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SYMPOSIUM REVIEW

Developmental aspects of a life course approach to healthy ageing

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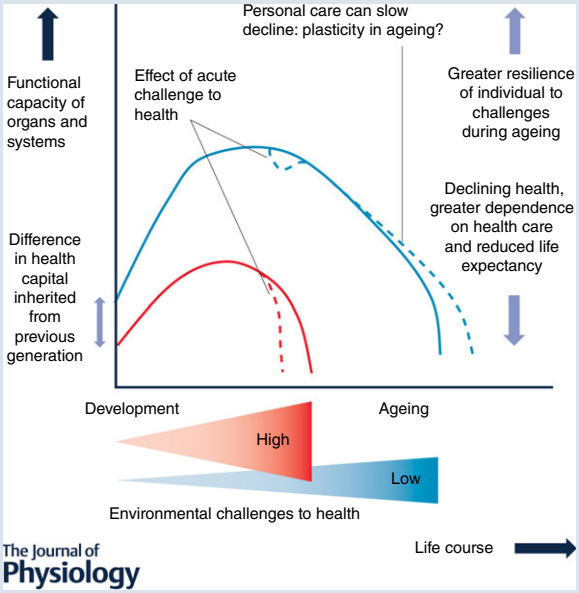

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Abstract We examine the mechanistic basis and wider implications of adopting a developmental perspective on human ageing. Previous models of ageing have concentrated on its genetic basis, or the detrimental effects of accumulated damage, but also have raised issues about whether ageing can be viewed as adaptive itself, or is a consequence of other adaptive processes, for example if maintenance and repair processes in the period up to reproduction are traded off against later decline in function. A life course model places ageing in the context of the attainment of peak capacity for a body system, starting in early development when plasticity permits changes in structure and function induced by a range of environmental stimuli, followed by a period of decline, the rate of which depends on the peak attained as well as the later life conditions. Such path dependency in the rate of ageing may offer new insights into its modification. Focusing on musculoskeletal and cardiovascular function, we discuss this model and the possible underlying mechanisms, including endothelial function, oxidative stress, stem cells and nutritional factors such as vitamin D status. Epigenetic changes induced during developmental plasticity, and immune function may provide a common mechanistic process underlying a life course model of ageing. The life course trajectory differs in high and low resource settings. New insights into the developmental components of the life course model of ageing may lead to the design of biomarkers of later chronic disease risk and to new interventions to promote healthy ageing, with important implications for public health.

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Abstract figure legend The life course model of ageing showing average hypothetical trajectories of functional capacity for organs and systems in individuals from low (red) and high (blue) income settings. Low income settings are associated with a poorer start to life in terms of inherited health capital. Functional capacity develops more slowly in a low income setting, but reaches a lower peak capacity earlier in the life course. Throughout life the environmental challenges to function are likely to be greater in the low income setting, leading to faster and earlier decline. In addition, an acute challenge such as an accident or infection in mid-life may produce a dip in function followed by recovery in a high income setting, but a drastic loss of function in a low income setting (dashed red line). Provision of personal care, most often in high income settings, can slow the rate of decline, sustaining resilience in a manner similar to plasticity (dashed blue line).

Abbreviations CVD, cardiovascular disease; DOHaD, developmental origins of health and disease; FMD, flow-mediated dilatation; NCD, non-communicable disease; NO, nitric oxide.

Introduction

There is increased awareness that the process of human ageing commences as early as conception with the inheritance of a specific genome, and it does not cease until death. Epidemiological studies have demonstrated that environmental influences during intrauterine and early postnatal life are associated with alterations in form and function across a range of systems, which establish predisposition to age-related system decline (Sayer *et al.* 1998). The biological process through which these changes in gene expression are established is known as 'developmental plasticity'. This process is ubiquitous throughout the animal world, and in some plants, and it provides the mechanism whereby a given genotype can develop into a range of phenotypes which are best adapted to the environment that they are likely to meet once development is completed, a concept formalized as a predictive adaptive response (Gluckman & Hanson, 2004). Such adaptive responses are usually thought to operate on Darwinian fitness, i.e. survival to the time of successful reproduction, rather than on ageing *per se*. New concepts challenge this view, and this paper reviews these using musculoskeletal and cardiovascular ageing as examples, and discusses some common underlying mechanisms. It concludes by noting the potential for translational public health strategies to promote healthy ageing by adopting a developmental perspective.

