

## Early diet and growth: impact on ageing

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The modification of ageing by nutritional intervention is well recognised. Post-weaning diet restriction is the only widely reproducible method to slow ageing, but the effects of prenatal and preweaning diet restriction have been less well characterised. There is some evidence that diet restriction instituted *in utero* or shortly after birth may have an opposite effect and be associated with increased ageing, and recent work suggests that it may shorten lifespan. Interest in this area has been rekindled by the growing body of epidemiological evidence showing that a number of age-related diseases are associated with poor growth and inadequate nutrition in early life. The relevance of this association to structural and functional ageing changes in different systems is now being considered. Work on musculo-skeletal ageing has demonstrated that loss of muscle strength and bone mass is greater in individuals who did not grow well in early life, and a range of studies suggests that maternal, developmental and nutritional factors are important. The underlying mechanisms remain speculative, and it remains to be determined whether they are system-specific or universal throughout the body. A new cohort of subjects aged between 60 and 70 years is being established to investigate how genetic factors interact with growth and nutritional influences to programme musculo-skeletal ageing in later life.

### Ageing: Musculo-skeletal ageing: Growth: Prenatal diet restriction: Programming

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#### Current concepts in ageing

Ageing is defined in common usage as to grow old or show the effects of the passage of time, and ageing across the species has been well described from the population level down to the consideration of changes at a molecular and

cellular level. Identifying the underlying cause of these changes has proved more problematic, and one review listed over 300 theories of ageing (Medvedev, 1990). However, there is growing support for the disposable soma theory which suggests that ageing has evolved because of the existence of a trade-off for individual species between the rate of reproduction and tissue maintenance and repair (Kirkwood & Austad, 2000). Both factors place large demands on available energy and other biological resources. For higher organisms like mammals, where somatic tissues are distinct from the germ-line, it suggests that the optimal level of investment in maintenance and repair of the soma is one which provides adequate protection against endogenous and exogenous damage, but which is always less than is required for indefinite survival. A high-risk environment is likely to favour fast reproduction at the expense of tissue maintenance; a low-risk environment favours the opposite.

This concept of ageing provides a framework for understanding the processes operating at an individual level. It suggests that the genetic and environmental determinants of both the need for maintenance and repair as well as the corresponding capacity to carry it out are likely to underlie

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the well-documented effects of ageing (Fig. 1). This model may explain the wide variation in rates of ageing that exists between individuals, and the role of environmental factors known to influence ageing, such as nutrition, are now being explored within this context.

### Diet-restriction studies

It has been known for more than 60 years that laboratory rats placed on energy-restricted diets after weaning age slower and live longer than their *ad libitum*-fed counterparts. In fact, diet restriction is the only intervention consistently shown to extend both median and maximal lifespan in mammals. Furthermore, the beneficial effects of lower food consumption have been demonstrated in animals given freedom of dietary choice, where longevity could be predicted entirely on the basis of dietary and growth responses in early post-weaning life (Ross & Lustbader, 1976).

Similar 'anti-ageing' effects of dietary restriction have been observed in insects, worms, protozoans and other lower animals (Weindruch & Walford, 1988), but only recently have studies been set up in non-human primates; three studies are now underway in the USA (Cefalu *et al.* 1999; Roth *et al.* 2000; Hotta *et al.* 2001). Consistent with findings from rodent studies, energy-restricted monkeys are smaller, mature later and appear to be exhibiting slower post-maturational age changes in different physiological and behavioural functions.

A further development in this field is the attempt to determine the mechanisms responsible for the beneficial effects of energy restriction. Leading hypotheses include changes in stress hormones, altered characteristics of glucose utilization, reduced glycation of macromolecules, decreased oxygen radical damage and changes in gene expression. Emerging work suggests that ageing is associated with the selective up-regulation of transcripts involved in inflammation and oxidative stress, and a down-regulation of genes involved in mitochondrial electron transport and oxidative phosphorylation in skeletal muscle from rhesus monkeys (Kayo *et al.* 2001). This observation is consistent with findings from rodent studies (Lee *et al.* 1999), but in contrast with the work in mice, adult-onset energy restriction to date has not been shown to inhibit these changes in middle-aged monkeys, suggesting species-specific effects of energy restriction.

