Statistical Methods

Mortality of G1 was analysed by tertiles of their parents' (G0) age-at-death. G1 entered the at-risk-population November 1st 1960 or, if it occurred later, after their first childbirth. They were followed until death, the date of permanent emigration or the end of follow-up (December 31st 2015). Mother's and father's age-at-death, separately and in combination, were used to predict G1 mortality in mid- and later life. Parental social class and marital status were adjusted for in the analyses, as was G1's birth order, birth year and adult social class.

Estimates of G1 mortality risk before and after adjustments were compared to evaluate any mediation. Distributions of the independent variables can be found in Table 13.1.

G0 mid-parental age-at-death was compared with their G1 sons' and daughters' age-at-death in separate analyses of a segment of G1, those born 1915–1917, using linear regression techniques, adjusting for G1 birth year and birth order. Further, G2 men's mortality at ages 50–65 was regressed on their resilience scores, with and without control for their adult social class. A regression coefficient was calculated for the association between G2 fathers' and G3 sons' resilience scores, controlling for G2 social class plus G2 and G3 conscription office. Finally, we examined whether parental and grandparental longevity (in G0 and G1) predicts resilience in subsequent generations of young men (G2 and G3), adjusting for conscription office and parental social class. Cox regressions with age as underlying time scale were used in analyses of G1 and G2 mortality. In all regressions, sibling-cluster robust standard errors based on shared mother or father were used to estimate 95% confidence intervals.

Statistical analyses were performed in Stata version 13.1.

13.4 Variables

13.4.1 Independent Variables

Age-at-death (G0) was calculated from exact birth and death dates for the entire G0; then stratified by approximate tertiles, based on gender-specific age-at-death distributions (Table 13.1). Mother's date-of-death was identified for 97% of G1 women and for 98% of G1 men. Father's date-of-death, however, was missing for 15 and 13% of G1 women and G1 men respectively; in 94% of these cases G1 was born outside marriage. An additional category was constructed ("Unknown age-at-death") to

Table 13.1 Distribution of the independent variables used in analysis of G0 and G1 (n = 9565)

	G1 men (n = 4871)		G1 women (n = 4694)	
	n	%	n	%
G1 characteristics				
Year of birth				
1915–1919	1222	25	1165	25
1920–1924	1677	34	1579	34
1925–1929	1972	40	1950	42
Social class in 1960				
Non-manual	1950	40	2196	47
Entrepreneur/farmer	2068	42	1645	35
Manual	720	15	699	15
Other	133	3	154	3
G0 characteristics				
Mother's marital status at birth of G1				
Married	3991	82	3750	80
Not married	880	18	944	20
Social class at birth of G1				
Higher and intermediate non-manual	444	9	371	8
Entrepreneurs and farmers	871	18	800	17
Lower non-manual	340	7	278	6
Skilled manual	657	13	694	15
Unskilled manual	2137	44	2154	46
Other	422	9	397	9
Mother's parity at birth of G1				
1st	1932	40	1817	39
2nd	1147	24	1131	24
3rd–4th	1058	22	1032	22
5th–6th	393	8	382	8
7th or higher	341	7	332	7
Age-at-death (mothers)				
Lowest third (16–73 years)	1630	33	1584	34
Intermediate third (74–84 years)	1678	34	1543	33
Highest third (85–105 years)	1453	30	1427	30
Unknown	110	2	140	3
Age-at-death (fathers)				
Lowest third (21–69 years)	1474	30	1370	29
Intermediate third (70–80 years)	1360	28	1248	27

(continued)

Table 13.1 (continued)

	G1 men (n = 4871)		G1 women (n = 4694)	
	n	%	n	%
Highest third (81–106 years)	1404	29	1377	29
Unknown	633	13	699	15
Age-at-death (combined)				
Both parents in youngest third	505	10	492	10
Intermediate	3271	67	3002	64
Both parents in oldest third	432	9	469	10
At least one parent unknown	663	14	731	16

allow G1 women and men who were born out of wedlock to be properly represented in analyses. When combining mother's and father's age-at-death, four categories were used: both parents in the oldest third, both parents in the youngest third; an intermediate category of other combinations and finally those for whom at least one parent's age-at-death was unknown.

Mid-parental age-at-death (G0) was calculated as father's plus mother's age-at-death divided by two, and used as a continous variable in one of the analyses.

Longevity (G0 and G1) was defined as survival until at least age 85.

Birth year (G1) was grouped as 1915–19, 1920–24, 1925–29. *Mother's parity (G0)* served as an indicator of G1 birth order and was grouped as 1; 2; 3–4; 5–6; 7+. Both factors were considered as potential confounders in analyses of G1 mortality.

Marital status (G0) was classified as: mother married or never married at the time of G1's birth, excluding divorcees (n = 20) and widows (n = 57).

Social class (G0) at the time of G1 birth was based on father's (G0) occupation when available; if not on mother's (G0) occupation. It consists of six categories: higher and intermediate non-manuals, entrepreneurs and farmers, lower non-manuals, skilled manuals, unskilled manuals and other, following Modin (2002). The category of "house daughters" (unmarried non-working mothers who lived with their parents) was merged with non-classifiable into 'other'.

Social class (G1) in 1960 was classified as manual, self-employed including farmers, or non-manual (Vågerö and Norell 1989). It was considered as a potential mediator between G0 social class and marital status at G1 birth on the one hand and G1 mortality on the other.

Social class (G2) in adulthood was obtained from the 1980 or 1990 censuses, reclassified as manual workers, self-employed including farmers, or non-manual.

13.4.2 Dependent Variables

All-cause mortality (G1) was followed-up until 2015 when the youngest members of G1 were 86 and the oldest 100 years old. G1 mortality was analysed as mortality before age 61 ("mid-life"), at 61–85 ("early old age") and at 86–100 years ("old age") for men and women separately.

Exact age-at-death (G1) was used as a continuous variable in a separate analysis of an almost entirely deceased segment of G1 born 1915–1917. Around 1% of these men (n = 7) and 2% of the women (n = 12) were alive at the end of follow-up, aged 98–100. For these we applied realistic annual death risks (0.33) year by year after 2015, to randomly assign a death year.

All-cause mortality (G2 men) was based on mortality at ages 50–65.

Resilience (G2 and G3 men) was based on semi-structured psychological interviews of all young men (age 18) at military conscription regarding their ability to resist severe psychological stress and to function in very adverse circumstances. Four different components were assessed, quantified and summarized as a nine step, normally distributed, ordinal scale, with a mean of 5.15 in both G2 and G3. The actual content and weight of the four components is kept confidential by military authorities. We used the summary score as a proxy for resilience/susceptibility, inspired by previous studies (Nilsson et al. 2001, 2004; Falkstedt et al. 2013). Lindqvist and Vestman (2011) gives a more detailed description of this measure.

13.5 Generational Links in Resilience and Mortality

13.5.1 Surviving to Old Age

For G1 men, both parents' ages-at-death were independently associated with their mortality before age 61 and at ages 61–85, but not later in life. This also holds when parental social class and family marital status at G1 birth are controlled for. For G1 women, mothers' age-at-death was associated with their own survival, across all observed ages, into very old age, also when parental social class and marital status at G1 birth are controlled for. Thus, G1 women with mothers in the highest third of age-at-death enjoyed a lower mortality risk before age 61, at 61–85 and at 86–100, independently of any influence from father's age-at-death. The pathway from mother to daughter appears to confer a remarkably consistent intergenerational influence on mortality across the observed ages (Tables 13.2 and 13.3).

Having two parents with high ages-at-death gave an even stronger gradient; for G1 men a distinctly reduced mortality risk at age 61–85 (HR = 0.66), and particularly before age 61 (HR = 0.59); for G1 women we observed HRs of 0.59 at ages 61–85 and of 0.72 at ages 86–100 years (Tables 13.2 and 13.3). Estimates of G1 mortality by G0 age-at-death were minimally influenced by controlling for G0 or G1 social class (data not shown). In that sense, G0 age-at-death is a distinct predictor of G1

Table 13.2 G1 men's mortality by G0's age-at-death: hazard ratios with 95% confidence limits. Mortality follow-up 1961–2015 (n = 4871)

	Mortality before age 61 (543 deaths)			Mortality between ages 61 and 85 (2797 deaths)			Mortality between ages 86 and 100 (876 deaths)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Mother's age-at-death									
Youngest third	1.00	1.00		1.00	1.00		1.00	1.00	
Intermediate third	0.99 (0.81, 1.21)	0.99 (0.81, 1.21)		0.96 (0.88, 1.05)	0.96 (0.88, 1.06)		1.08 (0.91, 1.28)	1.08 (0.91, 1.28)	
Oldest third	**0.75** (0.60, 0.94)	**0.76** (0.61, 0.95)		**0.77** (0.70, 0.85)	**0.78** (0.70, 0.86)		0.96 (0.81, 1.14)	0.97 (0.82, 1.14)	
(Unknown)	1.12 (0.65, 1.93)	0.97 (0.54, 1.72)		1.10 (0.85, 1.42)	0.97 (0.75, 1.27)		1.09 (0.72, 1.64)	1.11 (0.71, 1.74)	
Father's age-at-death									
Youngest third	1.00	1.00		1.00	1.00		1.00	1.00	
Intermediate third	0.87 (0.70, 1.08)	0.87 (0.70, 1.09)		0.94 (0.85, 1.04)	0.95 (0.86, 1.04)		1.14 (0.95, 1.36)	1.14 (0.95, 1.36)	
Oldest third	**0.79** (0.63, 0.98)	**0.80** (0.64, 1.00)		**0.82** (0.74, 0.90)	**0.82** (0.74, 0.91)		1.02 (0.86, 1.22)	1.02 (0.85, 1.22)	
(Unknown)	1.18 (0.90, 1.56)	0.91 (0.62, 1.33)		**1.15** (1.02, 1.30)	1.06 (0.89, 1.27)		1.10 (0.86, 1.39)	0.88 (0.60, 1.30)	

(continued)

Table 13.2 (continued)

	Mortality before age 61 (543 deaths)			Mortality between ages 61 and 85 (2797 deaths)			Mortality between ages 86 and 100 (876 deaths)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Both parents' age-at-death									
Both parents in youngest third	1.00		1.00	1.00		1.00	1.00		1.00
Intermediate	0.86 (0.65, 1.12)		0.86 (0.66, 1.13)	0.89 (0.78, 1.01)		0.89 (0.78, 1.01)	1.17 (0.93, 1.47)		1.17 (0.93, 1.47)
Both parents in oldest third	**0.58** (0.38, 0.88)		**0.59** (0.39, 0.90)	**0.66** (0.55, 0.79)		**0.66** (0.55, 0.80)	0.90 (0.66, 1.21)		0.90 (0.66, 1.21)
(At least one parent unknown)	1.16 (0.83, 1.63)		0.95 (0.63, 1.44)	1.09 (0.93, 1.28)		1.02 (0.84, 1.24)	1.17 (0.88, 1.56)		0.97 (0.65, 1.44)