Theories of ageing can be grouped using several criteria. One distinction views ageing as either genetically predetermined ('the biological clock' concept) or as a response to accumulated detrimental but otherwise random events over time (Medvedev, 1990). Another contrasts ageing which evolved as an adaptive process or as a non-adaptive by-product of other processes. These groups are not mutually exclusive. This paper starts from the premise that ageing is one aspect of a life course strategy initiated in early life in each individual as part of a cassette of evolved adaptive responses (Gluckman *et al.* 2007). In this sense, ageing can be considered as a

normal process: this in turn raises the question of whether abnormal ageing can occur. Clearly it can in unusual conditions such as progeria (Gabr *et al.* 1960). However, in the population as a whole there are wide variations in the rate of ageing in terms of declining functional capacity, which may be regarded in part either as normal responses to common challenges or as pathological processes. Distinguishing between these processes may have important consequences for the identification of individuals or groups at risk of accelerated ageing, and for interventions. In this paper we discuss these issues with specific reference to musculoskeletal and cardiovascular disorders, using a life course model of functional capacity.

Models of ageing

Accumulated damage. One model of ageing treats it as the result of a series of random events, and the role of chance in ageing is widely recognized (Bjorksten, 1958). The underlying mechanisms may be conceived in terms of molecular changes such as DNA damage (Varizi *et al.* 1994), or alteration in gene expression associated with errors in transcription (Kirkwood & Austad 2000). Human somatic cells are believed to possess the ability to undergo a finite number of possible mitoses (the Hayflick limit), although this may not be the basis for ageing (Williams, 1957). In cell lines, accumulation of errors in protein transcription (Miller, 1999), and of cross-links in macromolecules, may cause structural and functional changes associated with ageing. A number of theories have focused on the role of exposure to metabolic or waste products, for example reducing sugars or free radicals, as the cause of such deteriorative changes (Rattan, 2008). At a more holistic level, homeostatic systems such as the hypothalamic–pituitary axis or the immune system may play a fundamental role (see below) and a link has been proposed between psychosocial factors such as stress and ageing (Nilsson, 1996).

As proposed by López-Otín and colleagues (López-Otín *et al.* 2013), biomarkers (or hallmarks) of ageing can be grouped into primary (gene and protein stability, telomere length, epigenetic processes), secondary (regulation of nutrient sensing, mitochondrial function, cellular senescence) and integrative (stem cell provision and intercellular communication) mechanisms. The primary markers are believed to represent the underlying causes of ageing, while the secondary markers represent potential compensatory responses. The integrative markers are believed to contribute directly to ageing-related phenotypes of health and disease (López-Otín *et al.* 2013). López-Otín and co-workers provide an elegant model of temporal events, which may contribute either directly or indirectly to physiological disturbances related to ageing. Such temporal events interact at multiple levels of biological organization, which may involve several feed-forward and feedback mechanisms. Disturbances in homeostatic mechanisms which regulate these markers of ageing are likely to play an important role in the development of ageing-related disorders.

