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Review

Early-life events. Effects on aging

Eero Kajantie

National Public Health Institute, Helsinki, Finland

ABSTRACT

During the last two decades, a considerable body of evidence has emerged showing that circumstances during the fetal period and childhood may have lifelong programming effects on different body functions with a considerable impact on disease susceptibility. From a medical point of view, these long-term effects are today referred to as the Developmental Origins of Health and Disease (DOHaD) concept. The DOHaD concept may have a fundamental impact on our ideas about when and how to intervene in order to prevent aging-related loss of function and disease. The aim of this review is to provide a synopsis of epidemiological findings relating early-life conditions with key aging-related disorders, including cardiovascular disease, type 2 diabetes, depression, cognitive impairments and osteoporosis. There are several mechanisms that have been suggested as linking early-life events with late-life disease. This review will discuss programming of the hypothalamic-pituitary-adrenal axis function as one of the best characterised examples of such mechanisms.

Key words: Aging, Birth weight, Cardiovascular disease, Cognitive function, Cortisol, Depression, Gestational age, Osteoporosis, Programming, Stress

EARLY LIFE EFFECTS ON ADULT HEALTH

Environmental cues during early-life may have a fundamental impact on the organism's later development, structure, function and lifespan. This phenomenon has been long recognised in many fields of life sciences. It has been interpreted as an evolutionarily advantageous ability to adjust an individual's metabolism and behaviour to environmental conditions that are likely to prevail during the individual's life.[1]

Address for correspondence:
Eero Kajantie, National Public Health Institute,
Mannerheimintie 166, 00300 Helsinki, Finland,
Tel.: +358-9-47448610, Fax: +358-9-47448934,
e-mail: eero.kajantie@helsinki.fi

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Only recently has this idea gained wider acceptance in medical sciences. This was first prompted by a growing number of epidemiological studies, from the late 1980s onwards, that linked the prevalence of various common adult disorders with body size at birth. For example, a large number of studies in different populations[2-14] have shown an association of small body size at birth in subjects born at term with increased risk of adult cardiovascular disease. The evidence is equally clear regarding type 2 diabetes[15-18] and hypertension.[19-24] Other epidemiological studies have suggested an effect of small size at birth on a much wider range of disease, including osteoporosis,[25] spontaneous hypothyroidism,[26] schizophrenia[27] and depression,[28-31] whereas cancer has been associated, with large size at birth.[32,33]

DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

Epidemiological findings together with experimental work in animals produced the concept of programming, a process whereby a stimulus or insult at a sensitive period of development has lasting or lifelong influence.[34] In other words, one genotype may give rise to different phenotypes based on conditions during early development, which is referred to as 'developmental plasticity'.[1] In evolutionary terms, such plasticity during development may be advantageous in adjusting the metabolic needs or behaviour of an individual to environmental conditions that are likely to prevail during the life-course. However, the effects may be harmful, particularly if the environmental forecast is incorrect, for example, if the deficient nutritional conditions adjusted for *in utero* are not sustained during later life.[1,35] From a medical point of view, these long-term effects of early-life conditions are commonly referred to as the Developmental Origins of Health and Disease (DOHaD) concept.[36,37] The DOHaD concept may have a fundamental impact on the prevention of aging-related loss of function and disease. Studying the early-life determinants of adult health and disease has therefore been identified as a key target of research by numerous policy and funding agencies including the US National Institute for Child Health and Development,[38] the National Institute of Aging[39] and the WHO.[40]

The aim of this paper is to summarise epidemiological findings that link markers of early-life conditions with diseases that cause a significant burden to the aging population. In the interest of space, I will focus on cardiovascular disease, type 2 diabetes, cognitive impairment, depression and osteoporosis. For other common disorders such as cancer, the reader is referred to recent reviews.[32,33]