Statistically significant estimates (95% CI) in bold type
Models 1: Adjusted for G1 birth order and three bands of G1 birth years
Models 2: Model 1+ parents' social class and marital status at G1 birth and mutually adjusted
Models 3: Model 1+ parents' social class and marital status at G1 birth

Table 13.3 G1 women's mortality by G0's age-at-death: hazard ratios with 95% confidence limits. Mortality follow-up 1961–2015 (n = 4694)

	Mortality before age 61 (295 deaths)			Mortality between ages 61 and 85 (2061 deaths)			Mortality between ages 86 and 100 (1166 deaths)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Mother's age-at-death									
Youngest third	1.00	1.00		1.00	1.00		1.00	1.00	
Intermediate third	0.92 (0.71, 1.21)	0.92 (0.70, 1.20)		0.93 (0.83, 1.03)	0.92 (0.83, 1.03)		0.87 (0.75, 1.01)	0.87 (0.75, 1.01)	
Oldest third	**0.67** (0.49, 0.90)	**0.68** (0.50, 0.91)		**0.73** (0.65, 0.82)	**0.74** (0.66, 0.82)		**0.73** (0.63, 0.84)	**0.73** (0.63, 0.84)	
(Unknown)	0.71 (0.33, 1.53)	0.56 (0.26, 1.22)		0.83 (0.64, 1.08)	0.80 (0.61, 1.06)		0.92 (0.66, 1.28)	0.96 (0.69, 1.34)	
Father's age-at-death									
Youngest third	1.00	1.00		1.00	1.00		1.00	1.00	
Intermediate third	1.02 (0.74, 1.38)	1.00 (0.74, 1.37)		0.94 (0.84, 1.05)	0.94 (0.83, 1.05)		0.97 (0.83, 1.14)	0.98 (0.83, 1.15)	
Oldest third	0.92 (0.67, 1.25)	0.92 (0.67, 1.26)		**0.78** (0.69, 0.87)	**0.78** (0.70, 0.88)		0.90 (0.77, 1.05)	0.91 (0.78, 1.07)	
(Unknown)	**1.47** (1.03, 2.11)	1.60 (0.96, 2.66)		0.97 (0.84, 1.11)	0.83 (0.68, 1.01)		0.96 (0.80, 1.17)	**0.74** (0.56, 0.98)	

(continued)

Table 13.3 (continued)

	Mortality before age 61 (295 deaths)			Mortality between ages 61 and 85 (2061 deaths)			Mortality between ages 86 and 100 (1166 deaths)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Both parents' age-at-death									
Both parents in youngest third	1.00		1.00	1.00		1.00	1.00		1.00
Intermediate	0.85 (0.58, 1.24)		0.84 (0.58, 1.23)	**0.77** (0.67, 0.88)		**0.77** (0.67, 0.89)	0.90 (0.73, 1.10)		0.90 (0.73, 1.10)
Both parents in oldest third	0.83 (0.50, 1.39)		0.83 (0.49, 1.38)	**0.59** (0.48, 0.72)		**0.59** (0.48, 0.72)	**0.72** (0.55, 0.94)		**0.72** (0.56, 0.94)
(At least one parent unknown)	1.22 (0.78, 1.90)		1.16 (0.69, 1.95)	**0.84** (0.71, 1.00)		**0.74** (0.60, 0.92)	0.89 (0.70, 1.14)		**0.72** (0.53, 0.97)

Statistically significant estimates (95% CI) in bold type
Models 1: Adjusted for G1 birth order and three bands of G1 birth years
Models 2: Model 1+ parents' social class and marital status at G1 birth and mutually adjusted
Models 3: Model 1+ parents' social class and marital status at G1 birth

mortality. It appears to represent a different pathway from that of early or adult social class. In fact, parents' ages-at-death appear to be more consistent predictors of G1 men's and women's mortality than is their social trajectory.

Analyses of a segment of G1 (those born 1915–1917) showed that G1 tend to live longer than their G0 parents in all social classes and in both marital status groups. Median difference in age-at-death, comparing G1 men and their fathers, was +3.9 years; when comparing G1 daughters to their mothers it was +6.9 years (data not shown). The age-at-death distribution has thus shifted to the right when G0 and G1 are compared. Variation in age-at-death has also fallen. Standard deviations around mean age-at-death for G0 women are 16.5 years and for their G1 daughters 12.6 years, whereas for G0 men and their sons the corresponding figures are 14.3 and 12.7 (data not shown). The secular trend of falling variation in age-at-death is known from the literature (Smits and Monden 2009) and often explained by falling infant and child mortality rates. Here, however, it is based on falling adult mortality rates, since all individuals in G0 and G1 have survived childhood long enough to become parents.

Regressing the exact age-at-death of (G1) sons and daughters on (G0) mid-parental age-at-death (Fig. 13.3) gives modest regression coefficients with wide confidence limits of b = 0.11 (95% CI 0.02, 0.20) for sons, and 0.07 (CI −0.02, 0.15) for daughters. Offspring age-at-death varies considerably around parental age-at-death. Many other factors, beyond their parents' longevity and social class, influence longevity in the next generation. The phenomenon of "regression to the mean", observed by Galton already in 1886, indicates that a number of unobserved determinants, and their combinations, including chance, are at play. They operate in such a way that the discriminatory accuracy of mid-parental age-at-death is low. Your parents' age-at-death (or most other determinants) can therefore be a rather poor predictor of your own age-at-death. Figure 13.3a, b show the G1-G0 difference by G0 age-at-death: a steep negative regression line (in both graphs b = −0.9; p < 0.001). Thus, children of parents who lived relatively short lives enjoyed a much larger increase in lifespan compared to their parents than did others. As a low attained age is partly due to randomly distributed causes, we would expect a "regression to the mean" at both ends of the age-at-death distribution; the steeper the smaller the role of inheritance. We do indeed observe a strong regression to the mean, suggesting that (genetic or non-genetic) inheritance plays a modest role.

13.5.2 Resilience Analyses

We explored inheritance of resilience. Figure 13.4 gives an overview of the process by which the final numbers of G2 and G3 study subjects were selected for resilience analyses.

Linear regression reveals an association between G2 fathers and G3 sons in resilience scores, controlling for G2 adult social class (b = 0.21, 95% CI = 0.17,

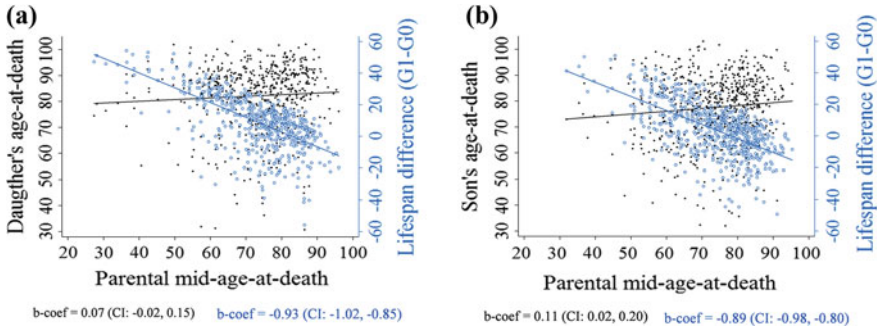

Fig. 13.3 **a** Age-at-death for G1 daughters (n = 529) by their parents' mid-age-at-death indicated by dots. G1-G0 difference in lifespan in years, indicated by circles. Based on G1 born 1915–17; **b** Age-at-death for G1 sons (n = 620) by their parents' mid-age-at-death indicated by dots. G1-G0 difference in lifespan in years, indicated by circles. Based on G1 born 1915–17

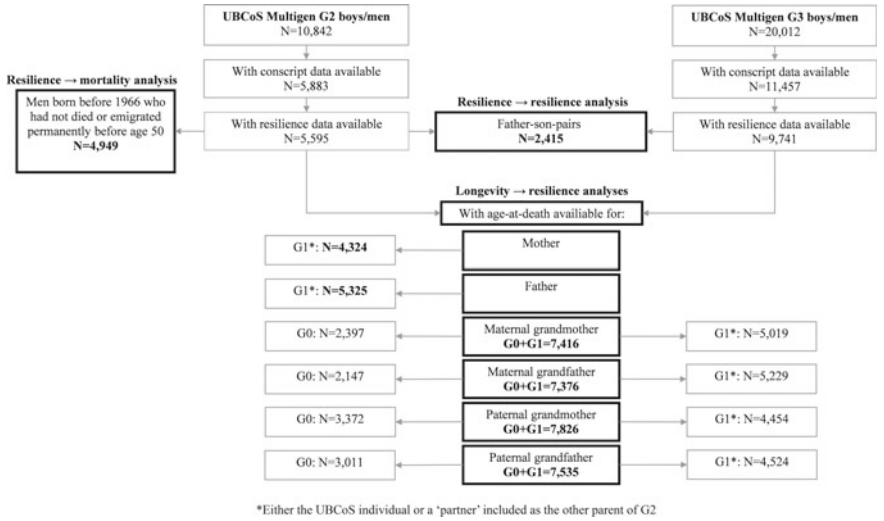

Fig. 13.4 Overview of the process by which the final numbers of G2 and G3 study subjects were selected for resilience analyses

0.25) (data not shown). It seems likely that resilience is also correlated between G0 and G1, beyond its link to social class.

Regressing G2 all-cause mortality at ages 50–65 on G2 resilience scores, controlling for G2 adult social class, gave a hazard ratio of 0.92 (95% CI 0.84, 0.99) per unit (Table 13.4). In fact, social class and resilience were both independent predictors of mortality (not shown). Thus, a large part of the mortality variation across resilience scores takes place within social classes. Excess mortality for the lowest resilience group can be calculated to be 2.02 (95% CI = 1.06, 3.86) compared to the highest.

Table 13.4 G2 men's mortality at ages 50–65 by a 1 step increase of their resilience score at age 18: hazard ratios with 95% confidence limits based on Cox regression. Mortality follow-up 2000–2015 (n = 4949)

	Mortality at ages 50–65 (193 deaths)	
	Model 1	Model 2
Resilience score at age 18	**0.90** (0.83, 0.98)	**0.92** (0.84, 0.99)

Statistically significant estimates (95% CI) in bold type
Model 1: Adjusted for four bands of birth years and conscription office
Model 2: Model 1+ social class at age 25–34

Table 13.5 G2 and G3 men's resilience score according to their parents and grandparents survival up to age 85: b-coefficients with 95% confidence limits based on linear regression

Longevity (≥85 years)	%[b]	G2 and G3 men's resilience scores at age 18		n[c]
		Model 1	Model 2	
Mother[a]	56	**0.27** (0.14, 0.39)	**0.22** (0.10, 0.35)	4324
Father[a]	36	**0.23** (0.11, 0.34)	**0.16** (0.04, 0.27)	5325
Maternal grandmother[a]	46	**0.14** (0.05, 0.23)	**0.13** (0.04, 0.22)	7416
Maternal grandfather[a]	30	0.02 (−0.08, 0.11)	0.00 (−0.09, 0.10)	7376
Paternal grandmother[a]	45	**0.10** (0.01, 0.19)	0.08 (−0.01, 0.16)	7826
Paternal grandfather[a]	27	0.03 (−0.07, 0.13)	0.01 (−0.09, 0.11)	7535

Statistically significant estimates (95% CI) in bold type
Model 1: Adjusted for conscription office
Model 2: Model 1+ parent's social class at age 31–61 (G1) or 25–34 (G2)
[a]Reference category: did not survive to age 85
[b]Proportion of parents/grandparents who survived to age 85
[c]Number of G2 and/or G3 men in the analysis

Looking closer suggests mortality to be a curvilinear function of resilience, with a disproportionately high mortality burden in the two lowest resilience groups.