There is limited evidence for the effects of selective energy restriction on ageing in man. Some of the most

detailed data has arisen from the natural experiment of Biosphere 2, a closed self-sustaining ecological space near Tucson, Arizona, USA, containing seven biomes including habitat for human subjects (Walford *et al.* 1999). In 1991, four men and four women were sealed inside for 2 years. During this time the daily intake of energy was less than anticipated due to crop failure. The low-energy nutrient-dense character of the diet resembled in principle that which has been shown to retard ageing in other species. Physiological variables including blood pressure, blood glucose and insulin levels were closely monitored during the 2 years of closure and for 30 months after release. Weight loss in the biosphere was associated with a reduction in blood pressure, glucose and insulin levels which were not sustained after returning to a normal diet. The human physiological responses closely resemble those seen in rodents and monkeys, but identification of effects on human ageing await longer follow up.

### Manipulating the early diet

The effects of early diet restriction on ageing have been little studied in any species (Aihie Sayer & Cooper, 1997). The few existing studies suggest that restriction of diet either *in utero* or immediately after birth and before weaning has an opposite effect to the beneficial effects of later intervention. 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 (Chow & Lee, 1964) and another study demonstrated earlier age-related haemoglobin decline in the offspring (Kahn, 1968). Further research showed that reduction of nutrition in prenatal and early postnatal life resulted in increased age-associated enzymes in the liver and kidney (Roeder, 1973), and produced evidence that early growth retardation by dietary restriction could lead to a permanent reduction in muscle mass (McCance & Widdowson, 1962; Winick & Noble, 1966). This work in the 1960s and 1970s led to the first clear formulation of the idea that diet restriction in the early stages of life may be associated with accelerated ageing (Roeder & Chow, 1972).

One study dating back to 1920 showed that alteration of diet shortly after birth, sufficient to slow growth, resulted in reduced lifespan (Brailsford Robertson & Ray, 1920). Recently, this finding has been explored further. Using a rat model the effect of prenatal exposure to a maternal low-protein diet on the lifespan of the offspring has been investigated (Aihie Sayer *et al.* 2001). Rat dams were fed either a control diet (180 g casein/kg) or a low-protein diet (90 g casein/kg) 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 the female rats exposed to a low-protein diet *in utero* was reduced by 11% ( $P=0.044$ ; Fig. 2). There was a similar but non-significant trend in the males. These findings are consistent with those of two recent studies which found that prenatal diet restriction was associated with a shorter lifespan; telomere

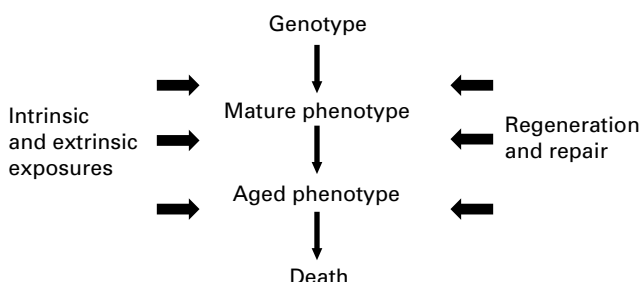
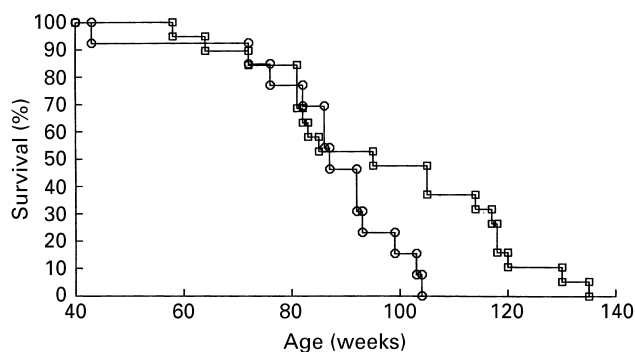


Fig. 1. Life-course model of ageing.