EARLY-LIFE ORIGINS OF SPECIFIC ADULT DISEASES

Cardiovascular disease. Low birth weight has consistently been shown as a risk factor of coronary heart disease[3,5,6,9-14,41] and stroke[4,11,13,42] in tens of studies from different populations in more and less affluent countries. The relationship is not limited to the extremes but is graded and linear, operating across the range of normal birth weights. Although more recent observations have suggested that premature birth is associated at least with risk factors of cardiovascular disease[23,43-46] and possibly rates of stroke,[11,47] most of the population-attributable risk is due to low birth weight in relation to duration of gestation, i.e. diminished fetal growth.[4,5,8,11,20,48] Human and animal studies suggest a number of different mechanisms that link early-life events with cardiovascular disease, but the contribution of each mechanism on a population level and their associations with specific pregnancy conditions remains poorly known. Many of these putative mechanisms operate through known cardiovascular risk factors. The association of lower birth weight with higher blood pressure is modest, approximately 2 mmHg per kilogram birth weight,[19,24] whereas the association with frank hypertension is stronger[49] and has in part been attributed to the number of nephrons[50] or the amount of elastin in blood vessel walls,[51] which are lower in individuals born small, a deficit that is likely to persist into adult life. The association of low birth weight with plasma lipids is also relatively modest: two recent meta-analyses have reported an overall association of approximately 0.04 mmol/l higher total cholesterol per one kg lower birth weight.[52,53] It is, however, of note that birth weight is only a rough indicator of intrauterine conditions. An illustrative example is provided by a study which showed that exposure to the Dutch World War II famine during early gestation was associated with an atherogenic lipid profile despite being unrelated to birth weight.[54]

Type 2 diabetes and impaired glucose tolerance are major risk factors of cardiovascular disease, most studies showing graded, linear associations with lower birth weight or thinness at birth.[15,17,55] However, in some studies an inverse J-shaped association is apparent,[56,57] with rates again increasing at the highest birth weights, perhaps because of genetic or programming effects associated with gestational diabetes. Again, on a population level, most of the association with low birth weight is probably attributable to slow fetal growth in people born at term,[17] although recent observations have also suggested an independent association of preterm birth with impaired glucose regulation.[18,43] Babies who have low birth weight lack muscle,[58] a deficiency that will persist into childhood,

since there is little cell replication in muscle after infancy.[59] Insulin resistance is thought to reflect poor muscular development and the development of a body composition with high fat but low lean mass, which are also associated with low birth weight.[49,60]

Childhood growth, cardiovascular disease and its risk factors. During recent years, it has been recognized that developmental phases predisposing to adult cardiovascular outcomes include not only periods during fetal life but extend into infancy and childhood as well. Growth trajectories may be dissimilar for different outcomes. Data from the Helsinki Birth Cohort Study have shown that the risk for coronary heart disease and type 2 diabetes or impaired glucose tolerance is further increased in 60-to 70-year-olds who are small at birth, thin or short in infancy, but put on weight rapidly between 2 and 11 years of age.[2,55] A similar growth trajectory has been shown to predispose to type 2 diabetes or impaired glucose tolerance in 26-to 32-year-olds in Delhi, India.[61]. People who suffer stroke are also thin or short at 2 years; however, their body mass index (BMI) and height remain at average or below at age eleven.[8] Recent findings also from the Helsinki Birth Cohort suggest that both of these trajectories of growth may lead to hypertension, which is an important risk factor for both coronary heart disease and stroke.[22] A number of mechanisms have been suggested to explain these links. Detailed studies of body composition in adults have shown that gain in weight and body mass index during infancy predict predominantly lean body mass, whereas fat mass is predicted by gain in weight and BMI later during childhood.[62,63] On a more general level, slow growth in height, in particular before the age of 2 years, is a well accepted indicator of childhood socioeconomic adversities, acting through a number of causal pathways that may be associated with increased risk of disease in later life.[64]

However, it would be a risky oversimplification to conclude that rapid growth during infancy is beneficial for all infants.[65] Findings in contemporary cohorts for example have shown associations of a more rapid weight gain in infancy with signs of insulin resistance at 8 years[66] and blood pressure at 22 years.[67] This is further illustrated by a series of randomised trials in infants born preterm, which have shown that the administration of nutrient-enriched formula or rapid weight gain during the first two weeks of life, are associated with cardiovascular risk factors such as increased fasting proinsulin concentration,[68] lower endothelium-dependent flow mediated artery dilatation[69] and higher LDL to HDL cholesterol ratio.[70] While it is difficult to extend these findings to the general population of healthy term infants, randomised trials of early feeding of healthy infants are currently underway[71] and are likely to shed more light on this question.

