

# **Early Life Effects on Aging**

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## **Introduction**

It is becoming increasingly apparent that the early environment both before birth and in infancy has profound effects on aging and long-term health. This is due to environmental programming whereby influences acting at critical periods of growth and development can permanently change structure and function with lifelong consequences. Many biological characteristics of the adult can be affected including the maximum size attained, the structure and function of different systems and the response to stimuli [1]. Nutrition is the most widely researched cause of environmental programming but other agents include physical factors such as temperature, light and noise.

## **Early Environment and Long-Term Effects**

Animal evidence to support environmental programming is extensive. Perhaps one of the most dramatic examples is that which occurs in the American alligator where egg incubation temperature has been shown to determine sex [2]. If the eggs are incubated at 30 °C, all the offspring are female. If incubated at 33 °C all the offspring are male. At temperatures between 30 and 33 °C, there are varying proportions of females and males. It is believed that the fundamental sex is female, and a transcription factor is required to divert growth along a male pathway. Instead of being controlled genetically by a sex chromosome, the transcription factor depends on the environment, specifically temperature. Adult vision has been shown to be influenced by early visual experience, for example unilateral deprivation of vision after birth can result in permanently reduced visual acuity in that eye [3]. This phenomenon has been described in man as well as in a number

of animal species. Hearing appears to be vulnerable to noise exposure in utero. For example an increase in the risk of suffering hearing loss at high frequencies has been reported for children whose mothers were exposed to high levels of noise during pregnancy [4] and prolonged noise exposure in pregnant sheep produces lambs with greater histological changes in their cochleae [5]. There is evidence that a number of species undergo a period of heightened susceptibility to noise during development [6] and the timing of the critical period varies according to species. It has been suggested that the critical period coincides best with maturation and innervation of the hair cells in the cochlea [7]. The most extensively researched cause of environmental programming, however, is nutrition and its effects on a number of long-term outcomes are well documented.

### **Nutritional Programming**

Fetal nutrition is the major regulator of fetal growth in late gestation and undernutrition at this stage has the immediate outcome of reduced growth [8]. Size at birth is determined primarily by the maternal uterine environment rather than parental genotype as evidenced by cross breeding and embryo transplant experiments in a variety of species [9] and small size at birth is seen with inadequate fetal nutrition. However there is an indirect relationship between fetal nutrition and maternal nutrition due to the existence of the maternal fetal supply line which includes maternal diet, maternal metabolism and endocrine status, uterine and umbilical blood flows and placental transfer capacity and metabolism. Fetal growth, fetal nutrition and maternal nutrition have all been investigated in relation to adverse long-term sequelae. Temporary undernutrition in early life may be associated not only with immediate reduced growth but also a permanent reduction in size [10]. Historical human population studies have shown that adult height is reduced following limited food availability in early life [11]. Paradoxically, early starvation may also be followed by adult obesity. Men exposed to famine in early gestation during the Dutch Hunger Winter of 1944–1945 became obese adults [12], possibly related to the setting of hypothalamic control of appetite in relation to body size in early gestation [13].

The effect of inadequate prenatal nutrition on the development and growth of different body systems has also been addressed. The endocrine system has been of particular interest as nutritional influences on fetal growth may be mediated by nutritional regulation of fetal endocrine status. The major hormones regulating fetal growth in late gestation are insulin and insulin-like growth factors (IGFs) [14]. In the rat, a low-protein diet during pregnancy reduces the B cell mass and reduces islet cell vascularisation of the offspring [15] with long-term effects on insulin and glucose levels [16]. Nutritional programming of specific organs has been studied. There is evidence

that brain growth and long-term function are affected by feeding in early life [17]. Another study showed improved visual function in children who had been breast rather than bottle fed [18]. Animal work has demonstrated that a prenatal low-protein diet may be followed by alterations in the growth plate of long bones, emphysematous changes in the lung [19], small kidneys [20], raised blood pressure [21] and fewer, less well-differentiated villi in the intestine [22].