**Fig. 2.** Kaplan-Meier survival curve for female rats. Data represents the percentage survival of nineteen control (180 g casein/kg; □) and thirteen low-protein (90 g casein/kg; ○)-exposed rats up to the age of 135 weeks. The average survival of low-protein-exposed rats was significantly lower than that for controls ( $P=0.044$ ). (Reproduced with permission from Aihie Sayer *et al.* (2001).)

shortening has been postulated as an underlying mechanism (Jennings *et al.* 1999; Vehaskari *et al.* 2001).

#### Fetal and infant origins of age-related disease

The effects of early dietary restriction on human ageing are not known. However, a number of epidemiological studies have shown that markers of 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 (Barker, 1998). 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. Correlations have been shown between poor early growth and the major cardiovascular risk factors, raised blood pressure (Barker *et al.* 1989), impaired glucose tolerance (Hales *et al.* 1991) and reduced arterial compliance (Martyn *et al.* 1995), all factors also associated with increasing age. There is preliminary evidence that individuals who are small in early life have 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 4 years less expectation of life than those with above average birth weight who reached 12.25 kg at 1 year (Osmond *et al.* 1993).

The associations between poor early growth and a number of age-related diseases have been replicated in several different countries, including the USA (Rich-Edwards *et al.* 1997), India (Stein *et al.* 1996), and China (Mi *et al.* 2000), as well as in the UK. The major determinant of fetal growth is nutrition (Gluckman & Harding, 1992), and the fetal origins hypothesis proposes that fetal undernutrition programmes the long-term adverse sequelae of small size at birth. Programming is the term used to describe persisting changes in structure and function caused by environmental influences acting at critical periods during early development (Lucas, 1991). Support for the nutritional programming of human long-term health has come from a study showing that maternal diet in pregnancy

influenced blood pressure in the adult offspring 40 years later (Campbell *et al.* 1996).

#### Programming musculo-skeletal ageing

The relevance of these epidemiological findings to human ageing in different systems has been explored (Aihie Sayer *et al.* 1998). The Hertfordshire Ageing Study involved tracing 1428 men and women born between 1920 and 1930 who had birth records containing their birth weight and weight at 1 year. 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 and markers of ageing in a number of different systems including the eye, ear, skin and muscle. Statistical analyses were used to quantify the relationship between the measures of early weight and each of the ageing measures. Lower weight at 1 year was associated with increased lens opacity, worse hearing, thinner skin and reduced muscle strength. These relationships were independent of adult size and other potential confounding factors (Table 1).

Few studies have looked at the influence of early growth on muscle. A recent study of young children reported that birth weight was associated with increased lean tissue in the upper arm, as assessed by upper arm muscle–bone area, but that fatness in the upper arm was less affected (Hediger *et al.* 1998). A study of 191 men, aged 17–22 years (Kahn *et al.* 2000), reported that thigh muscle–bone area in adulthood was strongly correlated with birth weight, but not with thigh subcutaneous fat area. Further work examined the relationship between birth weight and muscle mass, as estimated by urinary creatinine excretion, among 217 men and women aged 50 years. Adult muscle mass was predicted by low birth weight and small head circumference, but not by thinness at birth (Phillips, 1995). A study of adult body composition in 143 men and women aged 65–75 years, born and still resident in Sheffield, UK, involved assessment using dual X-ray absorptiometry (Gale *et al.* 2001). Neonatal anthropometric information included birth weight, birth length, head size and abdominal circumference. Low birth weight was associated with significantly lower adult lean mass in men ( $P<0.001$ ) and women ( $P=0.003$ ) and about 25% of the variation in whole-body lean mass was explained by birth weight. There was no significant relationship with fat mass, but low birth weight was associated with lower bone mass (Fig. 3). It has been suggested that allocation of cells to different body compartments (muscle, bone and fat) during critical periods of development may be influenced by early growth and nutrition.