Of special note is breastfeeding, which is associated with modest but consistent associations with a more favourable lipid profile,[72] lower blood pressure,[73,74] reduced risk of type 2 diabetes[75] and probably reduced risk of obesity[76,77] in later life. Breastfed infants grow more slowly than formula-fed infants, particularly after the age of 3 months.[78]

Depression. An association between lower birth weight and depression, evaluated at the age of 68 years by the self-reported Geriatric Depression Scale and the Geriatric Mental State semi-structured interview conducted by trained research nurses, has been shown among men born in Hertfordshire, England.[29] Data from the Hertfordshire cohort did not include length of gestation, and thus it remains unclear whether this association is attributable to slower intrauterine growth or shorter length of gestation, or both. A role of slow intrauterine growth is argued for by studies in 26-year-old women[30] and in women and men across ages 23, 33 and 42 years,[31] showing that the association between lower birth weight and depressive symptoms, measured by the self-reported Malaise Inventory is present —even though slightly weakened— after adjustment for gestational length. Associations between gestational length and depression were not, however, reported in these studies. A role of shorter gestational age was supported by a recent study in 1,371 members of the Helsinki Birth Cohort, showing an association of shorter gestational age with increased depressive symptoms as assessed by the Beck Depression Inventory (administered twice) and Center for Epidemiological Studies Depression scale.[79] The effect of low birth weight on depressive symptoms showed a threshold effect, being confined to people with a birth weight below 2500 g. These findings suggest that mechanisms linking early environment with late-life susceptibility to depressive

symptoms may include mechanisms leading to shorter duration of gestation as well as those related to slower intrauterine growth.

Cognitive function. People who are taller or have larger heads have better cognitive function. This has been known for more than a century and is observed throughout childhood,[80-84] adolescence[80,81,84] and adulthood[80,81,84,85] and in late life.[86,87] Longitudinal studies have concluded that body size at birth[81,83,88-90] and postnatal growth[81,83,89] have independent roles in predicting intelligence in later childhood or adulthood, although much of the benefit of adult height or head circumference on intelligence can largely be predicted by growth during the first years of life.[80,83] Nutritional influences and recurrent infections during early-life may play a major role in explaining these links.[80]

Tall height and large head circumference protect from cognitive impairments during late life.[86,87,91] It is therefore logical to assume that this protective effect has its origins during early-life. Although few studies have been able to assess this directly, there is circumstantial evidence from a number of studies. Gale et al[87] reported that higher intelligence test scores and slower decline in cognitive function over a 3.5-year period in 66-75-year-olds were predicted by head circumference in adulthood, not at birth. This was interpreted as an effect of early childhood because most of the postnatal head growth occurs during the first few years after birth. Abbott et al[86] showed in the Honolulu-Asia Aging Study that cognitive impairments were more common in 71-93-year-old men who were short; shortness and cognitive impairments were both associated with a range of childhood socio-economic adversities. The role of early-life cognitive function was further supported by the Nun Study, in which low idea density and low grammatical complexity in autobiographies written in early-life predicted low cognitive test scores and neuropathologically confirmed Alzheimer's disease in late life.[92]

Osteoporosis. Peak bone mass, which is attained in young adulthood, accounts for a major proportion of the variation in bone mass later in adult life.[93] More than 60% of peak bone mass is gained during puberty, which is an obvious target period to optimize peak bone mass accrual by interventions such as calcium supplementation or exercise. However, there is a growing body of evidence suggesting that a substantial proportion of peak bone mass is determined in part by growth earlier in life.[94] Epidemiological studies have demonstrated a relationship between body size at birth or in infancy with adult bone mass.[25,94,95] Low birth weight and slow growth in height during childhood are also directly associated with the risk of hip fracture.[96] In addition to pure bone mass accrual, the relationship has been suggested as being mediated through modulation of the set point for basal activity of endocrine systems such as the hypothalamic-pituitary-adrenal (HPA) and GH/IGF-I axes.[94]