Disposable soma. The adaptive pleiotropy or disposable soma theory proposes that some genes expressed in early life up to the time of reproduction promote Darwinian fitness but that they may have detrimental effects in the post-reproductive period (Kirkwood & Austad 2000). Many candidate ageing genes have been proposed but while their individual effects may be small collectively they may be important. In terms of the disposable soma theory, ageing may have evolved as part of the life course of a species because of the necessity for a trade-off between survival to achieve reproduction *versus* somatic processes such as maintenance and repair which place large demands on available energy and other biological resources. The theory suggests that the optimal level of investment in growth, maintenance and repair of the soma provides adequate protection against endogenous and exogenous damage for survival in the short term, but that this is less than that required for prolonged survival in the post-reproductive period. Life course theory suggests that developing in a high-risk environment will accelerate the acquisition of reproductive capacity at the expense of tissue maintenance/repair; a low-risk environment will delay reproductive function. Recently, there have been some excellent examples of this in wild animal populations (Dantzer *et al.* 2013), and some human observations support the concept (Sloboda *et al.* 2007). However, examination of the timing of fertility and mortality across a wide range of species (Jones *et al.* 2014) demonstrates considerable variations in the pattern across the life course, which questions the assumption that the disposable soma strategy has formed a fundamental part of evolution.

Life course perspective. The focus of most previous research on ageing is on influences operating in later life. However, there is considerable unexplained variation in age-related disease between individuals of a similar age and so predictive potential markers of ageing, which may be linked to early life processes, may be helpful (Menni *et al.* 2013). The life course approach to ageing suggests that the rate of decline in function for a particular organ or system is not only dependent on contemporary influences but on the level of peak function attained earlier in life, which in turn depends partly on developmental processes and early environmental influences (Dodds *et al.* 2014) (Abstract figure). The aged phenotype therefore results from intrinsic and extrinsic exposures across the life course and the corresponding response in terms of maintenance, regeneration and repair (López-Otín *et al.* 2013). This life course concept helps to explain the wide variation

in rates of ageing between individuals in a population at any time. The complexity may necessitate a systems biology approach (Kirkwood, 2011). The life course model of ageing (Abstract figure) also indicates that differences in both exposure and response underlie the variation in rates of ageing between systems in the same individual and between individuals, seen for example in high *versus* low resource settings. It also shows how the differences between high and low–middle income countries affect population ageing.

The life course model of ageing is also relevant to clinical practice as it may provide an opportunity to identify individuals at risk of accelerated ageing early in the life course, using early biomarkers of such risk (Martin-Ruiz *et al.* 2011). It also suggests that the window for instituting beneficial interventions should be widened to include early life, when adverse environments may have long-term effects on ageing (Drury *et al.* 2012). Furthermore, knowledge of underlying mechanisms may lead to the development of new interventions to regulate the rate of ageing or to minimize its detrimental effects.

Developmental plasticity

Plasticity is defined as the effect of a challenge to alter the structure or function of a system, often permanently. It should be distinguished from flexibility, in which a structure or function 'bends' when faced with a challenge, to return to its previous state when the challenge ceases, and from resilience, where the challenge is met with an opposing force (Hanson & Gluckman, 2014). Plasticity confers advantage in that it may diminish the effect of a similar challenge later, unlike flexibility, and it is less likely to lead to damage to the system, unlike resilience. There is growing recognition that the rate and manner in which individuals age can be significantly influenced by extrinsic factors at multiple points throughout life (Kuh, 2007). In animals endocrine, nutritional and other influences which affect development during critical periods of early life permanently alter the structure and function of the body's tissues and systems (Bertram & Hanson 2001; McMillen & Robinson, 2005; Gluckman *et al.* 2005). The effects rely on the principle of developmental plasticity, by which one genotype can give rise to a range of different physiological or morphological phenotypes in response to different prevailing environmental conditions during development (Gluckman *et al.* 2009; Bateson & Gluckman, 2011).