Ageing is associated with bone loss and osteoporosis, which is a skeletal disorder characterised by low bone mass and microarchitectural deterioration of bony tissue with a consequent increase in the risk of fracture. These fractures typically occur at the hip, spine and distal forearm. The bone mass of an individual in later life depends on 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

**Table 1.** The association between early weights and age-related outcomes adjusted for age and sex based on the Hertfordshire Ageing Study (Aihie Sayer *et al.* 1998)

Early weight		Mean ageing outcome							
		Lens opacity score		Hearing threshold		Grip strength		Skin thickness	
g	lb	LOCS III*	<i>n</i>	dBA*	<i>n</i>	kg	<i>n</i>	mm	<i>n</i>
At birth									
≤2500	≤5.5	2.27	16	24.4	16	28.5	16	1.19	16
2500–2950	5.5–6.5	2.36	94	29.3	93	30.3	95	1.27	95
2950–3400	6.5–7.5	2.38	224	29.2	231	31.0	231	1.24	231
3400–3860	7.5–8.5	2.38	205	28.7	217	32.2	217	1.24	217
3860–4310	8.5–9.5	2.29	84	28.4	89	32.5	89	1.22	89
>4310	>9.5	2.36	32	28.8	35	32.4	35	1.25	35
Multiple regression†		<i>P</i> =0.71		<i>P</i> =0.97		<i>P</i> =0.01		<i>P</i> =0.32	
At 1 year									
≤8.16	≤18	2.67	26	33.6	26	29.8	26	1.20	26
8.16–9.07	18–20	2.40	133	29.4	134	30.7	134	1.22	134
9.07–9.98	20–22	2.33	198	29.3	209	31.1	211	1.24	211
9.98–10.89	22–24	2.37	187	29.1	194	31.6	194	1.25	194
10.89–11.79	24–26	2.33	70	26.5	77	32.6	77	1.25	77
>11.79	>26	2.24	41	24.8	41	34.2	41	1.25	41
Multiple regression†		<i>P</i> =0.003		<i>P</i> =0.008		<i>P</i> =0.02		<i>P</i> =0.19	
All: Mean		2.36	655	28.8	681	31.5	683	1.24	683
SD		1.21		1.6		10.1		0.18	

\* Logarithms used in analysis, therefore means are geometric means.

† Adjusted for age, sex, current social class, social class at birth and height.

explain only a small proportion of the variation in individual bone mass (Ralston, 1998), and determinants of bone loss are incompletely understood. However, evidence is accumulating that early environmental influences are important and interact with genetic factors to determine bone ageing and osteoporosis in later life.

The first epidemiological evidence that osteoporosis might be programmed came from a study of 153 women born in Bath during 1968–9 who were traced and studied at age 21 years (Cooper *et al.* 1995). Data on childhood growth were obtained from linked birth and school health records. There were statistically significant associations between weight at 1 year and bone mineral content ( $P < 0.01$ ), but not density, at the lumbar spine and femoral neck; these relationships, moreover, were independent of adult weight or BMI. The major determinant of bone density in this study was physical activity during childhood and adolescence. The data therefore suggested a discordance between the processes that govern skeletal growth and those that influence accretion of mineral density. These findings have been replicated in an older cohort of 238 men and 201 women aged 60–75 years (Cooper *et al.* 1997) and these relationships remained after adjustment for known genetic markers of osteoporosis risk, such as polymorphism in the gene for the vitamin D receptor (Keen *et al.* 1997).