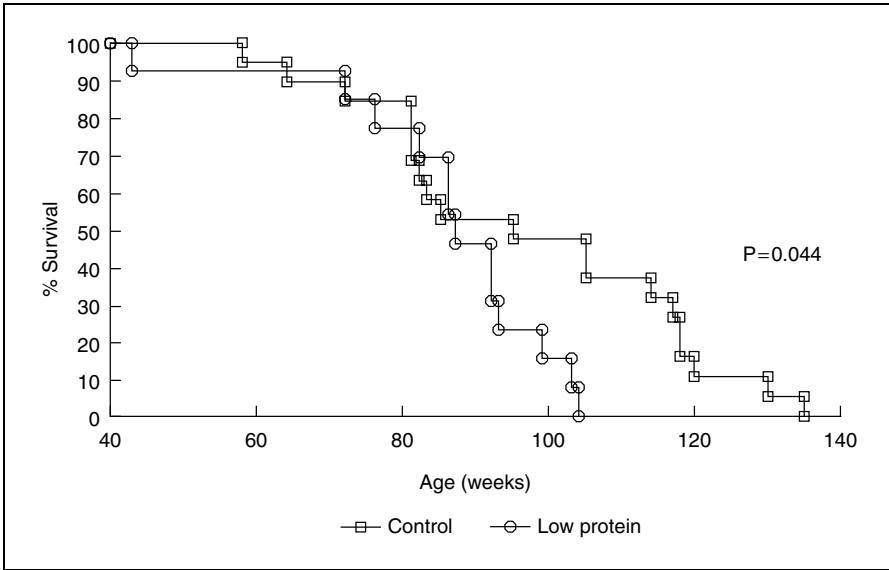
### **Prewaning Diet Restriction and Aging**

It is not in question that aging can be altered by nutritional intervention. The well-documented beneficial effects of postweaning diet restriction on aging include prolongation of lifespan, reduced incidence of a number of age-related diseases, and the attenuation of structural and functional changes associated with age. However the effects of diet restriction prior to weaning, both *in utero* and immediately after birth, have been little studied [23]. The few existing studies suggest that preweaning restriction of diet has an opposite effect. Early work focused on age-related changes. One study showed that maternal diet restriction resulted in progeny with permanent stunting of growth, anaemia and reduced resistance to hypothermia [24] and another demonstrated earlier age-related haemoglobin decline in the offspring [25]. Further research showed that a reduction of nutrition in prenatal and early postnatal life resulted in increased age-associated enzymes in the liver and kidney [26] and it was first proposed in the 1970s that diet restriction in the early stages of life may be associated with accelerated aging [27].

One early study on mice showed that an alteration in diet shortly after birth sufficient to slow growth resulted in reduced lifespan [28]. This finding has recently been explored further. One study investigated the effect of prenatal exposure to a maternal low-protein diet on lifespan in rats [29]. Rat dams were fed either a 180-gram casein/kg control diet or a 90-gram casein/kg low-protein diet from conception until the end of pregnancy. The diets were balanced in energy content through the addition of carbohydrate to the low-protein diet. At delivery all rats were transferred to a non-purified chow diet and following weaning the offspring were maintained on this diet throughout life. The average lifespan of female rats exposed to low-protein diets in utero was reduced by 11% (Fig. 1) [29]. There was a similar but non-significant trend in the male offspring. These findings are consistent with two other recent studies which found that prenatal diet restriction was associated with reduced lifespan [30, 31].

### **Fetal and Infant Origins of Human Aging**

The effects of early dietary restriction on human aging are not known. However, a number of epidemiological studies have shown that markers of



**Fig. 1.** Kaplan-Meier survival curves showing percentage survival of 19 control and 13 low-protein-exposed female rats up to the age of 135 weeks.