In addition, our results suggest that both mothers' and fathers' longevity (surviving to age 85) is associated with resilience in their male offspring. Intriguingly, the longevity of maternal grandmothers, but not of any of the grandfathers, is associated with their grandsons' resilience scores (Table 13.5).

Thus, resilience and long-term mortality are linked within a generation; for both there is a continuity across generations. Finally, longevity in the previous generation(s) is linked to resilience in their (male) offspring. All this suggests that resilience could play some role in the inheritance of longevity.

13.6 Discussion–Pathways to Longevity

13.6.1 Strength and Limitations of the Present Study

This study of UBCoS Multigen covers four generations and presents G0 lifespan data for the first time. The parents (G0) of the first generation, G1, are all dead. The use of G0 age-at-death as a predictor for events in later generations is a unique feature of this study. G0 were identified from G1 births 1915–29, but our analyses do not cover G0's children born outside that period. In some of the analyses, we used only a segment of G1, those born 1915–1917, giving rather low statistical power.

Parents are a healthy subset of all individuals and they tend to live longer than childless women and men (Hurt et al. 2006). To increase comparability between generations (G0 and G1), we restricted our analyses to those individuals in G1 who were themselves parents.

Data about resilience scores at age 18 were available for males in G2 and G3. This is a limitation, particularly because it excludes women. However, the observed associations in resilience could well be similar for women and for the two previous generations.

We calculate estimates of average causal effects in a population, or in segments of a population. These are useful when considering "causes of population incidence" (Rose 1985) or differences between groups. They are less useful as predictors of individual events of disease or death (Merlo et al. 2017), since individual responses to risk factors show a very large variation.

Having information for four linked generations is the unique strength of this study. Even though the available information is not identical for each generation, it provides an opportunity to better understand the nature of parent-offspring associations in achieving a high age

We consider possible pathways of longevity inheritance in the light of our theoretical proposals in the section below.

13.6.2 Social and Genetic Pathways

We lack behavioural and genetic data; this leaves many questions about the pathways and inheritance of longevity unanswered. Familial clustering of longevity could suggest a genetic pathway. Hjelmborg et al. (2006), however, found genetic influences to be less important for mortality before age 60 and to increase with rising age. We found that (1) parents' age-at-death is associated with mortality in G1 men and women both before and after age 60 and (2) no tendency at all for the association between G0 age-at-death and G1 mortality to increase with age. It is therefore likely to reflect a different kind of inheritance. Kowald and Kirkwood (2016) recently dismissed any possibility of aging being genetically programmed. The strong variation in G1 age-at-death around a specific value for G0 age-at-death (Fig. 13.3) gives some support

for their view. Any direct genetic influence is probably rather small. Pal and Tyler (2016) suggested that, rather than being genetically determined, lifespans are epigenetically determined, based on genome-wide responses to external events, during both development and aging.

Wilhelmsen et al. (2011) found that parents' survival had no influence on their sons' survival up to age 90. A possible explanation for the difference compared to the present study is that they measured parental survival by whether the parent was dead or alive when the son was 50 years old, ignoring later deaths and parental survival to more advanced ages. However, they did find a number of social and behavioural factors at age 50, such as smoking and a high coffee consumption, which predicted death before age 90 among the men. Both these behaviours may be considered ways of coping with stress and hardship, developed earlier in life.

G1 men and women born 1915–1917 had longer lifespans than their parents; daughters, especially, lived longer than their mothers. Female emancipation and social change during the 20th century has been accompanied by a stronger reduction in mortality among women than among men (Hemström 1998). Hemström used the term "male susceptibility" to explain the difference between male and female long-term mortality trends. This was a reference to male risk-taking behaviour, developed as a particular, non-healthy way of coping with adversity in modern society.

Zeng and Shen found resilience to hardship as well as social friendships to be important for longevity (Zeng and Shen 2010; Shen and Zeng 2010). Their emphasis on social support as an aspect of resilience resembles the way Cassel (1974) and Syme and Berkman (1976) originally conceived of general susceptibility. A relatively short lifespan could be considered the result of an underlying frailty or general susceptibility. In contrast, we can think about individuals who live long lives as being particularly resilient, able to cope with adversity at any age.

13.6.3 Resilience as a Possible Mechanism in the Intergenerational Transmission of Longevity

According to Windle's (2011) systematic review of the literature, resilience is used in many different contexts and with a variety of definitions. The core of the concept seems to be the personal capacity to "bounce back" in the face of adversity. Resilience may be developed early in life as a successful response to adversity (Garmezy 1993; Phillips et al. 2016). Repeated adversity is often linked to early social class, a marginal social position or lack of family resources, pointing to the importance of the social and material context. Repeated adversity, followed by repeated successful responses, should constitute a dynamic learning process. This process must be influenced both by luck and by cross-talk between genes and experience, finally resulting in a high degree of resilience. Escaping "*the long shadow of the past*", in fact. Alternatively, if repeated adversity is followed by repeated failure to cope, we may instead see

the gradual emergence of a "general susceptibility", crucially linked to the social environment, as Cassel suggested in 1976.

Early experience of adversity may thus be seen as a *switch* between the alternative paths of resilience and susceptibility, pressed relatively early in life. Hertzman and Boyce (2010) wrote in similar terms that "early experiences can produce small changes in trajectories, which can become magnified as individuals develop" (page 334).

In our study, resilience was identified at military conscription by a trained psychologist through a semi-structured interview. The interview covered past adjustment problems; conflicts and successes; responsibilities and initiatives taken at school, at home, at work and in leisure time. Mental energy, social maturity and stability were assessed. How a person would handle situations of severe stress in the future was assessed (with scores 1–9) against the background of his previous history. This is a strength of the present study.

We found a continuity of resilience from fathers to sons, independent of parental social class. Transmission of this characteristic across generations could happen through several mechanisms (not mutually exclusive), such as learning from parents or transmission of specific genes. Of theoretical importance is the hypothesis that early experience can also cause epigenetic modification of germ-line DNA and potentially influence gene expression and longevity in the next generation (Franklin et al. 2010; Vaiserman 2012; Rando 2016; Marsland 2017; Sharma 2017).

13.6.4 Biological Programming, Epigenetics and Social Epidemiology

Barker et al. (2001) suggested that optimal foetal growth created resilience to the health consequences (such as heart disease mortality) of poor living conditions. We believe that their focus was too narrow and suggest that human resilience is shaped over a much longer period which includes childhood and adolescence. Barker's concept of foetal programming has now been replaced by that of developmental programming. Interaction between genetic potential and early experience causes epigenetic changes during development.

Simpkin et al. (2017) found a number of developmental features to be linked to methylation patterns at birth and at age 7. They discussed whether *epigenetic age* should be seen as an aggregate measure of maturity in childhood. However, they cautioned against this, since they found it to be unrelated to the onset of puberty. Indeed, if individual response to early experience affects the way children develop (becoming resilient rather than susceptible, for instance), it would seem wrong to conceptualise this as a feature of maturity or epigenetic aging. Beach et al. (2016) called for an investigation into "SES risk exposure and protective factors that occur during pre-adolescence or later and that may be mediated by epigenetic change".

They found that "a supportive family at age 10–13 is associated with epigenetic pattern at age 19".

Thus, there is at least theoretical support for the idea that resilience/susceptibility in humans is epigenetically programmed early in life. This makes our measure of resilience at age 18 appropriate for studying the role of resilience in the inheritance of longevity. We found that the longevity of both parents (surviving to age 85) was associated with resilience in their male offspring. This is a parallel to Horvath et al. (2015), who reported that adult offspring of long-lived persons had a particularly low *epigenetic age*. Miller and colleagues, in turn, linked epigenetic age to resilience and self-control among young adults (Miller and Chen 2013; Miller et al. 2015).

Among adult humans, epigenetic changes of the genome are robust markers of biological age (Chen et al. 2016). *Epigenetic age* among adults predicts longevity independently of chronological age, even after adjusting for known risk factors. This suggests the intriguing possibility that *epigenetic age* (epigenetic age advancement) measured in adulthood or in old age, but not in childhood, is a correlate to general susceptibility/resilience at genome level. Whether resilience, in fact, is related to epigenetic age among adults, is a challenging research question.

The transmission of resilience across generations is a further question. If resilience is acquired in the parental generation, it could be transmitted to the next generation, either through an epigenetic pathway or through learning from parents, or through a combination of both. We found that both mothers' and fathers' longevity was associated with resilience in the following generation, consistent with both pathways. Genetic variants favouring brain plasticity could probably amplify the "switch" between susceptibility and resilience. Belsky and Beaver (2011) showed that "cumulative-genetic plasticity" interacts with parenting to shape adolescent self-regulation. The negative effects of poor parenting and the positive effects of good parenting were stronger among those with more plasticity.

The fact that the longevity of maternal grandmothers (but not any of the grandfathers) was associated with resilience in grandsons, is also compatible with the "*grandmother hypothesis"*, which postulates that grandmothers, in particular, invest in their grandchildren's future. A review by Strassman and Garrard (2011) found this "to hold only for the maternal and not the paternal grandmother".

13.7 Conclusion—How Is Longevity Inherited?

We conclude that parents' longevity predicts their children's long term mortality. This influence is modest but robust, not confounded by the social class and marital status of their parents at their birth, and distinct from their own social class trajectories. Kowald and Kirkwood (2016) posed the question of whether aging is genetically programmed. Their answer was no. We suggest that early "programming" of resilience, epigenetically and culturally transmissible across generations, is a more likely hypothesis. Individual resilience, we propose, is developed in the first part of life as a response to adversity and early experience in general. This is

in line with recent animal research which has shown that early life stress encodes lifelong susceptibility to stress via long-lasting transcriptional programming (Peña et al. 2017). Our finding that men with the lowest resilience scores disproportionally suffer midlife mortality is not surprising.

Risk factors, and social determinants of health, work on populations with considerable individual variation. Understanding longevity inheritance therefore calls for new ideas. A theory of longevity inheritance should bring together previous thinking around general susceptibility, frailty and resilience with new insights from epigenetics and social epidemiology.