HOW THE MEMORY OF EARLY EVENTS IS STORED AND LATER EXPRESSED: PROGRAMMING OF HPA AXIS (HPAA) FUNCTION

Figure 1 summarises current understanding of key mechanisms of programming. However, to what extent each mechanism contributes to the development of each phenotype is poorly understood. Perhaps the most obvious alterations are those in organ size, for example the lower amount of muscle,[58,59] of nephrons[50] or elastin in blood vessel walls[51] in individuals born small, which were discussed above in the context of insulin sensitivity and blood pressure. Early-life effects on immune function and inflammation have also been put forward as potentially important determinants of aging-related changes.[97] Equally well established is the concept of hormonal programming, i.e. permanent alterations in the regulation and the set point of the feedback systems of different hormonal axes.[98] The exact mechanisms by which hormonal alterations persist into adult life is, however, less clear, although there is evidence of changes in DNA methylation caused by early environmental conditions and sustained in adult life.[99]

In experimental animals, various interventions that increase fetal glucocorticoid exposure result in an offspring which is born small and presents in adulthood elevated blood pressure, hyperglycemia, anxiety and increased HPAA activity. However, more detailed studies have shown that the effects vary greatly depending on the time and nature of the stimulus and are associated with complex sets of alterations,

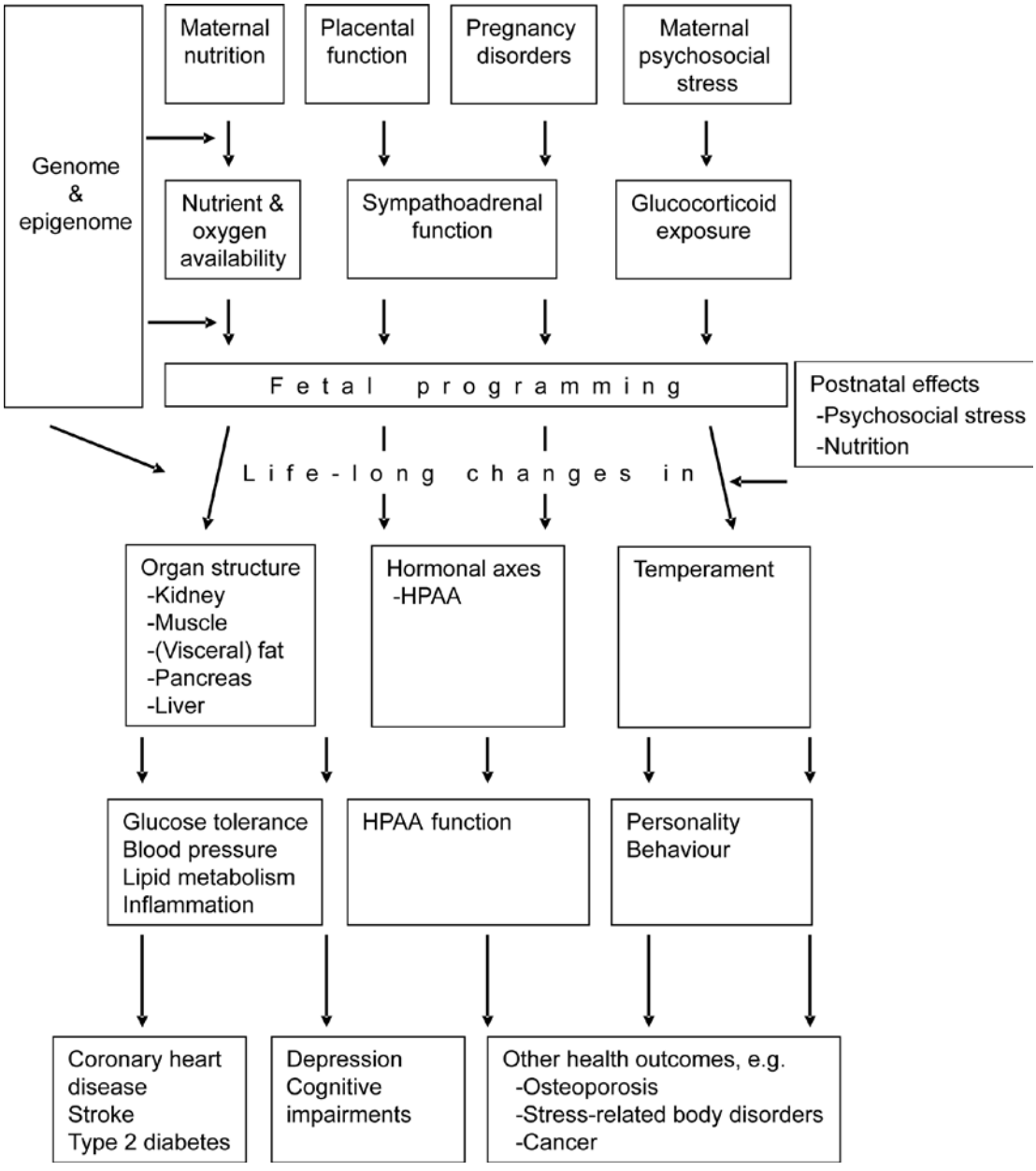

Figure 1. Conceptual model of possible pathways of fetal programming of stress-related adult disease.