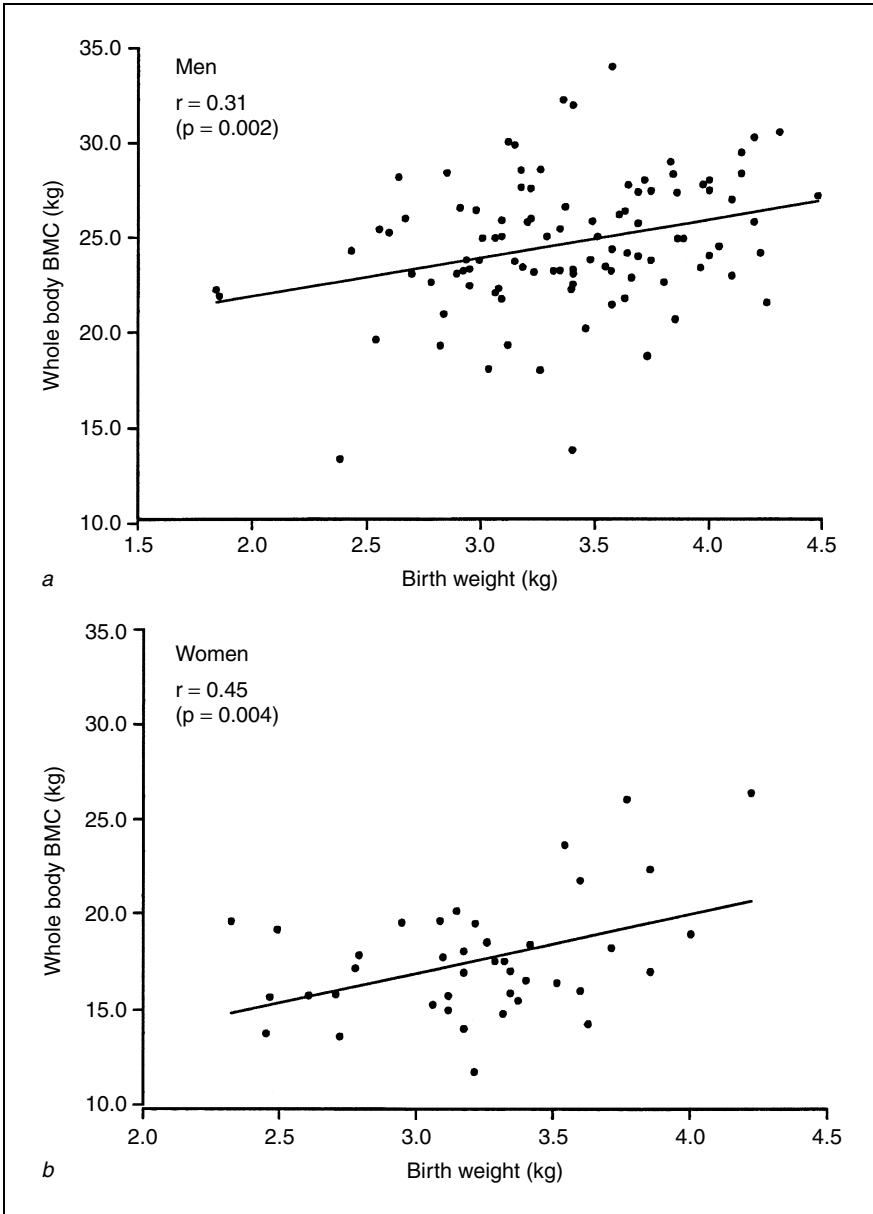
poor fetal growth, including low weight, thinness and shortness at birth, are associated with increased mortality and morbidity from cardiovascular disease and other age-related diseases [32]. These relationships hold true in men and women and are specific. For example, there is no relationship between birth weight and deaths from lung cancer [33]. Correlations have been shown between poor early growth and the major cardiovascular risk factors – raised blood pressure [34], raised plasma fibrinogen [35], and serum cholesterol concentrations [36], impaired glucose tolerance [37] and reduced arterial compliance [38]. Furthermore the people who were small in early life had a shorter lifespan. For example, among 10,000 British men and women, those who had below average birth weight and weighed less than 8.2 kg at 1 year had a 4-year lower life expectancy than those with above average birth weight who reached 12.25 kg at 1 year [33]. These associations have been replicated in several different countries including the United States [39], India [40] and China [41] as well as in Britain. As the major determinant of fetal growth is nutrition [8], the fetal origins hypothesis proposes that fetal undernutrition programs the long-term adverse sequelae of small size at birth. Support for human nutritional programming has come from a study showing that maternal diet in pregnancy influenced blood pressure in the adult offspring 40 years later [42].

Osteoporosis is another important age-related disease that has been associated with poor growth in early life. This is a skeletal disorder characterised by low bone mass and micro-architectural deterioration of bony tissue with a consequent increase in the risk of fracture [43]. The bone mass of an individual in later life depends upon the peak attained during skeletal growth, and the subsequent rate of bone loss. There is evidence to suggest that peak bone mass is inherited, but current genetic markers are able to explain only a small proportion of the variation in individual bone mass or fracture risk [44] and more recent research has demonstrated the importance of environmental influences acting during intrauterine and early postnatal life. One study of a cohort of men and women aged 65–75 years, born and still resident in Sheffield, has demonstrated a significant relationship between birth weight and adult bone mass (Fig. 2) [45]. These findings are consistent with results from two other British cohorts [46, 47] and a recent study showing that hip fracture was related to patterns of childhood growth [48]. Further evidence for the programming of osteoporosis comes from detailed physiological studies exploring the relationship between candidate endocrine systems that may be programmed (growth hormone – IGF-I; hypothalamic-pituitary adrenal, gonadal steroid) and age-related bone loss.