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Chapter 14
Early-Life Adjustment of Epigenetic Aging Clock

Alexander Vaiserman and Oleh Lushchak

Abstract There is accumulating evidence that adult-life health status and rate of age-associated functional decline may be programmed early in life. The key role of epigenetic mechanisms in mediating these life-long effects, including DNA methylation histone modification and regulation by non-coding RNAs, has been demonstrated. Early-life environmental conditions were repeatedly shown to significantly affect life-course change of epigenetic patterns known as "epigenetic drift". Epigenetic drift may arise following both stochastic errors in maintaining epigenetic marks and adaptive changes directly mediated by specific environmental cues. Recently, DNA methylation-based methods for determining rate of epigenetic aging were developed. Recent cohort studies using these methods have shown that ticking rate of epigenetic aging clock can be adjusted in early life, and that life-course dynamics of individual discrepancies between chronological and epigenetic age might be developmentally programmed. In this chapter, recent evidence suggestive of developmental programming of life-course dynamics of epigenetic drift is reviewed and discussed.

Keywords Developmental programming · DNA methylation · Aging-associated disorder · Aging rate · Epigenetic aging clock · Epigenetic drift

14.1 Introduction

It is commonly believed that genetic background and lifestyle factors are the major determinants of aging rate and life expectancy. However, accumulating data indicate that both individual aging trajectory and population mortality rate may substantially

A. Vaiserman (✉)
Laboratory of Epigenetics, Chebotarev Institute of Gerontology, 67 Vyshgorodska Str., Kiev 04114, Ukraine
e-mail: vaiserman23@gmail.com

O. Lushchak
Department of Biochemistry and Biotechnology, Vasyl Stefanyk Precarpathian National University, 57 Shevchenka Str., Ivano-Frankivsk 76018, Ukraine

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depend on developmental conditions (Tarry-Adkins and Ozanne 2014; Vaiserman et al. 2018). Molecular mechanisms underlying such life-long effects are not fully clarified yet, but modulating epigenetic pathways involved in regulation of gene expression is likely the most plausible explanation (Bianco-Miotto et al. 2017). Epigenetic modifications are heritable changes in gene function that are not caused by changes in DNA sequence. Basic components of epigenetic machinery include DNA methylation, modification of chromatin histones and regulation by non-coding RNAs.

Initially, epimutations (stochastic errors in maintaining epigenetic marks) occurring during the life course due to the limited capacity to maintain and repair correct epigenetic patterns were suggested to be the main cause of age-related disruption of normal epigenetic profiles (Holliday 1987). As the age-associated accumulation of epimutations ultimately results in an impairment of the proper gene responsiveness to environmental challenges and to gradual loss of phenotypic plasticity, this process is assumed to be one of the major causes of aging (Gravina and Vijg 2010). Moreover, since age-related demethylation of DNA can obviously cause chromosome instability, and hypermethylation of promoter regions of tumor suppressor genes may result in their suppression, accumulation of epimutations with age might likely contribute to the initiation and progression of various tumors (Jung and Pfeifer 2015; Feinberg et al. 2016). Accumulation of errors in maintaining correct epigenetic profiles inevitably causes an increase in variability of epigenetic marks during the life course of an individual. This process is commonly referred to as "epigenetic drift." It results in the gradual impairment of homeostatic mechanisms and appears to be a central hallmark of aging and one of the most important determinants of longevity (Mendelsohn and Larrick 2017).

The convincing evidence for epigenetic drift in humans has been provided from monozygotic (MZ) twin studies. Within-pair comparison in such twin pairs provides a valuable model for investigating factors contributing to epigenetic variability by controlling for genetic background effects. Despite MZ twins share the same genetic background, their epigenetic profiles were demonstrated to gradually diverge with advancing age (Fraga et al. 2005). Remarkably, those MZ twins who, in accordance with their questionnaire responses, had spent less of the lifetime together or/and had more differentiating natural health–medical histories, showed more pronounced divergences in epigenetic profiles. Similarly, it has been revealed in recent study by Li et al. (2018) that correlation in levels of the genome-wide average DNA methylation between non-twin first-degree relatives increased with time living together and decreased with time living apart. The interplay between life-course environmental conditions and age-associated methylation divergence has been also confirmed in a genome-wide longitudinal analysis of DNA methylation in MZ twins from birth to 18 months of age (Martino et al. 2013). Collectively, findings from these studies suggest that divergences in epigenetic profiles may occur not only through the stochastic epigenetic drift (caused, e.g., due to mistakes in the maintenance of the patterns of DNA methylation throughout cycles of replication), but can also be directly mediated by certain environmental conditions (Cortessis et al. 2012; Cunliffe 2015). So it can be assumed that epigenome may respond to environmental perturbations in an

adaptive manner to maintain normal homeostasis and performance (Vaiserman 2008, 2010). Thereby, the age-related modification of epigenome can be regarded as a process of memorization of environmental cues experienced by the organism over their lifespan. The process of epigenetic memory formation likely influences the rate of epigenetic drift. In this chapter, recent research findings evidencing the importance of early-life conditions for the life-course dynamics of epigenetic drift are reviewed and discussed.

14.2 Early Determinants of Epigenetic Drift

Numerous recent evidences demonstrated that both rate and direction of age-related epigenetic drift to a great extent depend on environmental conditions in early life (Li and Tollefsbol 2016). This is not surprising, because epigenome (a totality of epigenetic marks across the whole genome) is known to be most plastic throughout early development, especially during establishing the cell lineage-specific patterns of gene expression (Iurlaro et al. 2017; Burns et al. 2018). In mammals, including human beings, window of epigenetic plasticity extends from preconception through weaning (Vaiserman 2015). After establishing throughout the early developmental stages, most epigenetic marks are stably maintained during mitotic cell divisions. The epigenetic cell memory allows to maintain stable patterns of gene expression in certain cell lineages throughout whole life course. In modern scientific literature, this process is generally referred to as "epigenetic developmental programming" (Hochberg et al. 2011). Importance of this process in determining future health status underlies the recently proposed concept of the "first 1000 days", prioritizing antenatal period and first two years after birth as a developmental period critical for future health outcomes (Garmendia et al. 2014). The concept of predictive adaptive response (PAR) postulates that environmental cues early in life may be used by an organism to the rearrangement of epigenetic profiles in the way that may provide greatest fitness dividends during the adult life (Bateson et al. 2014). If a phenotype occurring in consequence of such adaptive strategy is properly matched to the developmentally predicted environmental conditions, it leads to survival benefits during adulthood. However, if early-life adaptive fine-tuning of epigenome subsequently turns out to be wrong and a mismatch occurs between the actual living conditions and developmentally programmed phenotype, it can lead to an elevated disease risk later in life (Godfrey et al. 2007). These theoretical considerations seem especially pertinent in the context of the discussed topic. Recent research findings evidencing the role of early-life environmental conditions in developmental programming of the life-course dynamics of epigenetic drift and organism's aging trajectory are reviewed in subsequent sections.

14.3 Evidence from Experimental Studies

Investigating the role of epigenetic regulation in developmental programming of aging and longevity phenotypes in humans is obviously problematic due to the restricted access to appropriate biological material. Therefore, human data on this issue are scarce by now, and most direct evidence for that came from animal models. One example is the study by Merkwirth and coauthors (2016), where perturbation of mitochondria throughout the larval development in *C. elegans* not only delayed aging but also maintained unfolded protein response [UPR(mt)] signaling. Epigenetic mechanisms potentially contributing to both lifespan regulation and mitochondrial proteostasis across the worm's life cycle have been elucidated. In particular, down-regulation of lysine demethylases such as JMJD-1.2/PHF8 and JMJD-3.1/JMJD3, was found to be potentially able to suppress lifespan and UPR(mt) induction, whereas gain of function was associated with extended longevity in a UPR(mt)-dependent manner.

Greer et al. identified ASH-2 trithorax complex that trimethylates histone H3 at lysine 4 (H3K4) (Greer et al. 2010). This factor was shown to play an important role in epigenetic programming of longevity in nematode. Developmental activation of specific longevity-regulating signaling pathways by misregulation of H3K4me2 resulted in a transgenerational lifespan extension in F2-F4 offspring, potentially suggestive of epigenetic memory (Greer et al. 2011). The possibility of epigenetic transgenerational effects on the worm's longevity was also confirmed by some other studies (Greer et al. 2016; Kishimoto et al. 2017).

Recently, Xia and de Belle (2016) reported transgenerational effects on reproductive activity and lifespan in *Drosophila melanogaster*. These effects were induced by post-eclosion manipulation with content of dietary proteins. Both low- and high-protein diets were shown to reduce longevity, whereas the intermediate-protein diet significantly extended lifespan up to the F3 generation. In a subsequent study of the same authors, feeding with a low-protein diet during the post-eclosion period caused shortened life expectancy in parental generation (F0) as well as in F2-generation offspring. This effect was accompanied by upregulation of the H3K27-specific methyltransferase, E(z), and increased level of H3K27 trimethylation, H3K27me3 (Xia et al. 2016). Remarkably, both RNAi-mediated knockdown of E(z) and pharmacological inhibition of its enzymatic function with a histone methyltransferase inhibitor, Tazemetostat (EPZ-6438), were shown to decrease levels of H3K27me3 across generations. Furthermore, treatment with Tazemetostat abolished the life-shortening effect of parental low-protein diet.

In rodents, confirmatory evidence has also been obtained on the role of environmental exposures such as stress, xenobiotic chemicals and malnutrition in epigenetic programming of pathways involved in the control of aging and longevity (for reviews, see Vaiserman 2014; Tarry-Adkins and Ozanne 2017; Ambeskovic et al. 2018). In particular, in the study by Heo et al. (2016), prenatal malnutrition resulted in disturbed DNA methylation patterns and dysregulated transcriptional activity of genes involved in aging-associated processes and metabolic disorders in young (9 weeks

old) rat offspring. Remarkably, these disrupted epigenetic patterns were shown to persist in prenatally exposed offspring until an advanced (20-month) age.

14.4 Evidence from Twin Models

The evidence for the role of developmental programming in epigenetic drift was obtained primarily from studies in MZ twins discordant for birth weight. Birth weight has been used in such research as a proxy for conditions of intrauterine development. This study design commonly relies on investigating twins raised in shared family living conditions. Such study design can provide control not only for the same genetic background but also for similar postnatal living environment. Clear evidence for discordance in gene expression profiles between MZ twins was revealed in two different cell types in research by Gordon et al. (2011). Among genes that demonstrated most pronounced discrepancy in expression patterns within pairs, there were genes responsible for metabolism, stress response and cardiovascular functioning. Findings from several twin studies also demonstrated that epigenetic variations induced early in life can persist into adult life. Even though very similar genome-wide DNA methylation profiles have been initially found in saliva samples from adult female MZ twins discordant for birth weight (Souren et al. 2013), persisting differences in DNA methylation profiles were observed in more recent studies. Importantly, most of the genes which were shown to be differentially methylated in this study are known to be involved in age-related processes. Significant association was, in particular, found between pronounced within-twin variation in fetal growth (discordance in birth weight more than 20%) and changes in DNA methylation of the *IGF1R* gene throughout adulthood (Tsai et al. 2015). A specific region on chromosome 1 was identified in an epigenome-wide DNA methylation analysis as being differentially methylated in birth-weight discordant adult MZ twins (Chen et al. 2016). This region has been found to cover two genes, *CRYZ* and *TYW3*, both associated with metabolic pathways. The genome-wide methylome analysis conducted in blood samples from adult MZ twins discordant for birth weight did not found any differences in profiles on DNA methylation between twins (Tan et al. 2014). The age-associated intra-pair differential methylation in extremely birth weight-discordant twin pairs was, however, revealed in particular sites.

