

# Fetal Origins of Stress-Related Adult Disease

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**ABSTRACT:** During the past decade, a considerable body of evidence has emerged showing that circumstances during the fetal period may have lifelong programming effects on different body functions with a considerable impact on disease susceptibility. The purpose of this article is to provide a synopsis of these findings and their role in explaining the development of stress-related adult disease. In the context of Per Björntorp memorial symposium, stress-related disease will be interpreted broadly, including cardiovascular disease and components of the metabolic syndrome, for which the evidence of fetal origins is most abundant. It has however become evident that early-life programming has a much broader potential effect on an individual's health. For example, perinatal variables, such as low birth weight, have been associated with increased prevalence of depressive symptoms. Mechanistic studies in animals and humans have shown that lifelong programming of the hypothalamic-pituitary-adrenal axis (HPAA) function by fetal life conditions is likely to be a key factor in mediating associations with these disorders, which frequently are characterized by HPAA overactivity. Preliminary observations suggest a similar important role for early-life programming of sympathoadrenal function. Reduced HPAA activity is characteristic of a number of stress-related disorders, including posttraumatic stress disorder; chronic pain; fatigue; and atypical, melancholic depression. It is therefore highly plausible that susceptibility to these disorders originates in a similar manner during early life, although direct evidence is to a great deal lacking. Important targets for future research include distinction between the effects of different pregnancy conditions, such as maternal malnutrition, preeclampsia, and maternal infection, which may have dissimilar late-life consequences. This will be a crucial step when the associations that are currently emerging will be translated into disease prevention.

**KEYWORDS:** programming; pregnancy; birth weight; gestational age; depression; metabolic syndrome; posttraumatic stress disorder; cortisol

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## EPIDEMIOLOGICAL STUDIES LINKING EARLY GROWTH WITH ADULTHOOD DISEASE

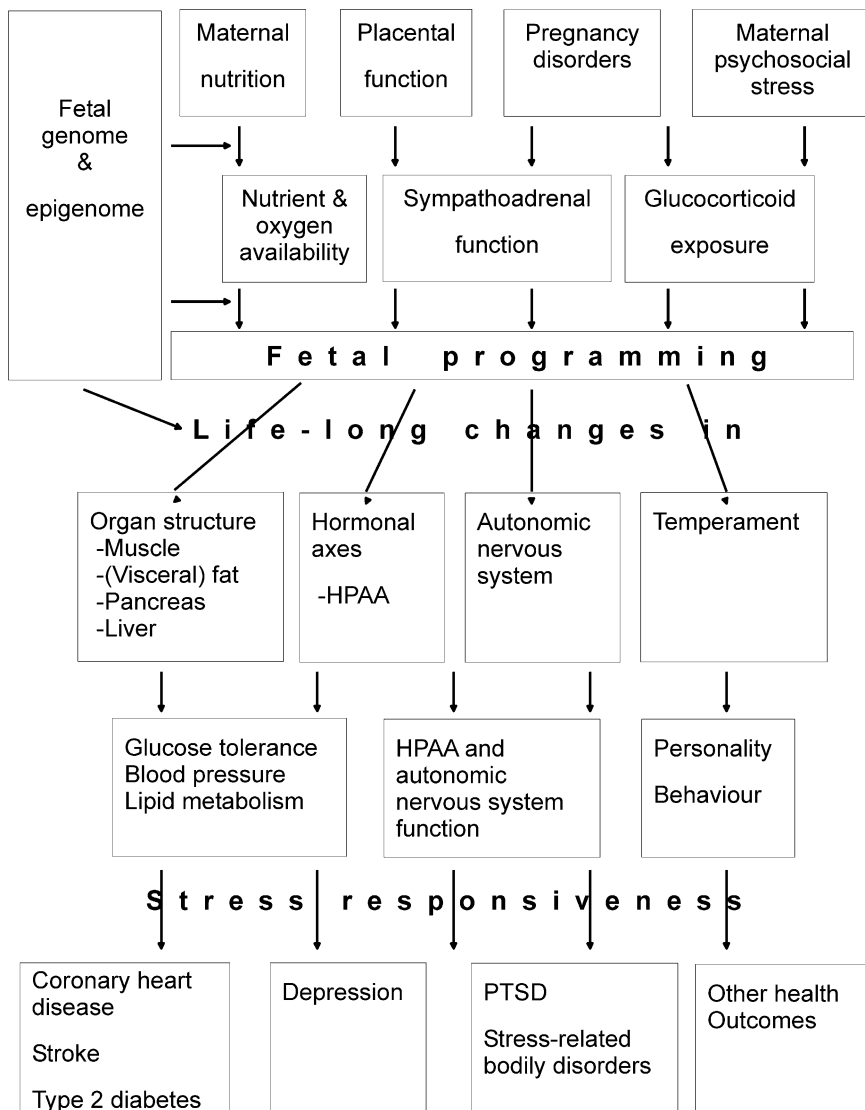
The concept of fetal or developmental origins of health and disease was introduced to the medical community by epidemiological studies that linked the prevalence of different common adult disorders with body size at birth, a rough but convenient indicator of conditions during fetal life. For example, there are over 100 epidemiological studies in different populations<sup>1–10</sup> that have shown an association between small body size at birth in subjects born at term and increased risk of adult cardiovascular disease. The evidence is equally clear regarding type 2 diabetes.<sup>11–13</sup> Other epidemiological studies have suggested an effect on a much wider range of disease, including osteoporosis,<sup>14</sup> schizophrenia,<sup>15</sup> and depression,<sup>16,17</sup> linked with small size at birth, and cancer, usually associated with large size at birth.<sup>18–22</sup>