among others, in the number of glucocorticoid, mineralocorticoid and corticotrophin-releasing hormone (CRH) receptors in different parts of the brain and in other organs. There are several recent reviews on experimental studies of HPAA programming[100-103] which are not reviewed here in detail.

Programming of the HPAA function by early-life conditions constitutes an illustrative example of how epidemiological observations can provide essential information in linking early-life events with adult health and disease. This is discussed in the following paragraphs, with focus on events during the fetal period and their repercussions in later life.

Early-life factors and HPAA function in later life. Early programming of HPAA has been assessed in a number of human epidemiological studies searching for a relationship of early-life markers such as body size and gestational age at birth with HPAA function

later in life. (For a review of published studies, see ref 98). A number of papers, in particular those on children, have reported that non-stimulated cortisol concentrations in general are unrelated to body size at birth.[104-107] By contrast, studies that have used a biochemical or psychosocial stimulation of the axis have mostly, although not always, shown an association of small size at birth with signs of hyperactive adult HPAA. This association has in turn been related to known cardiovascular risk factors, suggesting HPAA programming as a mechanism linking small size at birth with adult cardiovascular disease.[108-112] It has been stated that venipuncture for morning cortisol measurement, carried out in an unfamiliar clinic, may actually serve as a stress stimulation.[111] Both slow fetal growth and early gestational age are likely to play a role: some studies have shown high morning cortisol concentrations in adults born preterm[113] or, of borderline statistical significance, between higher morning cortisol and lower gestational age across its normal range.[104,111] One study showed that the association between low birth weight and high morning cortisol was confined to people born at a low-normal gestational age[114]. However, some studies have shown counterintuitive associations of low birth weight with low cortisol after a dexamethasone-CRH test,[115] or with low cortisol and ACTH during psychosocial stress.[116] This has been suggested as being a consequence of long-term hyperactivity of the HPAA in susceptible individuals,[116] although to confirm this further studies are needed.

HPAA function, fetal growth and gestational age. It is obvious that low birth weight or short gestational age are a sum of a complex interplay of different mechanisms regulating fetal growth and parturition.[117] Whether they can be used as markers of fetal glucocorticoid exposure is crucial in interpreting the epidemiological findings linking their variation with adult disease or HPAA function. Glucocorticoids are key regulators of fetal growth,[117] and the major regulator of fetal glucocorticoid exposure is the placental enzyme 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2), which converts cortisol to inactive cortisone and maintains fetal cortisol concentrations at several-fold lower levels compared to the maternal ones.[98,101,118] The activity and expression of this enzyme is reduced in intrauterine growth retardation[119,120] and pre-eclampsia[121,122] and some,[123] although not all,[124] observations suggest that its activity varies across the normal range of birth weights. Glucocorticoids have in addition an important role in the initiation of labour. A key regulator of human parturition is CRH, secreted in abundance by the placenta.[125] Glucocorticoids increase placental CRH synthesis.[126] CRH, by stimulating in turn fetal and/or maternal cortisol synthesis, creates a positive feedback loop that again raises CRH concentrations and subsequently leads to delivery.[125] It is therefore plausible that both weight and gestational age at birth serve as useful albeit non-specific indicators of existing individual differences in fetal or maternal glucocorticoid metabolism.

HPAA and adult disease. It has long been appreciated that increased HPAA activity is associated with many cardiovascular risk factors, depression, cognitive impairments and osteoporosis. A classical example is cortisol overproduction in Cushing's syndrome, key symptoms of which include abdominal obesity, impaired glucose tolerance, elevated blood pressure, depression, impaired cognitive function and osteoporosis.[127-130] However, several cross-sectional observations have shown that similar associations occur within the normal variation of HPAA function.[110,111,114,116,131-134] Although there remains a lack of carefully conducted longitudinal studies associating individual variations in HPAA function with subsequent development of disease, early-life programming of HPAA function is one of the best characterised candidate mechanisms to link early-life events with adult disease. It is also obvious that these effects are not limited to the fetal period. The effects of childhood abuse or neglect on adult HPAA function are well documented.[135] Also, normal variation in childhood environment is accompanied by individual differences in HPAA responsiveness to stress,[136] although little is thus far known about how these normal variations are related to HPAA function in adult life.