Organ systems are most susceptible to such effects during periods in which they are growing rapidly. During the embryonic period (the first 2 months of gestation in the human), progenitor cells undergo extensive differentiation without rapid cell replication. The highest growth rates are observed during the subsequent fetal period, and thus some organs are most susceptible to environmental cues at this point (Gluckman & Hanson, 2004). Relative growth slows in late gestation and continues to slow in childhood. This plasticity is lost later in life when the organism has a relatively fixed functional capacity, although there is a limited capacity for renewal through stem cells in some tissues and it is possible that developmental processes can influence the degree to which stem cell lineages can provide such renewal later on (Obernier *et al.* 2014). Developmental plasticity provides a fitness benefit through the ability to adapt to environmental changes over a relatively short time span, i.e. one generation (Gluckman & Hanson, 2004). In some circumstances, usually following potent disruptive exposures such as environmental chemicals, this benefit can be passed to several subsequent generations without the need for re-exposure to the stimulus (Skinner *et al.* 2010), although this is not necessarily true of milder, nutritional stimuli.

The concept of path dependency permits a trajectory of intrinsic capacity or health capital to be drawn for an individual (Abstract figure). This trajectory will be a composite of that for individual organs and systems, which have different sensitive periods when early life influences the rate of acquisition and the magnitude of the maximal functional capacity attained. The rate of decline in function or in overall health partly depends on the height of this peak, examples being the attainment prenatally and the later decline of renal nephrons and cardiomyocytes, of bone and muscle mass (see Fig. 1) in late adolescence, and of frontal cortical executive functions in early adulthood (Blakemore & Choudhury, 2006). In addition, the settings of some homeostatic control systems influencing metabolism or appetite are partly established in early life (Gahagan, 2012).

The life course trajectory can also be used to show when an individual's health declines to a critical stage of dependence on medical care or, conversely how great their resilience to challenges such as infection or injury will be. It also relates to their likely longevity, and animal studies show that developmental influences such as nutrition in prenatal and early postnatal life can have dramatic effects on lifespan (Jennings *et al.* 1999). This concept can be extrapolated to different socio-economic or resource settings (see Abstract figure) showing not only how potential longevity is influenced but also how resilience is affected. Intervention at early stages in the life course can have a dramatic effect on the entire trajectory, but some plasticity is manifest even in later life.

Evidence supporting a developmental contribution to ageing

Epidemiological studies showing the relationship between small size at birth and an increased risk of age-related disease led to the concept of the developmental origins of health and disease (DOHaD). Forsdahl (1977) showed that

the prevalence of arteriosclerotic heart disease correlated with past infant mortality in Norway and suggested that a poor standard of living in childhood and adolescence was a risk factor for later heart disease. Subsequently Barker (1995) showed that rates of death from coronary heart disease in different parts of England and Wales were correlated with previous rates of infant mortality. This led Barker and colleagues (Barker, 1998) to suggest that adverse environmental influences *in utero* and during infancy permanently change the body's structure, physiology and metabolism, increasing susceptibility to disease in later life.

As noted above, a range of animal studies were undertaken in parallel to investigate the mechanisms of developmental plasticity underlying DOHaD (e.g. Bertram & Hanson, 2001). The most commonly used models involve a prenatal nutrient imbalance induced by a reduction in overall maternal food intake, by protein restriction in an isocaloric diet or feeding a high fat diet (Langley-Evans *et al.* 1996; Brawley *et al.* 2004; Armitage *et al.* 2005). Other models include non-nutritional interventions such as glucocorticoid exposure or placental restriction to impact on early growth and development (Drake *et al.* 2005; Wadley *et al.* 2008). In the rat, maternal dietary restriction resulted in offspring with permanent stunting of growth, anaemia and reduced resistance to hypothermia in later life. Kahn (1968) demonstrated an earlier age-related decline in haemoglobin in the offspring of restricted mothers. Roeder & Chow (1972) suggested that dietary restriction in early life may be followed by accelerated ageing, in contrast with the slowing in ageing seen with this intervention in adulthood. Further work showed that reduced prenatal and early postnatal nutrition led to increased levels of age-associated enzymes in the liver and kidney and to a permanent reduction in muscle mass (Roeder, 1973). Prenatal dietary restriction is associated with shorter lifespan in female rats (Sayer *et al.* 2001), possibly via increased telomere shortening (Jennings *et al.* 1999). Effects on longevity were confirmed in a mouse model where dams were fed either a control or a low protein diet from conception until the end of pregnancy (Ozanne & Hales, 2005). The average lifespan of the female offspring exposed to a low-protein diet *in utero* was reduced, especially if they showed catch-up growth postnatally (as suggested by the 'mismatch' model: Gluckman & Hanson, 2006).