A recent epidemiological study has considered the relationship between poor early growth and aging changes in different body systems [49]. This was carried out in Hertfordshire, UK, where birth and infant records dating back to the early part of the last century were available. 1,428 men and women born between 1920 and 1930 with records of early weight were traced. Of these, 824 agreed to home interview by one of four nurses, and information on medical and social history, including smoking and drinking habits, was obtained. Social class was defined from occupation. After interview, 717 attended a local clinic for measurement of current size, grip strength, skin thickness, eye examination and a hearing test. Statistical analyses were used to quantify the relationship between birth weight, weight at 1 year, and each of the aging measures. Lower weight at 1 year was associated with reduced grip strength, thinner skin, increased lens opacity, and worse hearing (Table 1) [49]. The finding that lower adult grip strength was also associated with reduced birth weight was consistent with a study published this year showing that birth weight was significantly associated with adult muscle mass (Fig. 3) [45].

### **Mechanisms for Nutritional Programming of Aging**

There is growing evidence that aging processes may be associated with nutrition and growth in early life. The mechanisms remain speculative. The aged phenotype may be viewed as the result of intrinsic and extrinsic



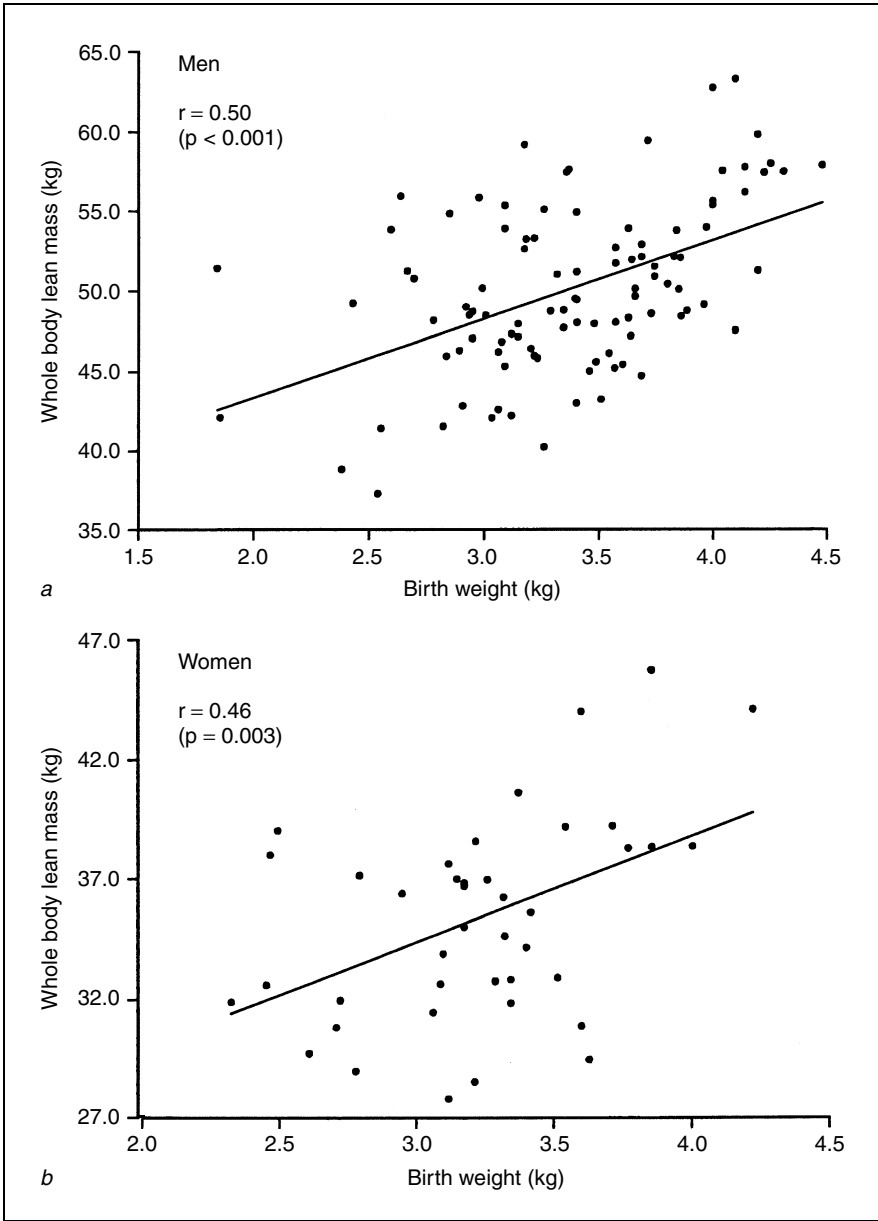
**Fig. 2.** The relationship between birth weight and whole body bone mineral content (BMC).