Consistent evidence for a dependence of life-course dynamics of epigenetic drift from programming events early in life has also been obtained from non-MZ twin models. In analyzing findings from seven twin and/or relative studies, Li et al. (2018) revealed that correlations between levels of the genome-wide average DNA methylation are very high at birth and they remain high during the whole life course in both twin and non-twin first-degree relatives. These data are suggestive of life-long persistence of early-life programming events at the level of the genome-wide DNA methylation.

14.5 Evidence from Natural Experiments

Convincing evidence indicative of important role of epigenetic mechanisms in mediating a link between developmental programming events with adverse health outcomes in later life have been also reported in studies conducted using quasi-experimental design. This research design (also commonly referred to as "natural experiment") is defined as "naturally occurring circumstances in which subsets of the population have different levels of exposure to a supposed causal factor, in a situation resembling an actual experiment where human subjects would be randomly allocated to groups" (Last 1995). The long-term health consequences of early-life exposure to the Dutch famine (a massive famine that took place in the German-occupied part of the Netherlands in 1944–45) are the most studied in this context to date. In the cohorts born throughout this famine, the signs of accelerated aging have been repeatedly reported. These signs included reduced cognitive performance, impaired physical functions, increased stress responsivity, atherogenic plasma lipid profiles, enhanced risks for developing depression and cardio-metabolic diseases (Lumey et al. 2011; Roseboom et al. 2011; Bleker et al. 2016), and also elevated mortality rates at older ages (van Abeelen et al. 2012). These unfavorable health outcomes were shown to be accompanied by persisting changes in epigenetic profiles.

While no association was observed between the prenatal exposure to Dutch famine and the overall DNA methylation level in adulthood (Lumey et al. 2012), methylation levels of particular genes in the whole blood samples from adult offspring were found to be strongly associated with the prenatal exposure to famine. Among the genes shown to be differentially methylated between prenatally famine-exposed individuals and non-exposed control persons, there were genes such as *IGF2* (Heijmans et al. 2008) as well as *GNASAS*, *IL10*, *LEP*, *ABCA1*, *INSIGF* and *MEG3* (Tobi et al. 2009) known to be involved in developing cardio-metabolic phenotypes. More recently, differential methylation patterns were obtained in genomic regions extended along pathways associated with growth and metabolism in subjects periconceptionally exposed to the Dutch famine (Tobi et al. 2014). Early, but neither mid nor late gestation, has been identified as a critical time window for inducing persistent changes in the DNA methylation patterns (Tobi et al. 2015). Even though it has still not been revealed whether there is a correlation between the DNA methylation levels and the gene expression levels, modifications in the profiles of DNA methylation found in this study were clearly associated with impaired metabolic homeostasis in adult subjects who have been prenatally exposed to famine (Lumey et al. 2007; Tobi et al. 2018).

Similar findings have been reported in study conducted to examine the long-term health outcomes associated with perinatal exposure to the famine of 1974–75 in rural Bangladesh (Finer et al. 2016). In this research, those offspring who have been perinatally exposed to famine were found to be at higher risk of developing type 2 diabetes and obesity throughout adult life compared to unexposed control individuals. These adverse health outcomes have been associated with substantial

differences in methylation levels in metastable epialleles such as *PRDM-9*, *PAX8*, *VTRNA2-1*, near *ZFP57*, near *BOLA* and *EXD3*.

14.6 Developmental Adjustment of Epigenetic Clock

In recent years, DNA methylation has acquired a substantial interest as a useful biomarker of aging allowing to quantify the rate of individual aging as well as inter-individual variations in functional declines and timing of onset of pathological conditions throughout the life course (Levine et al. 2018). The most famous of them is the multi-tissue algorithm developed by Horvath (2013). This approach allows to calculate the biological age estimates that correlate with chronological age above $r = 0.90$ across the full age range of tissue samples.

Recently, multiple studies have demonstrated that rate of ticking of epigenetic clock, estimated using the DNA methylation-based methods, can be adjusted during early life, and that discrepancy between the individual's epigenetic and chronological age can be programmed in early development. The conclusive evidence for this came mainly from data obtained in cohort studies. Most of these studies used the Horvath's method to evaluate differences between actual chronological age and calculated DNA methylation age (Horvath 2013). The dependence of the adult epigenetic aging rate (age acceleration, AgeAccel) from childhood conditions has been estimated, for example, in the study by Simpkin et al. (2016). In this research, AgeAccel values were defined as residuals from regressing epigenetic age on actual age. In two birth cohorts, an association between birth weights and measures of AgeAccel during adolescence has been observed. In analysis of the DNA methylation patterns across the five time-points in mother-child pairs belonging to a Britain's birth cohort, adolescent AgeAccel values were shown to be associated with maternal alcohol consumption during pregnancy. In the subsequent longitudinal study carried out using the same birth cohort, strong associations have been found between AgeAccel and developmental characteristics such as weight, height, body mass index and fat mass throughout childhood and adolescence (Simpkin et al. 2017). An inverse association between AgeAccel and pubertal tempo in girls has been revealed in a longitudinal Growth and Obesity Cohort Study (Binder et al. 2018). Similar findings have been reported in two Finnish follow-up cohorts where developmentally established values of AgeAccel remained unchanged over the rest of the life cycle, even in the oldest-old ages (Kananen et al. 2016). On the basis of evidence from these studies, the epigenetic clock theory of aging has been recently introduced by Horvath and Raj (2018), which postulated that epigenetic clocks link developmental and maintenance processes to aging.

14.7 Hypothetical Considerations

Based on the theoretical frameworks and empirical findings discussed above, it may be suggested that life-course dynamics of epigenetic aging may be programmed by events early in life and that the pattern of this relationship may differ depending on the type, duration and intensity of exposure, as well as on the stage affected. Most data on the mode of this relationship correspond to intuitive views. Exposure to unfavorable environmental conditions early in life might lead to an increased rate of accumulating epimutations without accelerating the epigenetic aging rate. In terms of parameters of regression model, these processes could result in an increase of the intercept parameter without altering the slope parameter in a regression model describing such a relationship. Such mode of relationship might be referred to as a "premature epigenetic aging" (PEA). Inadequate process of developmental programming owing to, for example, mismatched epigenetic adaptation, could, by contrast, lead to an increase in the slope parameter and to an "accelerated epigenetic aging" relative to a "normal epigenetic aging" rate (AEA and NEA, respectively). The scheme presenting hypothetical trajectories of life-course dynamics of epigenetic aging is shown in Fig. 14.1.

Several research findings regarding the long-term health outcomes of programming events early in life are counterintuitive, however, and require additional assumptions to be made. For instance, in analyzing the paradoxical deceleration of old-age mortality rates reported across many developed societies throughout the second part of the past century, it has been revealed that many centenarians paradoxically come from sub-cohorts who were frail during their childhood (Yashin et al. 2001). The authors of this research hypothesized that more vulnerable (and likely more labile) individuals might better improve their stress reactivity than the more robust (and rigid) ones. Such an adaptive strategy could lead to survival benefits to originally more vulnerable organisms at their older ages.

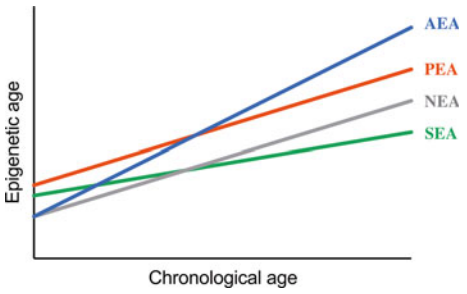

Fig. 14.1 The scheme presenting hypothetical trajectories of life-course dynamics of epigenetic aging. In the scheme, "normal epigenetic aging" (NEA) is shown with grey line, "premature epigenetic aging" (PEA)—red line, "accelerated epigenetic aging" (AEA)—blue line and "slowed epigenetic aging" (SEA)—green line

Additional epidemiological evidence for this assumption came from research conducted to test so-called hygiene hypothesis first formulated by Strachan (1989) to explain the relationship between the lack of microbial exposures owing to the over-hygienic conditions during childhood and elevated risk for developing autoimmune and allergic pathological conditions throughout later life. The over-hygienic conditions are becoming increasingly widespread currently across developed societies, and this trend is believed to be a leading cause of increased incidence of antibiotic resistance and permanently growing number of individuals having weakened or suppressed immune system in developed countries (Bloomfield et al. 2016). The basic assumptions and predictions coming from this hypothesis were repeatedly confirmed through many experimental and observational studies, although lack of microbial exposure can be not the sole causal factor (Maia Rda and Wünsch Filho 2013). Early-life under-using of immune system was also shown to cause not only atopic, but also autoimmune conditions (Kramer et al. 2013). This seems to be especially important since immunosenescence is presently considered to be among the main processes underlying aging. Remarkably in the context discussed, even although inflammaging is traditionally considered to be one of the leading causes of most aging-associated pathological conditions, such purely negative interpretation of the role of immune senescence in aging processes is currently challenged by many gerontologists. Many experts in the field of biogerontological research are increasingly tend to consider these changes to be adaptive and potentially advantageous rather than be solely detrimental (Fulop et al. 2018). In spite of the fact that these alterations in immune system function may apparently lead to many different pathological states, such changes can potentially contribute to the development of extended longevity phenotypes. It is even assumed by some authors that human life expectancy may be substantially shortened without the presence of the immunosenescence/inflammaging (Fulop et al. 2018). An important thing in the context of the discussed topic is that complex interaction between epigenetic and immune pathways may likely play an important role in these effects (Grolleau-Julius et al. 2010; Jasiulionis 2018). Taking into account the fact that these processes can significantly affect epigenome, they could likely decelerate the rate of epigenetic clock-ticking by increasing the regression intercept parameter and by decreasing the slope value ("slowed epigenetic aging") (SEA), even though the initial level of the rate of accumulating epimutations might be higher in developmentally exposed populations than in non-exposed ones. Remarkably, in the study by Marioni et al. (2018), epigenetic age was found to be increased at a slower rate than the chronological one across the life course, especially in the oldest population groups. The selection bias due to that healthier individuals might be more likely to achieve older ages has been proposed by the authors to explain these research findings. Alternatively, it can be assumed that these data may be explained by inducing the process of epigenetic adaptation. More in-depth studies are, however, needed to make definitive conclusions on this matter.