### THE CONCEPT OF PROGRAMMING

The aforementioned epidemiological findings together with related experimental work have brought up the concept of programming—a process whereby a stimulus or insult, at a sensitive or ‘critical’ period of development, has lasting or lifelong significance.<sup>23,24</sup> In evolutionary terms, such plasticity during development may be advantageous in adjusting the metabolic needs or behavior of an individual for 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.<sup>25</sup>

### MECHANISMS OF PROGRAMMING

Figure 1 summarizes current understanding on 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 amount of nephrons<sup>26</sup> or elastin in blood vessel walls<sup>27</sup> which are lower in individuals born small, a deficit that is believed to persist to adult life and may have a substantial impact on the regulation of blood pressure reactivity. Equally well established is the concept of hormonal programming, that is, permanent alterations in the regulation and the set point of the feedback systems of different hormonal axes. The exact mechanisms how hormonal alterations persist into adult life is however less clear. A recent observation showed nicely how lifelong effects could be set off by DNA methylation. Different licking and grooming behaviors of the mother are a key feature of a well-known rat model, and pups that are more intensely licked and groomed are



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

known to be less fearful in adult life.<sup>28</sup> Pups subject to less licking and grooming were shown to have increased methylation of the glucocorticoid receptor gene promoter in the hippocampus, resulting in decreased transcription factor binding and consequently decreased hypothalamic-pituitary-adrenal axis (HPAA) feedback inhibition. Notably, a causal role of DNA methylation was

supported by that the transcription factor binding was reversed by a histone deacetylase inhibitor, which in addition reversed the HPA axis stress response to the level of rats exposed to high licking grooming.<sup>29</sup>

### **PROGRAMMING OF HPA FUNCTION**

In experimental animals, various interventions that increase fetal glucocorticoid exposure result in offspring that is born small and is in adulthood characterized by elevated blood pressure, hyperglycemia, anxiety and increased HPA activity. However, more detailed studies have shown that the effects vary greatly depending of the time and nature of the stimulus and are associated with complex sets of alterations in the number of, for example, glucocorticoid and CRH receptors in different parts of the brain and other organs. There are several recent reviews on this topic which is not reviewed here in detail.<sup>30-32</sup>

Early programming of HPA has been assessed in a number of human observational studies assessing a relationship of early-life markers such as body size and gestational age at birth with HPA function later in life. These are summarized in Table 1. A number of studies, in particular those performed in children, have measured non-stimulated cortisol concentrations which in general have been unrelated to body size at birth.<sup>34-39,49,52</sup> By contrast, studies that have used a biochemical or psychosocial stimulation of the axis have mostly shown an association between small size at birth and signs of hyperactive adult HPA, which has in turn been related to known cardiovascular risk factors, suggesting HPA programming as a mechanism linking small size at birth with adult cardiovascular disease.<sup>42-48</sup> It has been argued that morning serum cortisol measurement, obtained by venipuncture with subjects attending an unfamiliar clinic in the morning may actually serve as a stress stimulation.<sup>44</sup> However, even in human studies there has been a degree of inconsistency<sup>50,53</sup> suggesting a more complex overall picture, which is discussed in more detail later in this article.