The relevance of these findings to humans in terms of structural and functional ageing in different body systems

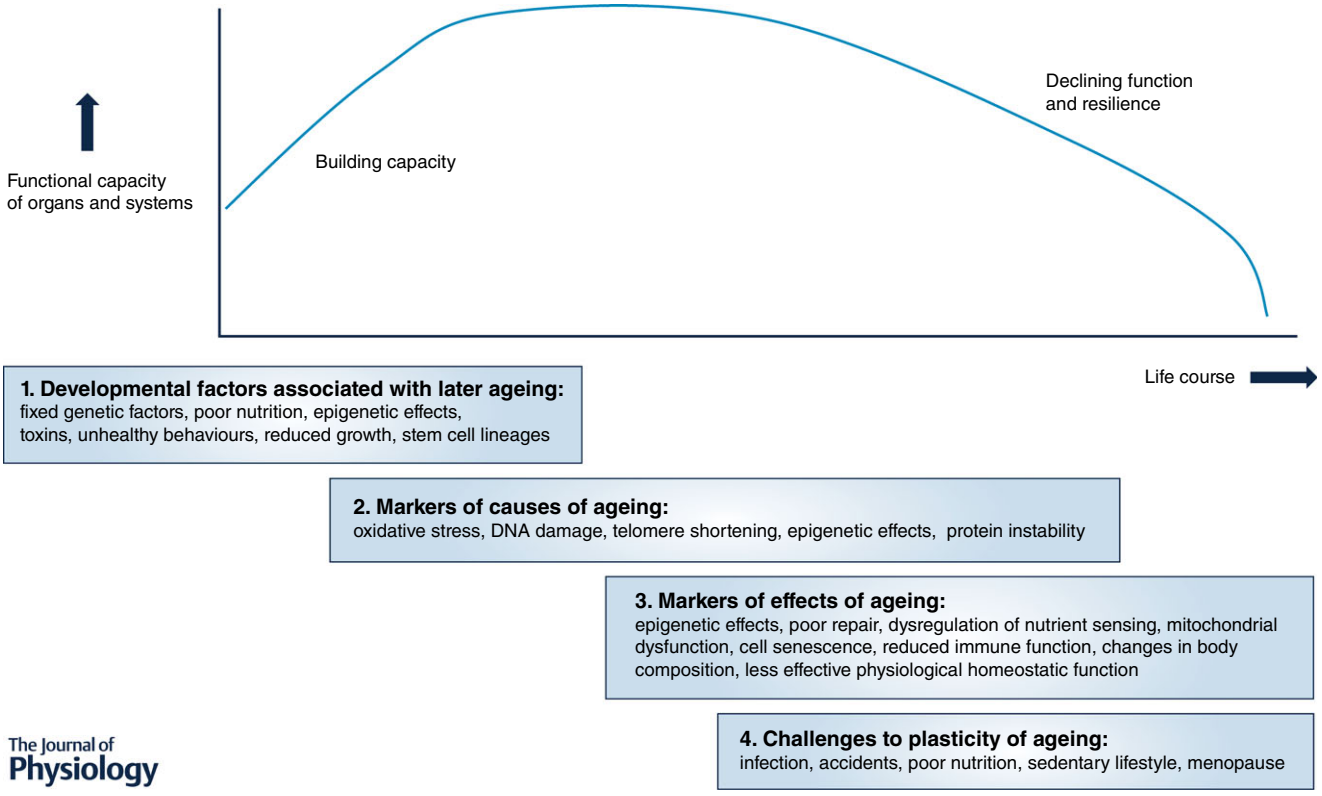

Figure 1. Factors acting across the life course
(1) Developmental factors which are associated with later ageing. (2) Markers of the causes of ageing. (3) Markers of the effects of ageing. (4) Factors which challenge the plasticity of ageing. Some of these factors give insights into underlying mechanisms and some may serve as useful biomarkers of risk or biological age.