14.8 Conclusions and Perspectives

Biogerontological investigations are traditionally focused on the later stages of life cycle. There is, however, accumulating evidence that the rate of age-associated functional declines and the risk for developing chronic aging-associated disorders may, to a large extent, depend on the early-life conditions. Raising awareness of the crucial role of developmental programming in etiology and pathogenesis of later-life pathological states and highlighting mechanisms contributed to these processes induce growing interest in research in this field.

In present-day developed countries, the processes of developmental programming are likely to be of particular importance because substantial lifestyle changes (sedentary behavior, westernized diet, etc.) that have taken place in recent decades may conflict with developmentally programmed adaptive epigenetic strategies. From these hypothetical considerations, two important points follow for further research and practical applications. First, further developments in epigenetic methodology would provide a possibility to recognize individuals at risk for development of particular age-associated pathological conditions in consequence of malprogramming early in life long before clinical manifestation of these disorders. Second, epimutations, unlike genetic mutations, are known to be potentially reversible; therefore, they can be corrected by specific pharmacological and/or nutritional interventions. The implementation of epigenome-targeted interventions in public healthcare would further allow affect the life-course dynamics of epigenetic age and slow down the rate of ticking of epigenetic clock to decelerate or delay the aging-associated processes.

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Part IV
Perspectives and Implications

Chapter 15
Public Health and Social Policy Perspectives on DOHaD

M. Lelinneth B. Novilla, Michael C. Goates, Michael D. Barnes and Justin M. Packer

Abstract This chapter introduces the role of public health to the developmental origins of health and disease (DOHaD) primarily through social policy approaches. Social policies affect people's well-being. The chapter provides background to various levels of prevention and actions needed in relation to DOHaD. DOHaD research underscores the importance of an individual's circumstances and surrounding environment, particularly during the most vulnerable times of life, which provide great implications for improving social policy. Several social and environmental factors are discussed in relation to DOHaD, including among underserved or disadvantaged populations. The lack of action on social policy may well be due to policymakers' lack of awareness of DOHaD. Suggestions for improving social policy incorporate peer-reviewed-policy recommendations. Finally, the chapter concludes with multiple factors that both public health practitioners and policymakers can consider to more systematically develop social policies in response to the mounting evidence supporting DOHaD.

Keywords Developmental origins of health and disease (DOHaD) · Life-course · Social policy · Public health

15.1 The Scope of Public Health's Responsibility

Public health serves the population. Its responsibility to society has been traditionally abbreviated into three words: ***promote***, ***protect***, ***prevent***. Public health promotes and protects the health of families and communities through healthy behavior, education, research, health services, policy advocacy, disaster response, and by preventing disease, injuries, and disabilities (Institute of Medicine—Committee for the Study of the

M. L. B. Novilla · M. D. Barnes (✉) · J. M. Packer
Department of Public Health, Brigham Young University, Provo, UT, USA
e-mail: michael_barnes@byu.edu

M. C. Goates
Harold B. Lee Library, Brigham Young University, Provo, UT, USA

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Future of Public Health 1988; Centers for Disease Control and Prevention 2014). To safeguard the health of populations, public health has three core functions: to assess the health needs of communities, to develop policy, and to assure the "conditions in which people can be healthy" (Institute of Medicine—Committee for the Study of the Future of Public Health 1988). These core functions were expanded by the Public Health Functions Steering Committee of the U.S. Centers for Disease Control and Prevention (CDC) into the ten essential health services that are necessary to improve population health:

> (1) monitor health status to identify and solve community health problems; (2) diagnose and investigate health problems and health hazards in the community; (3) inform, educate, and empower people about health issues; (4) mobilize community partnerships and action to identify and solve health problems; (5) develop policies and plans that support individual and community health efforts; (6) enforce laws and regulations that protect health and ensure safety; (7) link people to needed personal health services and assure the provision of health care when otherwise unavailable; (8) assure competent public and personal health care workforce; (9) evaluate effectiveness, accessibility, and quality of personal and population-based health services; and (10) research for new insights and innovative solutions to health problems (Centers for Disease Control and Prevention 2018).

The principles and practice of public health are rooted in the words of Winslow (1920), bacteriologist and first head of Yale's Department of Public Health, whose definition set the standard for public health:

> Public health is the science and the art of preventing disease, prolonging life, and promoting physical health and efficiency through organized community efforts for the sanitation of the environment, the control of community infections, the education of the individual in principles of personal hygiene, the organization of medical and nursing service for the early diagnosis and preventive treatment of disease, and the development of the social machinery which will ensure to every individual in the community a standard of living adequate for the maintenance of health; organizing these benefits in such fashion as to enable every citizen to realize his birthright of health and longevity.

Public health is a collective societal effort. Even the health sector does not have the sole jurisdiction on population health. Every discipline, every sector can contribute to the nation's health. Winslow's definition made it clear that health and longevity are basic human rights. Ensuring such rights is the principle aim of "organized community efforts" (Winslow 1920) of public, private, and voluntary health and safety agencies, healthcare providers, and various organizations, which collectively constitute the public health system (Centers for Disease Control and Prevention 2018).

15.2 Upstream Public Health and the Social Determinants of Health

Prevention is a core public health responsibility. It is classified into various levels of strategies: primordial, primary, secondary, tertiary, and quaternary (Leavell and Clark 1965; Last 2007). Except for primordial-level strategies aimed at addressing the community determinants of health, the rest of the levels of prevention strategies focus on individual-level behavior, risk factors, screening, care and rehabilitation.

A guide to choosing the most effective prevention strategy is conveyed in the classic public health parable attributed to medical sociologist Irving Zola (McKinlay 1975). In this parable, a man was constantly rescuing people who fell into a fast-flowing river and were swept downstream (McKinlay 1975). Although rescuing people who were swept downstream is crucial, similar to the public health duty of responding and assisting in emergencies, this parable concluded with an emphasis on moving "upstream"—addressing the factors that cause people to fall into the river in the first place, a key public health mandate on health promotion and disease prevention. This river story has given rise to the terms "upstream," "midstream," and "downstream" as a way of classifying public health efforts according to the direction and setting of intervention.

Moving "upstream" is acting on the root of the problem. It is finding out why the problem occurred in the first place in order to effectively and sustainably control the downstream consequences of chronic diseases and health inequities. Because upstream interventions target macro-level determinants or the "causes of the causes" (Marmot 2006), the more upstream an intervention is, the larger the number of people benefited, and the more meaningful its impact on population health.

Upstream determinants are the conditions in which people are born, live, work and play that influence health and are collectively referred to as the social determinants of health (World Health Organization 2008; Solar and Irwin 2010). These are the social, economic, political, and environmental structures that shape how money, power, and resources are distributed in society, consequently resulting in health inequities. The impact of these macro-level structural determinants are mediated by "midstream" or intermediary factors at the local and regional levels and include housing, employment, food security, health care system, and even health behavior (Solar and Irwin 2010). Both upstream and midstream causes result in the "downstream" consequences of chronic disease, injury, and disability (Solar and Irwin 2010). Such fallout is made worse by the inequities in access, quality, and delivery of care, particularly among marginalized populations.

15.3 Developmental Origins of Health and Disease (DOHaD)

Important as healthcare is, it is not a major determinant of population health. Four other factors have a far greater influence in shaping population health: genetics, behavior, social, and environmental factors. When broken down into the impact of each of these factors on premature deaths in the U.S. population, healthcare accounts for only 10% of health outcomes, behavior accounts for 40%, genetics at 30%, with both social and environmental factors collectively at 20% (McGinnis et al. 2002). Therefore, the key to impacting population health lies in addressing the nonmedical determinants through practice, research, and policy: behavior and social factors, which together make up 60% of untimely deaths (McGinnis et al. 2002; Schroeder 2007).

Social factors, such as education, socio-economic class, ethnicity, poverty, employment, housing, food security, even the neighborhood where one lives, can adversely impact health. A growing body of research has repeatedly affirmed the characteristic l pattern of early deaths, unhealthy behavior, and chronic diseases among those within the financially-challenged brackets of society (Isaacs and Schroeder 2004; Adler et al. 1993; McDonough et al. 1997; Marmot 2001). Such deleterious impacts of social factors on health can be explained not only by material deprivation, as in the absolute and relative scarcity of resources and opportunities, but also biologically, through the pathophysiological and emotional impact of stress on the body (Marmot 2006; Schroeder 2007).

Although one's genetics predetermine susceptibility to disease, studies have also shown that environmental exposures within and outside the womb can alter the expression of inherited risks. These associations led to the Barker Hypothesis, which is currently referred to as the Developmental Origins of Health and Disease or DOHaD. Originally developed by British epidemiologist Barker (1990), DOHaD posits that events in early life exposures could explain an individual's risk for noncommunicable disease later in life.

In 1993, Barker and colleagues studied the association between the anthropometric measures of newborns (birthweight, birth length, Ponderal Index, head circumference, and placental weight) and deaths later in life from cardiovascular disease in a cohort of 10,100 men and 5,600 women born between 1911 and 1930 from Hertfordshire, England (Barker 1994). Their results showed a significant inverse correlation between small birthweight and the risk of developing and dying from heart disease. This relationship remained significant with weight at one year of age and premature mortality among those younger than 65 in both men and women (Barker 1998). Barker's findings showed that infants who were small at birth, a measure of fetal undernutrition, had the greatest risk for cardiovascular disease and metabolic syndrome as a factor of (1) maternal nutritional status and body composition before, during, and after pregnancy; (2) maternal diet during pregnancy; and (3) postnatal nutrition and growth (Barker 1994, 1998). Two other sets of data from Sheffield and Preston likewise supported the Hertfordshire findings. The Sheffield data showed a

decreasing trend in cardiovascular mortality with increasing head circumference and Ponderal Index (PI) at birth (Barker et al. 1993; Wilson 1999). Similarly, the Preston study, which looked at the risk of hypertension in adult life, showed among the low placental weight group, those with adult hypertension were also more likely to have had a low Ponderal Index, where Ponderal Index serves as a measure of leanness calculated as birth weight/birth length^3 (Wilson 1999; Barker et al. 1992). These and other animal and human population studies have investigated the underlying mechanisms that explain how in utero exposure to a stressful environment leads to programmed outcomes for chronic diseases (Morrison et al. 2018). Such research affirms a prevention approach with an upstream focus on the social, economic, and environmental factors that influence the mother's nutritional status before, during, and after pregnancy and the baby's growth and development within and outside the womb.