### **PROGRAMMING OF AUTONOMIC NERVOUS SYSTEM FUNCTION**

There is evidence from animal studies that conditions during the fetal period or early childhood, such as nutrition, stress, and temperature, may have persisting effects on sympathoadrenal function.<sup>54</sup> However, only a small number of human studies have assessed the relationship between early-life conditions and the normal variation in indices of autonomic nervous system function. In a study of middle-aged men and women born in Preston, England, low birth weight was found to be associated with higher resting heart rate, a rough indicator of sympathetic activity.<sup>55</sup> In young adult twins, birth weight was associated with sympathetic activity as indicated by cardiac preejection period: lower birth weight was associated with higher baseline sympathetic activity

and higher reactivity to a stressor consisting of reaction time and mental arithmetic tasks. However, in comparisons within twin pairs, the association was seen in same-sex dizygotic but not in monozygotic twin pairs, arguing for a role of genetic factors in explaining the association.<sup>56</sup> This study showed no association between birth weight and respiratory sinus arrhythmia, a commonly used indicator of parasympathetic activity. A sex difference in sympathoadrenal programming was suggested by a study of young adults exposed to a brief psychosocial stressor, which showed an association between low birth weight and higher blood pressure reactivity in females but not in males.<sup>57</sup> As opposite to these findings, a study of 13 young adults born with low birth weight at term showed lower muscle sympathetic nerve activity as compared with controls with normal birth weight.<sup>58</sup>

### **HPAA, AUTONOMIC NERVOUS SYSTEM, DEPRESSION AND THE METABOLIC SYNDROME**

A major risk factor for the development of cardiovascular disease is the cluster of abnormalities referred to as the metabolic syndrome. Although different criteria for the syndrome have been established,<sup>59-61</sup> its defining features include abdominal obesity, insulin resistance, hypertension, and elevated triglyceride, and reduced HDL cholesterol concentrations. The syndrome is increasing in epidemic proportions worldwide with accelerating urbanization, sedentary lifestyle, and increased nutrient intake. Stress is tightly involved in the development and pathophysiology of metabolic syndrome.<sup>62,63</sup>

An important comorbidity of the metabolic syndrome is depression.<sup>64</sup> Because treatment and prevention strategies for depression and the biochemically measurable components of the metabolic syndrome may be dissimilar, it is important to recognize whether there is a direct causal link between the two or whether they share common, perhaps in some other way preventable susceptibility factors. A causal component is supported by longitudinal studies suggesting that the development of the metabolic syndrome<sup>65,66</sup> and carotid arteriosclerosis<sup>67,68</sup> is influenced by depression and related personality characteristics, such as anxiety and hostility.<sup>69</sup>

The idea that depression and the metabolic syndrome share early-life vulnerability factors is supported by findings that, similarly to other components and comorbidities of the metabolic syndrome,<sup>1-13,44-46</sup> the risk of depression is associated with small body size at birth. A study in 68-year-old subjects showed an association between low birth weight and depression in men but not in women,<sup>16</sup> whereas another U.K. study in 26 year olds showed a similar association in women but not in men.<sup>17</sup> In the Dutch Hunger Winter Study, where the period of famine can be sharply defined, exposure to famine during the second or third trimester of fetal life is associated with increased risk of hospital treatment for major affective disorder.<sup>70</sup>

TABLE 1. Studies assessing the relationship of body size and gestational age at birth with indicators of HPAA function later in life