**Table 1.** The association between early weights and age-related outcomes adjusted for age and sex

Early weight	Mean	Aging	Outcome	
	Lens opacity score (LOCS III) <sup>a</sup>	Hearing threshold, dBA <sup>a</sup>	Grip strength kg	Skin thickness mm
At birth, g [lb]				
≤2,500 [≤5.5]	2.27 ( <i>n</i> = 16)	24.4 ( <i>n</i> = 16)	28.5 ( <i>n</i> = 16)	1.19 ( <i>n</i> = 16)
-2,950 [-6.5]	2.36 ( <i>n</i> = 94)	29.3 ( <i>n</i> = 93)	30.3 ( <i>n</i> = 95)	1.27 ( <i>n</i> = 95)
-3,400 [-7.5]	2.38 ( <i>n</i> = 224)	29.2 ( <i>n</i> = 231)	31.0 ( <i>n</i> = 231)	1.24 ( <i>n</i> = 231)
-3,860 [-8.5]	2.38 ( <i>n</i> = 205)	28.7 ( <i>n</i> = 217)	32.2 ( <i>n</i> = 217)	1.24 ( <i>n</i> = 217)
-4,310 [-9.5]	2.29 ( <i>n</i> = 84)	28.4 ( <i>n</i> = 89)	32.5 ( <i>n</i> = 89)	1.22 ( <i>n</i> = 89)
>4,310 [>9.5]	2.36 ( <i>n</i> = 32)	28.8 ( <i>n</i> = 35)	32.4 ( <i>n</i> = 35)	1.25 ( <i>n</i> = 35)
Multiple regression <sup>b</sup>	<i>p</i> = 0.71	<i>p</i> = 0.97	<i>p</i> = 0.01	<i>p</i> = 0.32
At 1 year, kg [lb]				
≤8.16 [≤18]	2.67 ( <i>n</i> = 26)	33.6 ( <i>n</i> = 26)	29.8 ( <i>n</i> = 26)	1.20 ( <i>n</i> = 26)
-9.07 [-20]	2.40 ( <i>n</i> = 133)	29.4 ( <i>n</i> = 134)	30.7 ( <i>n</i> = 134)	1.22 ( <i>n</i> = 134)
-9.98 [-22]	2.33 ( <i>n</i> = 198)	29.3 ( <i>n</i> = 209)	31.1 ( <i>n</i> = 211)	1.24 ( <i>n</i> = 211)
-10.89 [-24]	2.37 ( <i>n</i> = 187)	29.1 ( <i>n</i> = 194)	31.6 ( <i>n</i> = 194)	1.25 ( <i>n</i> = 194)
-11.79 [-26]	2.33 ( <i>n</i> = 70)	26.5 ( <i>n</i> = 77)	32.6 ( <i>n</i> = 77)	1.25 ( <i>n</i> = 77)
>11.79 [>26]	2.24 ( <i>n</i> = 41)	24.8 ( <i>n</i> = 41)	34.2 ( <i>n</i> = 41)	1.25 ( <i>n</i> = 41)
Multiple regression <sup>b</sup>	<i>p</i> = 0.003	<i>p</i> = 0.008	<i>p</i> = 0.02	<i>p</i> = 0.19
All	2.36 ( <i>n</i> = 655)	28.8 ( <i>n</i> = 681)	31.5 ( <i>n</i> = 683)	1.24 ( <i>n</i> = 683)
Standard deviation	1.21	1.6	10.1	0.18

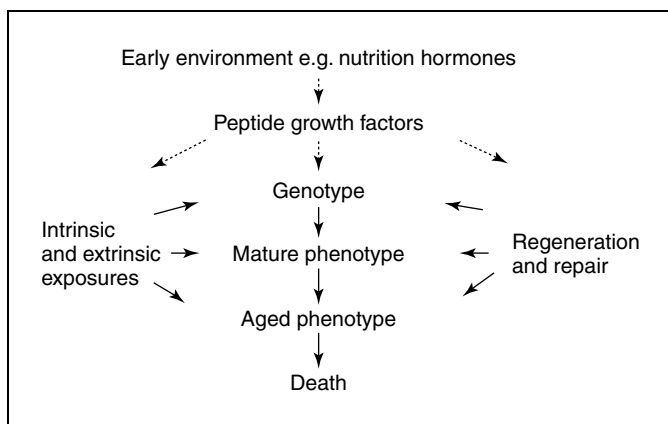
<sup>a</sup> Logarithms used in analysis are therefore geometric means.  
<sup>b</sup> Adjusted for age, sex, current social class, social class at birth and height.