Other concepts, such as the Life Course Theory and the Fetal Origins Hypothesis, have been studied in relation to DOHaD. The Life Course Theory, also known as the Life Course Perspective or Life Course Approach, was developed in the 1960s and analyzes the course of an individual's life within structural, social, and cultural contexts. While DOHaD tends to emphasize environmental conditions both before and immediately after birth, the Fetal Origins Hypothesis proposes that the gestational period has significant impacts on the developmental health and wellbeing outcomes for an individual ranging from infancy to adulthood. This hypothesis has been expanded to cover associations between fetal undernutrition and other non-communicable diseases (NCDs) such as metabolic syndrome or syndrome X, type 2 diabetes mellitus, pulmonary disease, abnormal cognitive development, Wilms' tumor, leukemia, breast cancer and prostate cancer (Barker 1994; Wilson 1999).

To date, DOHaD's findings underscore the importance of an individual's circumstances and surrounding environment, particularly during the most vulnerable times of life. It constitutes a paradigm change "impact[ing] psychological, social, economic, ethical and legal sciences" and "forming a basis for prevention policies across the globe" (Rial-Sebbag et al. 2016). The research on DOHaD establishes the basis for how health and disease factors emerge before birth and through life and is increasingly used to understand the building of one's health capital (Rial-Sebbag et al. 2016; Junien et al. 2016). This new understanding on the susceptibility for chronic disease and its development over the life course could redefine how we look at prevention, shifting the discussion towards translational interventions to achieve effective disease prevention. More than ever, this calls for knowledge sharing and collaboration to maximize opportunities for discovery and replication (Prescott et al. 2016).

15.4 Public Health and DOHaD

15.4.1 The Public Health Response to DOHaD

Though the supportive scientific evidence is strong, there is still a current dearth of articles and systematic reviews on public health programs and policies that were specifically influenced by the Developmental Origins hypothesis (Barnes et al. 2016). Further, there is limited evidence that public health practitioners and policymakers are aware of the DOHaD hypothesis. Even more scarce is the evidence demonstrating the influence of DOHaD in legislating bills or in designing public health programs and interventions.

Although researchers have recommended future programs and policies grounded in the DOHaD hypothesis, a scoping review of the literature from January 2016 to June 2018 shows a gap in the application of a DOHaD framework in public health and policy. Nevertheless, public health programs and interventions exist whose underlying principles can be linked to the prenatal origin of the risks for adult-onset NCDs (see Table 15.1). Though not exhaustive, the following examples may form a foundation upon which future public health programs, services, policies and interventions may build.

15.5 Public Health's Role in Developing and Informing Social Policy Based on DOHaD

One of the primary roles of public health is to develop and inform social policy. Throughout history, public health practitioners have regularly and successfully advanced social policy changes by shedding light on various public health concerns and by engaging directly in the policymaking process. For example, the sanitation movement of the mid-nineteenth century resulted in sweeping changes to urban infrastructure, such as implementation of large-scale sewer systems, zoning ordinances separating residential and industrial areas, and other urban planning decisions (Perdue et al. 2003).

DOHaD findings serve as an evidence-based foundation for directing key prevention-based policies primarily at the societal level (Rial-Sebbag et al. 2016). Thus, focusing health promotion efforts on DOHaD and addressing it through public policy could prove crucial. This is particularly true in low- and middle-income countries where the prevalence of NCDs risk destabilizing local economies (Reddy and Mbewu 2016). The "Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa," is an example of an effective policy that utilizes the DOHaD framework (Reddy and Mbewu 2016). This initiative, started in 2003, allows pregnant women and those who are planning to become pregnant should have access to food, multivitamins and antiretroviral therapy to improve women's health before and during pregnancy (Reddy and Mbewu 2016). This serves

Table 15.1 Public health and policy implications of the Developmental Origins of Health and Disease (DOHaD)

Developmental Origins of Health and Disease (DOHaD)	Public health implications	Policy implications
The Manifesto of The International Society for Developmental Origins of Health and Disease (DOHaD) reflects how far the original Barker Hypothesis has gone and it articulates how the translation of the DOHaD research findings could make a significant difference in reducing the risks and the burden of chronic diseases The Society, comprised of scientists from around the world and from various backgrounds, aims to promote research coordination and public health implementation of findings on early developmental exposure and chronic diseases, including the funding, training opportunities, research discussions, and the translation of findings into significant interventions International Society for Developmental Origins of Health and Disease (2015), **The Cape Town Manifesto, November 2015** (Selected paragraphs) "Whether acting through the mother, father or directly on the infant and child, adverse environmental exposures during early development shape the body's responses to later challenges such as unhealthy diets, sedentary lifestyle, inadequate sleep, excess screen time, high levels of stress and exposure to environmental toxicants. These biological responses are exacerbated by the rapid changes in lifestyle occurring between generations with urbanisation and socio-economic progress in low- and middle-income countries, in migrants and displaced populations. Reducing the burden of NCDs across the life course thus requires interventions to promote healthy early development, beginning even before conception, as well as interventions aimed at sustaining health in children, adolescents and adults." "Harmful environments during early development may cause failure to achieve full physical and mental potential, and a loss of human capital. Combined with increased susceptibility to NCDs, this widens inequalities in health and has adverse economic consequences for individuals, families and communities. Moreover, an unhealthy lifestyle in prospective parents, along with NCDs such as diabetes, cardiovascular disease or obesity before conception and in pregnancy, passes greater risk of NCDs to the next generation. This perpetuates cycles of poor health, reduced productivity and shorter life expectancy, trapping populations in a trough of low human capital from which they cannot easily escape."	**Public Health Programs** Designing public health programs that account for the multiple "hits" or biological insults that occur at critical periods throughout the life course with emphasis on appropriate solutions (Winett et al. 2016) Establishing an integrated health system with a multi-sector delivery of health services and a comprehensive approach to disease prevention that addresses the multiple nutritional and environmental stressors to maternal and child health (Barnes et al. 2016; Heindel et al. 2015) Focusing on upstream health by promoting conditions that support healthy environment, lifestyle and behavior (Barnes et al. 2016) Potentially using epigenetic profiling in looking at childhood experiences and the risk for adult-onset NCDs (Barnes et al. 2016)	Supporting health and economic policies directed at improving living conditions by emphasizing the long-term impact of the DOHaD hypothesis, particularly among pregnant women (Reddy and Mbewu 2016) Creating and supporting policies on the education, respect, and autonomy of women and how social, economic, political, historical, and ideological factors affect the health and nutrition of mothers and children (Moore and Davies 2001) Advocating for policy changes based on the DOHaD that emphasize societal-level versus individual-level accountability in addressing health inequalities (Ismaili M'hamdi et al. 2018; Haas and Oi 2018; Hanson and Gluckman 2016) Implementing multidisciplinary and multi-sectoral discussions on prevention by combining the DOHaD and the United Nations' Sustainable Development Goals (Pentecost et al. 2018) Designing global programs and policies to increase awareness of the life course and transgenerational effect of the DOHaD (Heindel et al. 2015) Incorporating a knowledge of ecological health in the education, examination, and clinical training of physicians (Reddy and Mbewu 2016)

(continued)

Table 15.1 (continued)

Developmental Origins of Health and Disease (DOHaD)	Public health implications	Policy implications
	Women's Nutrition Promoting women's and children's health and involving other stakeholders in inclusive life course approaches (Kajee et al. 2018)	Creating policies that will address the advertising of unhealthy foods and increasing the intake of fruits and vegetables (Prescott and Logan 2017)
	Prenatal Nutrition 1. Maternal nutrition programs (Binns et al. 2001); UNICEF's Care Initiative (Moore and Davies 2001) 2. Protein-calorie and micro-nutrient supplementation to pregnant women to reduce insulin resistance and arterial stiffness (Uauy et al. 2011) 3. Prenatal care (Barnes et al. 2016; Binns et al. 2001; Soubry 2018; Paneth 2016)	Providing public health and policy interventions and a Health in All Policies approach to improve the health of pregnant women and children (Barnes et al. 2016; Reddy and Mbewu 2016)
	Intrauterine Nutrition **Postnatal Nutrition and Early Childhood** 1. Child health clinics and growth monitoring to address under- and over-nutrition (Binns et al. 2001) 2. Promoting exclusive breastfeeding in the first six months of life especially in low- and middle-income countries (Binns et al. 2001) 3.Providing protein-calorie supplementation to children under 5 (Uauy et al. 2011)	Investing in family-based interventions and parenting workshops (Barnes et al. 2016) and on formal and informal education that focus on key points of the DOHaD trajectory (Davies et al. 2018)

(continued)

Table 15.1 (continued)

Developmental Origins of Health and Disease (DOHaD)	Public health implications	Policy implications
	Precursor Conditions to Chronic Diseases • Obesity • Insulin Resistance • Metabolic Syndrome Developing a prevention agenda centered on pregnancy and the first two years of life and on increasing physical activity among mothers and children to reduce obesity (Moore and Davies 2001; Uauy et al. 2011) Promoting increased initiation and duration of exclusive breastfeeding (Binns et al. 2001)	Using innovative health messaging directed at children and adolescents (Davies et al. 2018) Changing existing public health policy by targeting risk factors for NCDs by having stricter tobacco control policies (reducing smoking in pregnancy) and a Strategic Plan for NCDs on hypertension, smoking, obesity, sedentary lifestyle, and an unhealthy diet (Reddy and Mbewu 2016)
	Non-communicable Diseases (NCDs) • Type 2 Diabetes Mellitus • Cardiovascular Disease (CVD) • Stroke • Hypertension Continuous monitoring of indicators to determine NCD trajectory (maternal weight before and during pregnancy; stunting and wasting) (Uauy et al. 2011) Introducing public health initiatives directed at indigenous populations such as the "Strong Women, Strong Babies, Strong Culture" among Australian aborigines (Moore and Davies 2001)	Providing social grants for women and children to reduce NCDs in South Africa and other low- and middle-income countries (LMICs) (Reddy and Mbewu 2016) Introducing a tax for sugar-sweetened beverage (South Africa) (Davies et al. 2018)

(continued)

Table 15.1 (continued)

Developmental Origins of Health and Disease (DOHaD)	Public health implications	Policy implications
	Communicable Diseases • HIV/AIDS—public health interventions that focus on both treatment and provision of food to address food insecurity, which could exacerbate the infection, especially among pregnant women, ex: Operational Plan for Comprehensive HIV and AIDS Care Management and Treatment for South Africa (Reddy and Mbewu 2016)	
	Adolescent Health Promote reproductive health programs with emphasis on delaying pregnancy among adolescents (Moore and Davies 2001)	Transforming communities into biodiverse neighborhoods, particularly vacant lots in urban areas, to encourage physical activity, positive neighborhood perceptions, and reduced violence, while promoting access to such communities (Prescott and Logan 2017)

as an example for other countries whose economic situations could be improved if public programs and policies are modeled after the DOHaD hypothesis (Reddy and Mbewu 2016).