Most evidence relating the intrauterine environment to later osteoporosis stems from studies utilizing non-invasive assessment of bone mineral. The clinically important consequence of reduced bone mass is fracture, and data are now available that directly link growth rates in childhood with

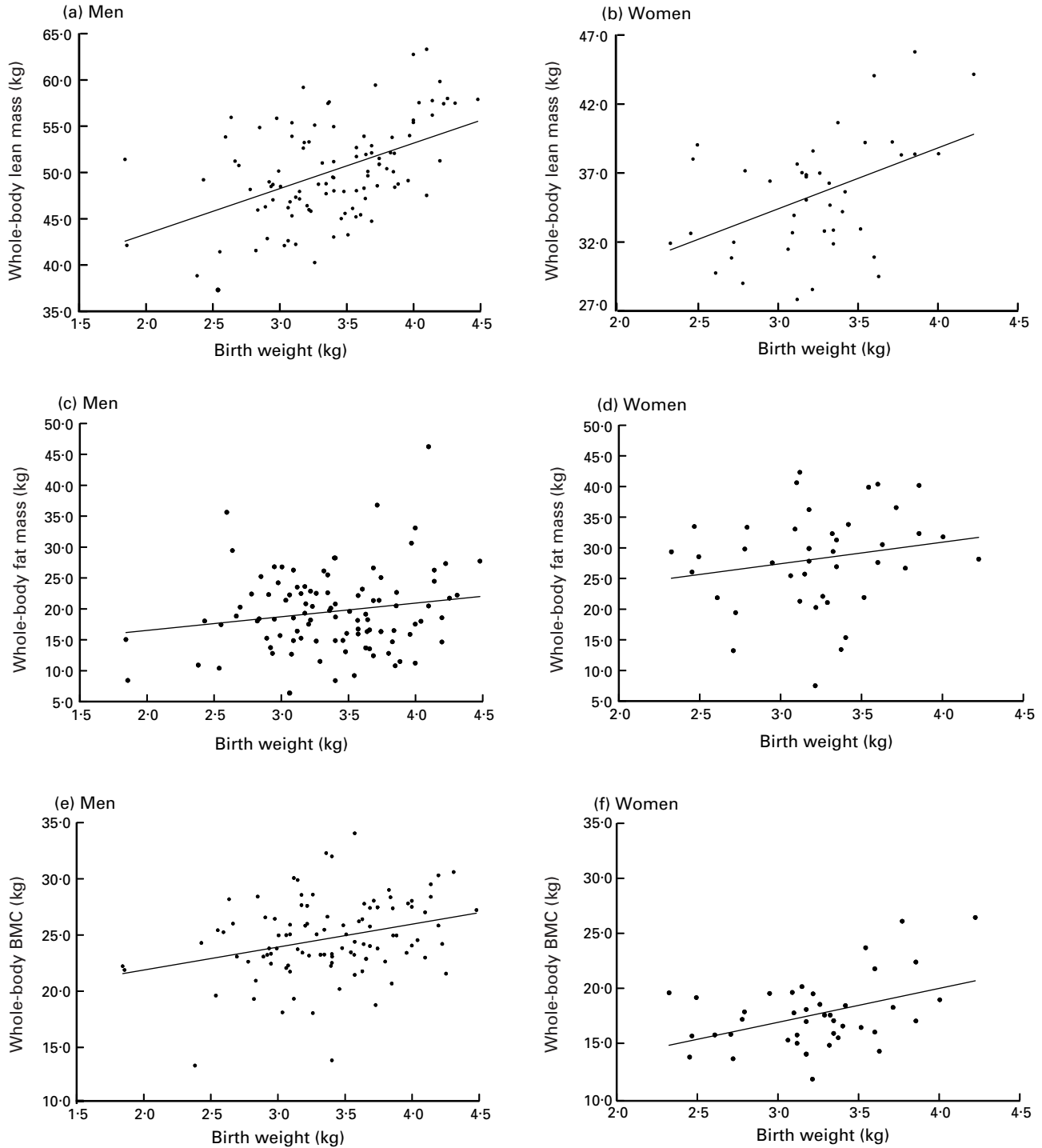
the risk of later hip fracture (Cooper *et al.* 2001). Studies of a unique Finnish cohort in whom birth and childhood growth data were linked to later hospital discharge records for hip fracture have permitted follow-up of about 7000 men and women who were born in Helsinki University Central Hospital during 1924–33. Body size at birth was recorded, and an average of ten measurements were obtained of height and weight throughout childhood. The Finnish hospital discharge registration system was used to assess hip fracture incidence in this cohort. After adjustment for age and sex, there were two main determinants of hip fracture risk, tall maternal height and low rate of childhood growth. In addition, the observation that fracture subjects were shorter at birth, but of average height by age 7 years, suggests that hip fracture risk might be particularly elevated among children in whom growth of the skeletal envelope is forced ahead of the capacity to mineralize.