exposures occurring from conception onwards and the corresponding response in terms of regeneration and repair. This has been called the lifelong exposure-response model of aging [50]. It follows that early nutrition may influence aging in a number of ways (Fig. 4) [50]. Early nutrition directly affects growth. This is mediated through endocrine factors released into the circulation and by paracrine peptide growth factors, such as IGFs acting locally. Undernutrition in fetal life may be associated with permanent stunting of growth [24] and can therefore affect aging by setting a lower peak from which age-related decline will occur. Nutrition in early life also affects the setting of a number of hormonal axes and early undernutrition is associated with long-term insulin resistance and higher circulating glucose levels [16]. Both proteins and nucleic acids are modified by reducing sugars in a process called non-enzymatic glycosylation. The extent of the modification is dependent on both the glucose concentration and length of exposure; a higher



**Fig. 3.** The relationship between birth weight and whole body lean mass.





**Fig. 4.** Lifelong exposure-response model of aging illustrating potential mechanisms for the influence of early nutrition on subsequent aging.

glucose concentration and extended exposure lead to the formation of larger amounts of glycosylation end-products. This process is of particular relevance to long-lived molecules and is associated with altered function as well as structure [51]. It has been proposed that such changes are relevant to aging as well as diabetes in causing features such as increased atherosclerosis, cataracts and cross-linkage of collagen.

The ability to respond to deleterious exposures is increasingly being recognised as an important determinant of aging. The responses include repair and replacement of damaged molecules and cells. The disposable soma theory proposes that the avoidance of aging with perfect repair and regeneration processes does not occur because the energy requirements would jeopardise reproduction and therefore not be of evolutionary benefit [52]. There is some evidence that both repair and regeneration are maximal in embryonic and fetal life. At this early stage, these processes are regulated by peptide growth factors, which are widely synthesised and act within the local tissue environment. The IGFs and transforming growth factors are thought to be of prime importance in cellular maintenance [53]. Many cells continue to express growth factors even after differentiation, suggesting that growth factors continue to be involved in cell function in later life. There is some evidence that chronic early undernutrition permanently reduces IGF production [54] and this may be a further mechanism by which prenatal and early postnatal undernutrition have long-term effects on aging.

The programming of repair processes is likely to be most important in systems in which there is little turnover. This may explain the findings

in the Hertfordshire study described earlier where the systems in which aging changes were related to early growth shared the feature of having a high proportion of long-lived molecules and cells. For example, the lens contains crystallins that, once formed are never turned over [55]. They are synthesised in the outer cortex of the lens and gradually move to the centre as new crystallins are formed. The centre of an adult lens therefore contains molecules formed in utero and maintenance processes through life are essential to maintain integrity. The cochlea of the ear contains long-lived collagen molecules and hair cells that, like brain cells, are not replaced [56], and muscle and skin contain large amounts of collagen as well as elastin, which undergo slow turnover. At present, the mechanisms for the nutritional programming of aging remain speculative. However, work is underway to investigate molecular repair mechanisms and their relationship to early growth and nutrition. Markers of DNA repair capacity including telomere length will be measured in a large molecular epidemiological study based in Hertfordshire.

## Conclusions

Animal intervention studies and human observational studies provide growing evidence for the influence of the early environment on aging in later life. This may be explained by environmental programming whereby a stimulus or insult acting at critical periods of growth and development has lasting or lifelong effects. Inadequate nutrition and poor growth in early life are associated with a reduction in lifespan, an increased incidence of a number of age-related diseases and greater structural and functional changes associated with age. The underlying mechanisms remain speculative but may include a permanent reduction in size, resetting of hormonal axes and the impaired development of repair process.

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## Discussion

*Dr. Roberts:* In the epidemiological relations that you showed you used birth weight or weight at 1 year as opposed to BMI or height. How different are the results when you use BMI or height?

*Dr. Aihie Sayer:* The early measures we used in this study were determined by the cohort. They were cohort-specific, depending on what had been recorded historically in a particular group of subjects. The Hertfordshire studies had results for both birth weight and weight at 1 year, so we could look at size in terms of weight, but we could not calculate BMI because we did not have length at birth. There are data sets available that include birth length – for example, in the Preston data we were able to look at BMI at birth and the effects were very similar to birth weight.

*Dr. Roberts:* In your Southampton study you have measured length, I know. But in those cases where weight is used as a surrogate for height or length, one assumes it is a surrogate for fatness as well, but it may not be.