When interpreting studies in this field, it is important to remember that a hypoactive HPAA is also a key feature of disorders such as posttraumatic stress disorder,[137-139] fibromyalgia[139,140] and chronic fatigue syndrome.[139-141] While there is emerging evidence that susceptibility to these disorders could be programmed during early-life,[98] data so far remain inconclusive.

ASSOCIATIONS OF ADULT HEALTH STATUS WITH SPECIFIC PRENATAL CONDITIONS

Although birth measurements are convenient indicators of fetal environment, their value in indicating specific pregnancy conditions is relatively poor. The programming consequences of specific pregnancy conditions are important to recognise because they might offer different strategies for prevention. This is especially true for the programming of the HPAA, which in animal models can be achieved by various kinds of maternal stress, nutrient restriction and various postnatal conditions. In humans, the data are considerably more sparse.

There are some epidemiological studies that have assessed the effects of maternal undernutrition, most notably the Dutch Hunger Winter study. This study, in which the period of famine was sharply defined, has shown that the effects of undernutrition vary according to the time of the exposure.[142] For example, exposure to famine during the first trimester, while unrelated to birth weight, is associated with an atherogenic lipid profile[54] and increased blood pressure response to psychosocial stress;[143] insulin secretion seems to be most sensitive to exposure during the second trimester,[144] and exposure during the second or third trimester is associated with increased risk of hospital treatment for major affective disorder.[145] However, exposure to famine was not associated with HPAA function, as assessed by 0.25 mg dexamethasone or 1 μg ACTH tests[146] or psychosocial stress test,[147] although the stressor used produced only small cortisol responses.

It is well established that maternal psychosocial stress is associated with shortened duration of gestation[148] and alterations in the child's subsequent behaviour.[103,149] While maternal stress during pregnancy and maternal salivary cortisol concentrations have also been directly associated with salivary cortisol in prepubertal children and adolescents,[150,151] not much is known about the significance of this phenomenon with regard to health during later life. This is an important arena of research because maternal psychosocial stress may be more accessible to prevention than many medical disorders of pregnancy.

Preeclampsia is a disorder which complicates 3-5% of pregnancies and is characterised by maternal hypertension, proteinuria and, frequently, placental dysfunction and fetal growth retardation. Preeclampsia is associated with reduced activity of placental 11β-HSD2.[121,122] It thus seems that preeclampsia constitutes a promising model of fetal glucocorticoid excess, although there are surprisingly few studies assessing its long-term effects on the fetus. In comparing 60 12-year-old children born after a preeclamptic pregnancy with controls matched for sex, gestational age and intrauterine growth restriction, exposure to preeclampsia was associated with higher blood pressure but no difference in cortisol or DHEAS concentrations.[152] However, the careful matching of the controls may have attenuated the differences. Other maternal conditions likely to have specific relevance to HPAA programming include polycystic ovary syndrome[153,154] and associated hyperandrogenemia, chorioamnionitis, which is associated with reduced placental 11β-HSD2 function,[155] and maternal treatment with antenatal glucocorticoids administered to reduce the complications of preterm birth.

FUTURE PROSPECTS

The hypothesised effects of early-life environment on aging-related adult disease may have a fundamental impact on our understanding of these disorders and their prevention. Considerable research effort is however required before specific hypotheses with practical relevance to disease prevention are proved or disproved.

It is often not sufficiently acknowledged that commonly used indicators of early environment, such as birth weight, are a product of a large number of factors during pregnancy. Common pregnancy conditions that may result in low birth weight or short duration of gestation include maternal malnutrition, maternal psychosocial stress, disorders associated with placental insufficiency such as preeclampsia and maternal infection. These and other disorders may be dissimilar with regard to their programming effects on later stress-related disease. Studying the possible programming effects of specific pregnancy conditions will be a crucial step in translating the information into disease prevention.

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