DOHaD studies draw attention to the fact that the health of mothers and children are of foremost importance while also emphasizing the need to include fathers and the whole family unit as additional foci of interventions. This is supported by DOHaD research showing that the female and male gametes in the pre- and periconceptual periods of development are both *targets* and *vectors* of epigenetic changes resulting in multigenerational effects (Chavatte-Palmer et al. 2016). Such findings can influence changes in traditional public health programs. For instance, Pentecost and colleagues (2018) called for inclusive interventions that go beyond mothers or pregnant women to involve men and adolescents. Similarly, Prescott and colleagues (2016) emphasized the need for ecological justice that recognizes both support and responsibility to be distributed across individuals, and includes the recognizing that the influence of the father's environment on children's health outcomes and in supporting the health of fathers (Soubry 2018). Such an approach invests in preventive measures to ensure that later life disease and disability is reduced (Haas and Oi 2018). These comprehensive efforts will help overcome the criticism that DOHaD focuses on maternal conditions alone without consideration for the environment of fathers, thus erroneously perpetuating the notion that pregnant women and mothers alone are responsible for the health outcomes of their children.

Because individual experiences and exposures can impact future generations, public health practitioners and policymakers need to consider a life-course approach for multiple windows of interventions over time. For instance, both the UN's Sustainable Development Goals and DOHaD emphasize that "early exposures in life affect not only future health, but that the effects of [such] exposure can be transmitted across generation" (Vaiserman et al. 2017). To implement such a focus on prevention, multi-sectoral and multi-disciplinary discussions are critical in translating science into policy so that health impacts can be felt. Conferences or summits have been used to create awareness about DOHaD and to facilitate collaborations. For instance, the Prenatal Programming and Toxicity (PPTox) Conferences help to create cross-sectoral collaborations that facilitate more in-depth research on the impact of environmental stressors to human health during key phases of development (Heindel 2018). The resulting action from these discussions may help form ongoing collaborations and research for more specific interventions based on DOHaD concepts. It should be evident for policymakers that investing in prevention-focused research, policy, and programs can help reduce the prevalence of NCDs.

Lessons from DOHaD studies prompt public health to take a broader and upstream stance on prevention that addresses root causes—the socio-ecological context in which risk factors exist and are perpetuated that impact not only mothers and children but also fathers and the whole family. This may mean modifying current public health priorities to emphasize family-level 'health, education, and empowerment' (Hanson and Gluckman 2016) throughout the life course.

15.6 Moving Forward: Overcoming the Barriers in Translating DOHaD into Research, Practice and Policy

There are multiple factors hindering action on DOHaD for both public health practitioners and policymakers. First, there is little evidence to suggest sufficient awareness of the DOHaD framework among typical public health practitioners and policymakers. While the core concepts of DOHaD resonate with public health's focus on health promotion and disease prevention, few public health practitioners are familiar with DOHaD as the unifying framework for these concepts. For example, public health practice has long focused on primary prevention strategies—interventions directed at individual-level risk factors to prevent disease occurrence such as behavioral interventions to reduce cardiovascular disease. A current call to action invites public health to direct its strategies further upstream—at the societal-level health determinants that result in health disparities especially among at-risk populations. Upstream approaches include examining for lead in drinking water sources or in old housing, both of which disproportionately affect those in the lower socio-economic bracket. Such action can reduce the unethical and preventable cognitive impairment in children. These public health prevention strategies are supported scientifically by a DOHaD framework. However, awareness for DOHaD is clearly lacking among public health practitioners, thus limiting its utilization within a discipline that aims to improve population health.

Second, it is challenging to translate the results of animal-based DOHaD studies into meaningful changes in public health practice and policy. While such baseline research is critical to our understanding of the underlying biological processes in DOHaD, there can be a substantial delay in applying the findings at the clinical and population-levels. More cross-sectoral collaboration is necessary to translate the findings from basic biological research to actual community health practice (Winett et al. 2016). Laboratory findings need to be connected to the social and environmental realities of individuals and communities to become actionable for public health practitioners.

Third, for biologic research to have greater impact, there is a critical need to consider societal-level perspectives along with individual lifestyle factors. There is a tendency for researchers to discuss the implications of DOHaD from an individual responsibility level rather than from a societal-level accountability. For example, lifestyle issues such as an individual's stress, nutrition status and other factors are commonly cited as the focus for DOHaD findings, but may not also acknowledge environmental factors such as socio-economic status or access to education as contributory needs. While personal lifestyle factors are important, policymakers need to recognize the important interplay between personal choices and environmental factors (Delpierre et al. 2016). Researchers can help in identifying the policy and social responsibility implications of their studies.

Fourth, parallel research tracks associated with the DOHaD hypothesis are receiving substantial research attention on their own, but little has been done to unify these

research tracks into a more holistic framework. For example, several environmental factors have been implicated in disease burden as part of the DOHaD framework. However, these environmental factors are being investigated independently without consideration of their possible additive or synergistic effects such as under- and over-nutrition (Gluckman et al. 2010); exposure to various environmental chemicals that act as endocrine disruptors (Grandjean et al. 2008); and the impact of prenatal stress on glucocorticoid levels (Entringer et al. 2010; Harris and Seckl 2011). Moreover, there is relatively little coordination in the translation of the epigenetic impact of various environmental factors. This calls for a greater emphasis on developing comprehensive environmental research and public health programs using the DOHaD framework (Heindel et al. 2015).

Fifth, there are substantial challenges in developing a meaningful synthesis of research ideas and findings across parallel research tracks (Winett et al. 2016). The seemingly disparate fields of epigenetics, social determinants of health, and family studies have important implications in creating a comprehensive DOHaD framework, though each has a vastly different research history and lexicon. A few empirical studies have tried to bridge the gap between research tracks. For example, some studies have looked at the social determinants of DNA methylation and telomere length (Notterman and Mitchell 2015). Others have drawn connections between family functioning or family conflict and gene expression level (Ehrlich et al. 2015; Robles et al. 2018). The number of these research studies are relatively few and many of them have been based on animal models. Consequently, additional research studies are needed to further elucidate the biological and social connections in a DOHaD perspective. Longitudinal studies on human subjects would greatly assist public health practitioners to implement a DOHaD framework that affects individuals, families, and communities.

Sixth, multi-disciplinary studies are critical to help validate DOHaD to policymakers (O'Donnell and Meaney 2017). However, researchers must also present actionable policy and public health recommendations. Researchers speak of the policy implications of their DOHaD findings, but few offer ways in which such implications could be feasibly acted upon at the policy level.

Seventh, greater effort is needed to recommend or develop specific interventions that are actionable for public health practitioners. It is not sufficient to merely identify the social and biological determinants of health and disease in early life. This information needs to be taken a step further and developed into an actionable plan to target the most vulnerable populations using targeted disease prevention and health promotion approaches. As research recommendations shift towards interventions and the translational strategies for disease prevention, DOHaD meetings will be needed to foster collaboration and the sharing of information and data (Prescott et al. 2016). Studies that demonstrate measurable improvements in health outcomes from a specific intervention will go a long way in bringing DOHaD to the forefront of public health practice.

Eighth, there is a need for more thoughtfully-coordinated research designs to identify emerging topics that contribute to larger social policy efforts. Topics for DOHaD research that supports social policy considerations include research designs to (1)

initiate the use of a life course analysis for one generation using phenotypic data collected before conception to capture the human life cycle well into the demands of aging (Hanson and Gluckman 2016); (2) reduce the prevalence of mental disorders over a lifespan through interventions and study designs that extend beyond observational research to examine factors such as maternal diet and exercise during pregnancy (Van Lieshout and Krzeczkowski 2016); (3) examine the potential long-term health consequences to offspring of reproductive technology, such as in vitro fertilization, given the sensitivity of the embryo to its environment (Feuer and Rinaudo 2016); and (4) focus on epigenetic research that can inform policies and human practices to improve health and well-being (Dickinson et al. 2016). Ultimately, specialized research techniques and designs should emphasize findings that are replicable and comparable (Hanson and Gluckman 2016; Gage et al. 2016).

Ninth, health promotion interventions should be planned to address a wider range of actors and actions that include not only women, mothers, or pregnant women, but also men and adolescents (Pentecost et al. 2018). A potential public health intervention could use the "first-hit/second-hit framework" to advance an understanding of DOHaD's etiology in program planning efforts (Winett et al. 2016). For instance, Barker's work showed how an initial insult or a "first hit" occurs before birth leading to the epigenetic programming of risk in the fetus. However, multiple varied stressors are further experienced in childhood and during critical developmental periods across the life course. These comprise the "second hits" such as behavioral, environmental, and/or social influences (Winett et al. 2016). This framework offers a systems viewpoint that expands on the range of possible solutions compared to a variable-by-variable approach to a problem (Winett et al. 2016). Such an approach to multi-faceted health problems can identify better starting points for public health interventions, in turn, demonstrating how the timing and effects of multiple insults across the lifespan can shape the trajectory of individual health and the health of future generations.

Finally, DOHaD research needs to be translated into social policies and public health priorities that can positively affect the family and household settings throughout the life course. Three decades of epidemiological research have shown that adverse events in utero can trigger epigenetic alterations leading to an increased predisposition to developing and dying from chronic diseases. The most proximal influence on the mother and her child is the family. Within the family, daily interactions, rituals, and routines become the building blocks of individual behavior and lifestyle, which in turn impact the health of children, adolescents, women, men, and future mothers and fathers. This does not discount the role of community or societal-level influences. Both family and community-levels factors can adversely affect the health of three generations: the mother, the child, and the next generation. Therefore, implementing the DOHaD message from a life course context necessitates the active involvement of the family. Public health programs and interventions can target not only specific periods of prenatal development, but also other periods of exposure to various risks across the life course.

15.7 Conclusions: DOHaD Implications for Social Policy

DOHaD research underscores the importance of an individual's circumstances and surrounding environment, particularly during the most vulnerable times of life. The greatest implications of these findings may very well be aimed at improving social policy. Social policies affect people's well-being. The lack of action on social policy may well be due to the lack of awareness on DOHaD among policymakers. Understanding the etiology of DOHaD and its potential if used during program planning is vital for policies to have long-lasting effects (Winett et al. 2016).

Developing and enacting social policy is often a difficult and drawn-out process. First, policymakers may have a limited understanding of the health concerns in their communities, often requiring substantial educational outreach efforts from public health practitioners. Second, scientific research alone is often not enough to convince policymakers to act on a specific health concern. Results of scientific inquiry must be contextualized to local circumstances to gain the attention of policymakers. For instance, what are the social consequences of a certain scientific finding to the communities within a policymaker's jurisdiction? Making connections between research findings and actual people is essential to move social policies forward that can make significant impacts on population health.

Social responsibility for health will require serious ethical debate and prompt new actions from policymakers to counteract health inequalities (Ismaili M'hamdi et al. 2018). The next step is to develop policies aimed at addressing social and health needs while expanding funding opportunities for prevention efforts. Although existing research is promising, ongoing research must be supported, strengthened, and prioritized to better understand the environmental factors that surround individuals, families, and relational groups (Delpierre et al. 2016). Cross-disciplinary collaborations in public health that focus on actions across the life course will be able to shape the prioritization and delivery of disease prevention and intervention activities that have been born through decades of DOHaD research.

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