*Dr. Meydani:* Have there been studies that have separated undernutrition from energy restriction in very early life and examined the effects on later outcomes?

*Dr. Aihie Sayer:* As far as I understand it, the literature on preweaning diet restriction in animals is very sketchy. The interventions that have been applied in the postweaning diet restriction model do not exist in the preweaning model.

*Dr. Rosenberg:* I am interested in the effect of early nutritional exposure on later insulin sensitivity and resistance. I know that Yajnick has shown that low birth weight is associated with evidence of insulin resistance even early in life at age 4 or so [1]. Could you comment on how the Southampton group is now looking at the evolution of these effects later in life?

*Dr. Aihie Sayer:* There have been several convincing studies now from different groups looking at the regulation of insulin and glucose metabolism. Small size at birth in humans is certainly associated with impaired glucose tolerance in later life, related to insulin resistance and maybe also to insulin deficiency [2]. That study has been replicated many times. From animal models, there is evidence of changes in the pancreatic islet cells with reduced vascularization, reduced levels of insulin, and correspondingly higher levels of glucose. One could postulate that this might well have effects later in life. If there is permanent resetting of that axis, then exposure to raised levels of glucose, for example, would constitute an increased internal source of damage from glycation products.

*Dr. Burckhardt:* You showed that in certain studies birth weight plays a different role from weight at age 1 year – thus the situation changes. This means that birth weight is one thing and what happens in the first year of life has other implications. Nutrition during the first year is the mother's affair and not the baby's – it is not an *ad libitum* situation. So my question is, do you have any data which show that the birth weight of the baby influences the behavior of the mother? Does the mother of an underweight baby behave differently in giving food to her baby than a mother of a normal weight baby?

*Dr. Aihie Sayer:* That's a good question. You might imagine that that would be the case, and that an underweight baby would get increased feeding during the first year of life. I certainly think that is possible. Though we don't have data on that at present, we will have this information prospectively as part of the Southampton women's survey. It is worth emphasizing that the birth weights I'm talking about fall within the normal range. We are not talking about low birth weight; we are talking about weights which would not of themselves create concern. Also these data are from the early part of the 20th century when very small babies rarely survived. It seems unlikely that there were many surviving neonates at that time who were small enough to change their mothers' behavior dramatically, although we can't test that. The issue about birth weight *versus* weight at 1 year is interesting. We sometimes see an effect with birth weight, sometimes with weight at 1 year, sometimes with both. You are right to emphasize that weight at 1 year is about postnatal nutrition and what the

mother does, but there is also some evidence that weight at 1 year is related to late gestation and to the growth trajectory set up at that stage.

*Dr. Serrano Ríos:* Do you have data on insulin-like growth factor and leptin concentrations in the umbilical vein in low birth weight babies, compared with normal-sized babies? We have data showing that leptin levels in the umbilical vein at birth may be predictive of the future metabolic utilization of substrate. There are also studies from Hoet and his Belgian group showing that organogenesis of the pancreas – not only the endocrine pancreas but the exocrine pancreas as well – is greatly impaired when rats are given a low protein diet during the period of gestation [3]. I would like your comments please.

*Dr. Aihie Sayer:* Hoet has done wonderful work, showing dramatic effects on the pancreas and pancreatic function with a maternal early diet model. Your question about leptin is interesting. Though we haven't got results yet, David Phillips in Southampton is currently looking at leptin levels in a cohort of individuals for whom we have early growth data. You also asked about growth factors. We have looked at insulin-like growth factor levels in relation to birth size and we are now going on to look at adult growth factor levels. The growth hormone axis is difficult to study, as the levels fluctuate and there is a circadian cycle. We are working on how best to allow for these variations.

*Dr. Payette:* With respect to birth weight and weight at 1 year, one way to look at that would be to do a correlation analysis between those variables. Did you do that?

*Dr. Aihie Sayer:* Yes, we have. Birth weight and weight at 1 year are highly correlated – the larger you are at birth, the larger you are at 1 year. You can put both into a regression model and see which one is having the most effect. In the Hertfordshire cohort it was generally weight at 1 year, but in other data sets both had a similar effect in the regression model.

*Dr. Hirsch:* Do you know if there are differences between the babies depending on whether they are breast-fed or bottle-fed?

*Dr. Aihie Sayer:* We do have limited information on whether the babies were breast-fed or bottle-fed, but unfortunately it is not complete enough to allow any conclusions to be drawn. We are in the process of collecting this information prospectively.