Reference	Number of men + women	Age (years)	Early-life indicator	HPAA measurement	Effect of	
					Low birth weight	Low gestational age
33	31 + 23	8-10	Birth weight	Salivary cortisol before and during a stressor	→	
34	423 + 347	8	Birth weight	Serum fasting cortisol Androstenedione DHEAS	↑ ↑ ↑	
35	Total 1,152	5-14	Birth weight, length, and gestational age	Morning salivary cortisol	→	→ (↑)
36	874 + 894	10-12	Birth weight and gestational age (self-report)	Salivary cortisol at 0700, 0730, and 2000 h	→	→
37	134 + 50	3-15	SGA, short AGA, and normal-height AGA	Serum cortisol seven times during a 24-h period	→	
38	38 + 36	10	Birth weight adjusted for gestational age	Salivary cortisol awakening response 1600 h 2100 h	→ → →	
39	20 + 35	12	SGA (<-2 SD) and AGA	Serum fasting cortisol DHEAS	↑ ↑	
40	23 + 29	22-25	Birth at term, preterm AGA, or preterm SGA	Fasting plasma cortisol 24-h urinary cortisol metabolites	↑ Women ↑ Men →	→ Women ↓ Men →
41	53 + 47	19-21	Birth at term, preterm AGA, or preterm SGA	Serum fasting cortisol		
42	102 + 0	19*	Birth weight and gestational age	Salivary cortisol after TSST	↑	↑
43	4 + 36	39*	Birth weight difference in twins	Serum cortisol at baseline	↑	↑
44	89 + 78 92 + 104 0 + 306 35 + 33	21* 51* 64* 20	Birth weight, length, and gestational age	Serum cortisol after 1 µg ACTH Serum fasting cortisol	↑ ↑ ↑ ↑	→ (↑)
45			Birth weight	Serum cortisol at baseline After 1 µg ACTH	↑ ↑	
46	370 + 0	59-70	Birth weight	Serum fasting cortisol	↑	
47	205 + 0	66-77	Birth weight	Serum cortisol after overnight 0.25 mg DEXA	→	

Continued.

TABLE 1. Continued

Reference	Number of men + women	Age (years)	Early-life indicator	HPAA measurement	Effect of	
					Low birth weight	Low gestational age
48	0 + 106	67-78	Birth weight	After 1 µg ACTH Urinary cortisol metabolites Serum cortisol after overnight 0.25 mg DEXA	↑ U-shaped →	→
49	45 + 38	65-72	Birth weight	After 1 µg ACTH Urinary cortisol metabolites	↑	→
50	157 + 264	65-76	Birth weight, length, and gestational age	Serum cortisol at 20-min intervals for 24 h Serum fasting cortisol and cortisol/CBG ratio	→ ↑↓†	→ ↑↓†
51	0 + 151	68-76	Birth weight, length and gestational age	Serum cortisol after overnight 0.25 mg DEXA	↑↓† →↓†	↑↓† →↓†
52	0 + 151	68-76	Birth weight, length, and gestational age	Serum cortisol after 1 µg ACTH Salivary cortisol awakening response 24-h profile	→	→
53	123 + 0	60-69	High (>3.86 kg) and low (<3.18 kg) birth weight	Serum cortisol and ACTH after 100 µg CRH	→	→
				Same test after overnight 1.5 mg DEXA Salivary cortisol awakening response	↓	→

NOTE: AGA = appropriate for gestational age; DEXA = dexamethasone; SGA = small for gestational age; TSST = Trier Social Stress Test, a psychosocial stressor consisting of a speech and an arithmetic task in front of a committee.

\*Mean.

†In subjects born between 37 and 39 weeks' gestation, low birth weight predicts higher cortisol, whereas in subjects born after 40 weeks of gestation, low birth weight predicts lower cortisol concentration.

‡In subjects born after 40 weeks of gestation, low birth weight predicts lower DEXA-suppressed cortisol; no association in those born before 40 weeks.

It has long been appreciated that both metabolic syndrome and depression are typically associated with increased HPA axis activity. A classical example is cortisol overproduction in Cushing's syndrome, key symptoms of which include abdominal obesity, impaired glucose tolerance, elevated blood pressure and depression.<sup>71</sup> However, several observations have shown that similar associations occur within the normal variation of HPA axis function. The metabolic syndrome or its components, such as elevated blood pressure, reduced insulin sensitivity or serum triglycerides, have been associated with increased serum fasting<sup>44-46,50,72</sup> or ACTH-stimulated<sup>45,47,51</sup> cortisol or 24-h urinary cortisol metabolite secretion.<sup>73</sup> Recent research has also brought up associations of both conditions with alterations in autonomic nervous system function: middle-aged men with the metabolic syndrome have increased 24-h urinary catecholamine output and lower high-frequency component of heart rate variability indicating disturbances in both sympathetic and parasympathetic function.<sup>73</sup> These findings point to the importance of the HPA axis and autonomic nervous system stress responses in mediating the link between early-life events and adult metabolic syndrome and depression.