Further evidence for the programming of osteoporosis comes from a series of detailed physiological studies demonstrating a link between age-related bone loss and endocrine systems that may be influenced by the early environment (growth hormone–insulin-like growth factor I, hypothalamic–pituitary–adrenal and gonadal steroid axes; Cooper *et al.* 2000). A study of newborn babies has shown that the nutrition, body build and lifestyle of pregnant women influence the bone mass of their offspring (Dennison *et al.* 1997). A rat model of maternal protein restriction has been designed to investigate the cellular changes underlying the relationship between early growth and adult bone mass.

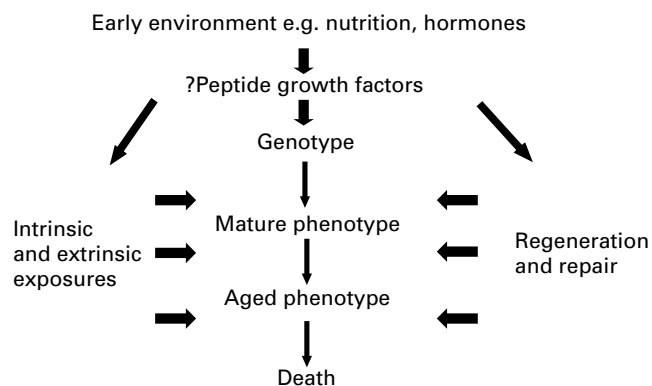
**Future developments**

There is growing evidence that ageing processes are associated with growth and nutrition in early life and this information may be incorporated into the life-course model of ageing (Fig. 4). Early nutritional factors may influence

ageing through effects on growth, but also potentially by altering exposure to deleterious endogenous influences, such as circulating glucose levels, and by programming molecular and cellular repair capacity. These influences would be predicted to be particularly important for systems containing high proportions of long-lived components such



**Fig. 3.** The relationship between birth weight and whole-body lean mass (a,b), fat mass (c,d) and bone mineral content (BMC; e,f) after adjustment for age, in men (a,c,e) and women (b,d,f) born and resident in Sheffield. Correlations with birth weight were: for lean mass 0.50 ( $P < 0.001$ ) for men, 0.46 ( $P = 0.003$ ) for women; for fat mass 0.19 ( $P = 0.06$ ) for men, 0.19 ( $P = 0.242$ ) for women; for BMC 0.31 ( $P = 0.002$ ) for men, 0.45 ( $P = 0.004$ ) for women. (Reproduced with permission from Gale *et al.* (2001).)



**Fig. 4.** Life-course model of ageing and early environmental influences.

as the musculo-skeletal system. The mechanisms remain speculative, but may operate through the resetting of peptide growth factors which are known to mediate the effects of nutritional and hormonal factors on early growth (Owens, 1991), and also may influence repair capacity both *in utero* and longer term (Han & Fowden, 1994). It remains to be determined whether the mechanisms are system-specific or universal throughout the body. Future development of this work will include identification of markers of molecular repair capacity in the musculo-skeletal system. A new cohort of subjects born between 1931 and 1939 is being established to investigate how genetic factors interact with growth and nutritional influences to programme musculo-skeletal ageing in later life.

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