*Dr. Rosenberg:* There is a great deal of interest in how much of the variance in later health effects can be predicted by these early life measures. You have a huge amount of data on this from your studies in Southampton and from other studies. Are you prepared to make any judgments about the percentage of the variance relating to cardiovascular disease, high blood pressure, insulin resistance, and so forth, at age 50 and beyond, that might be entrained by these early life effects, either birth weight or weight at 1 year?

*Dr. Aihie Sayer:* If you look at the amount of the variance that is explained by known risk factors, it is small – both with respect to traditional adult risk factors and the early life ones. The size of effect of the early life factors is comparable with that of the traditional factors, but the proportion of the total amount of variance is still small. We need mortality data to work out how much of the absolute risk is accounted for by the early life data. The people who were recorded in the ledgers are dying now – they are in their 70s – and we are collecting the data. We will be able to answer this question much better when we have a larger number of deaths within the group.

*Dr. Roberts:* There are quite major differences in formulas which may be interesting to analyze for long-time effects. For example the Nestlé Carnation formula is marketed as a 'standard' formula, but in terms of its composition it is quite different from what used to be marketed as a traditional formula. So it will be important to look

at the differences within formulas as well as between breast feeding and formula feeding.

*Dr. Aihie Sayer:* I agree. We really don't know what formula milks were being fed in the 1920s. The current prospective study will allow us to compare different types of early formula diets.

*Dr. Endres:* As formulas tend to change every 2 or 3 years it may be difficult to analyze their effects in the long term, though I agree it would be very interesting. One recent paper about long-term outcome that is relevant to this discussion was by Lucas [4], who showed that those infants who had been breast fed for only for 4 weeks had a lower blood pressure in adolescence than formula-fed infants. In the short-term, it is also known that breast feeding appears to lead to better intelligence at 8–9 years of age [5].

*Dr. Serrano Ríos:* Do you have information about individuals who were supposed to have had fetal undernutrition and who continued to be undernourished after birth, in comparison with those who caught up and were no longer considered malnourished? It is very striking how the insulin resistance syndrome, with metabolic changes, is now becoming as prevalent in developing countries as in the developed countries, once you have adjusted for lifestyle changes. Presumably people in developing countries are at higher risk of developing undernutrition during fetal life. So to what extent do you think that postnatal nutritional status can influence the likelihood of these individuals developing cardiovascular disease in adult life? I think this has very important implications in many countries.

*Dr. Aihie Sayer:* Of course, with the human data we haven't got nutritional data in most of the studies. What we have is a proxy with small size, and we haven't got prospective information on size until adulthood. But your point on the developing world is very valid. You are absolutely right – the prevalence of impaired glucose tolerance is shooting up in places like India. There is evidence there of a strong association between small size at birth, presumably related to undernutrition at that stage, and the high rates of impaired glucose tolerance in later life [6]. What the right form of nutrition should be after undernutrition in early life is the six million dollar question. There is evidence that overnutrition later in life has an additive effect to poor nutrition early on, so there is a lot to look at there.

*Dr. Meydani:* There have been some recent studies [7] showing that exposure during fetal life to high cholesterol diets increases the risk of cardiovascular disease, so it seems that nutritional status during fetal development is important, at least as far as cardiovascular disease is concerned.

*Dr. Ferry:* Do you think that a low protein diet during pregnancy, which has consequences for the pancreas, may increase susceptibility to disease in old age? We know that a low protein diet in old people can have dramatic consequences for pancreatic function.

*Dr. Aihie Sayer:* Malnutrition in old age is a major risk factor for pathology in all the systems, so that would fit into the general picture.

*Dr. Arnaud:* I am aware of a study showing that dehydration during pregnancy increases the appetite for salt in the newborn infant [8]. A higher sodium intake may also influence the development of cardiovascular disease, so the link may not only be with nutrition. Dehydration may be important too.

*Dr. Aihie Sayer:* I don't know that study, but it reinforces the fact that maternal diet and nutrition have profound influences and can affect the balance of many things. It is a challenge to determine what the most important factors that cause long-term sequelae are.

*Dr. Taylor:* Cataract incidence in India is increasing. Do you think there is a link with the low birth weight/impaired glucose tolerance problem you outlined earlier?

*Dr. Aihie Sayer:* The prevalence of impaired glucose tolerance is rising steeply in India, and we have shown from several studies in different Indian populations that low birth size is associated with impaired glucose tolerance in early and later adult life. We haven't looked at cataract but you could imagine that high glucose levels, diabetic status, and cataracts are likely to be closely linked.

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