It is of note that there is a subset of depression patients with atypical, melancholic forms of the disorder that are rather characterized by hypoactivity of the HPA axis, resembling that seen in many stress-related bodily disorders.<sup>74,75</sup> Whether this phenomenon is related to the blunted HPA axis responses that have also been suggested to be a feature of a proportion of patients with the metabolic syndrome<sup>76</sup> is not clear, but these divergent phenotypes are nevertheless important to keep in mind when interpreting the studies in this field.

### **IS THERE EVIDENCE ON EARLY PROGRAMMING OF STRESS-RELATED BODILY DISORDERS?**

Birth measurements or other retrospective data are only rough indicators of fetal environment and thus require large numbers of subjects to be studied. This limits the studies to phenotypes with data readily available from healthcare registers or obtainable by simple clinical examinations or standardized questionnaires. However, for many stress-related disorders such as chronic fatigue, chronic pain, fibromyalgia posttraumatic stress disorder, data from healthcare registers are not available and diagnostic tests or surrogate assessments are more difficult to use in large-scale population studies. Consequently, there is little direct evidence linking these disorders with markers of intrauterine environment, such as size at birth. However, there is emerging evidence that the proposed endocrine mechanisms of stress-related bodily disorders, in particular hypocortisolism,<sup>77</sup> are related to conditions during fetal life.<sup>50,51,53</sup> Moreover, it is widely acknowledged that events during early childhood have long-lasting effects on susceptibility to posttraumatic stress disorder, which is also characterized by hypocortisolism.<sup>78</sup>

## IS HYPOCORTISOLISM PROGRAMMED *IN UTERO*?

We have studied a cohort of 421 men and women born at term in Helsinki, Finland, now aged 65–76 years. Our findings have proposed an explanation for the inconsistencies between previous studies by showing that in subjects born between 37th and 39th weeks' gestation, small size at birth was associated with high adulthood fasting cortisol concentration, consistent with findings in most previous populations, while in subjects born after 40 weeks' gestation the relationship was reversed: individuals born small had low fasting cortisol concentrations.<sup>50</sup> To extend these findings, we studied 151 women from this cohort with more detailed HPA axis tests. With regard to morning cortisol after overnight low-dose (0.25mg) dexamethasone suppression, the finding was similar: lower values in subjects born small after 40 weeks' gestation but no relationship with birth weight in subjects born before.<sup>51</sup> Cortisol after low-dose (1  $\mu$ g) ACTH was unrelated to birth weight or gestational age.

Obviously, our findings need to be replicated before any firm conclusions can be drawn. Is there any conceivable mechanism explaining the gestational age interaction? A key regulator of human parturition is corticotropin-releasing hormone (CRH), secreted in abundance by the placenta. In contrast to their effects in the hypothalamus, glucocorticoids increase placental CRH synthesis. CRH, by stimulating fetal cortisol synthesis, which in turn again increases placental CRH synthesis, creates a positive feedback loop that invariably raises CRH concentrations and subsequently leads to delivery.<sup>79,80</sup> It has become increasingly clear that environmental stressors are related to preterm delivery,<sup>81,82</sup> which is associated with CRH expression in the placental and fetal membranes. Therefore, one might speculate that the group of subjects who were small, short, and of below average gestational age could be the result of premature activation of the maternal/fetal HPA axis and perhaps susceptible to adult hypercortisolism and increased cardiovascular risk. Conversely, the group of subjects born small at above average gestational age, could be hypothesized to be more susceptible to hypocortisolism and its consequences in adulthood. Although this idea has been supported by other findings showing weak relationships between longer duration of gestation and reduced HPA axis activity,<sup>35,41,44</sup> not all findings have been consistent<sup>42</sup> and this hypothesis remains to be confirmed.

## ASSOCIATIONS WITH SPECIFIC PRENATAL CONDITIONS

Although birth measurements are convenient indicators of fetal environment, their value in indicating specific pregnancy conditions is poor. The programming consequences of specific pregnancy conditions are important to recognize because they might offer different strategies for prevention. This is especially true for the programming of the HPA axis, which in animal models can be achieved by a number of different ways of maternal stress, nutrient

restriction, and postnatal conditions. In humans, the data are considerably more sparse.

There are some 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 greatly according to the time of the exposure.<sup>83</sup> For example, exposure to famine during second or third trimester was associated with increased risk of hospital treatment for major affective disorder.<sup>70</sup> Whether this association is related to alterations in HPA function is not known.

It is well established that maternal psychosocial stress is associated with shortened duration of gestation and alterations in offspring behavior.<sup>81,82,84</sup> While maternal stress during pregnancy and maternal salivary cortisol concentrations have also been directly associated with salivary cortisol in prepubertal children,<sup>38,85,86</sup> not much is known about the significance of this phenomenon with regard to health during later life.

Preeclampsia is a disorder, which complicates 3–5% of pregnancies and is characterized by maternal hypertension, proteinuria, and frequently placental dysfunction and fetal growth retardation. Preeclampsia is associated with increased sympathoadrenal function<sup>87</sup> and reduced activity of placental 11 $\beta$ -HSD2,<sup>88</sup> an enzyme that protects the fetus from excess maternal cortisol. It thus seems a promising model of fetal glucocorticoid excess, although there are surprisingly little studies assessing its long-term effects on the fetus. When 60 12-year-old children born from a preeclamptic pregnancy were compared with controls matched for sex, gestational age, and intrauterine growth restriction, exposure to preeclampsia was associated with higher blood pressure and serum adrenalin but no difference in cortisol or DHEAS concentrations.<sup>89</sup> However, the careful matching of the controls may have attenuated the differences. Other pregnancy conditions likely to have specific relevance to stress medicine include chorioamnionitis, which is associated with reduced placental 11 $\beta$ -HSD2 function,<sup>90</sup> and maternal treatment with antenatal glucocorticoids to reduce the complications of preterm birth.

## SEX DIFFERENCES

Being male or female is one of the most important predictors of many stress-related diseases. Cardiovascular disease<sup>91</sup> is more frequent in men than in women of the same age and population group, whereas depression,<sup>92</sup> post-traumatic stress disorder,<sup>93</sup> stress-related bodily complaints, such as fibromyalgia<sup>94</sup> and chronic pain,<sup>95</sup> are more likely to occur in females. Carrying a male fetus implies a greater risk for various pregnancy complications including gestational diabetes.<sup>96</sup> Studies of physiologic response to acute psychosocial stress show clear and consistent differences according to sex and hormonal status.<sup>97</sup> Between puberty and menopause, women usually show lower HPA and autonomic responses than men of same age, although at least HPA responses

are higher in the luteal phase, approaching those of men. After menopause, there is an increase in sympathoadrenal responsiveness, which is attenuated during oral hormone replacement therapy, with most evidence suggesting that HPA activity shows the same trends. There is thus good reason to ask to what extent the sex differences in disease epidemiology actually are a consequence of differences in susceptibility to stress. The question may be important from the fetal origins perspective, because pregnancy seems to be associated with rather specific alterations in stress responsiveness that are not readily explained by accompanying changes in sex steroid concentrations: while the baseline cortisol concentrations and sympathetic nervous activity are increased, the stress response of these systems is attenuated.<sup>97</sup> Animal experiments suggest that this may be an important mechanism in transforming information about the prevailing conditions to allow the developing fetus to adjust its metabolism and behavior for its future environment. Interestingly, these studies show considerable sex differences in the consequences that maternal psychosocial stress, such as crowding has on the offspring. These are typically characterized by masculinization of behavior in females and infantilization of behavior in males.<sup>98</sup> Although the relevance of these findings to human health are not entirely clear, a pragmatic message for researchers is that study designs on the stress-related health field should take into account the effects of sex and hormonal status.

## FUTURE PROSPECTS

The hypothesized effects of fetal environment on stress-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 can be proved or disproved. This includes experimental data on the mechanisms of early programming of hypocortisolism and other associated endocrine features as well as epidemiological data, prospective or retrospective, linking these disorders with markers of early environment.

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 include maternal malnutrition, 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 condition will be a crucial step in translating the information into disease prevention.

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