was explored in the Hertfordshire, UK, ageing study (Sayer *et al.* 1998). For men and women born in Hertfordshire between 1920 and 1930, and for whom archived birth records documented weight at birth and at 1 year of age, markers of ageing in the eye, ear, skin and muscle were measured. Low birth weight was associated with reduced bone mass and muscle strength, but poor infant growth with a greater range of markers of ageing, including increased lens opacity, worse hearing, thinner skin, and reduced muscle strength.

Cardiovascular and metabolic disease

Ageing is an independent risk factor for cardiovascular diseases (CVD) including atherosclerosis, coronary heart disease, hypertension and stroke. The life course approach to ageing is supported by the trajectory of blood pressure with age (Wills *et al.* 2011). Age-related changes in the functional phenotype of both large and small arteries and in the microvasculature are thought to occur in the absence of conventional risk factors and to accelerate the development of CVD (Donato *et al.* 2015). Support for a developmental contribution to increased risk of CVD came originally from epidemiological studies that demonstrated an association between low birth weight and markers of adult cardio-metabolic disease, including hypertension, coronary heart disease and stroke, insulin resistance and type 2 diabetes (Barker, 1998). The relationship is not limited to the extremes but is graded and linear, operating across the range of normal birth weights (Hanson & Gluckman, 2014), and growth in infancy and childhood also affects long-term cardiovascular health (Eriksson *et al.* 2001). Although the association between low birth weight and higher adult blood pressure is only about 2 mmHg (kg birth weight)$^{-1}$, the association with clinical hypertension is stronger, and this has been attributed in part to the reduced number of nephrons or the amount of elastin formed by vascular smooth muscle in individuals born small (Luyckx & Brenner, 2015). There is also evidence that the shape and size of the placenta influence subsequent risk of CVD in the offspring (Barker *et al.* 2010). These effects may depend on the mother's nutritional state, for example if the placental surface expands to compensate for fetal undernutrition but affects the load on the developing circulation. They may also reflect effects of the mother's body size on the transport of nutrients across the placenta (Lewis *et al.* 2010, 2012), which can affect a range of fetal organs.

Cardiovascular risk factors in childhood such as high blood pressure and increased body mass index (BMI) are associated with arterial wall thickening in adults, which in turn predicts the formation of arterial plaques and later CVD (Norman & Bonamy, 2005; Norman, 2008). In very low birth weight infants, arterial stiffness has been reported as early as the first week after birth attributed to altered deposition and/or organization of vascular elastin (Ligi *et al.* 2010; Simeoni *et al.* 2011). Impaired endothelium-dependent and -independent vasodilatation is evident at birth, at 3 months of age, in later childhood and in early adult life in individuals born preterm, with low birth weight or with poor fetal nutrition. For example, a significant, graded, positive association between birth weight and flow-mediated dilatation (FMD) assessed in the brachial artery has been reported in British children aged 9–11 years (Leeson *et al.* 1997). The association is not affected by adjustment for childhood body build, cardiovascular risk factors, parity, social class, or ethnicity. Recently, arterial stiffness in 9-year-old children was shown to be inversely related to mother's consumption of oily fish in late pregnancy but not to child's oily fish consumption (Bryant *et al.* 2015).

Several studies show that such early changes in vascular structure and function persist into adulthood. In the Cardiovascular Risk in Young Finns study, impaired fetal growth was associated with impaired FMD and preclinical atherosclerosis in young adults (24–45 years) born preterm or at term with impaired fetal growth (Skilton *et al.* 2011). Small size at birth, in terms of both thinness and low birth weight, is associated with later type 2 diabetes and impaired glucose tolerance, perhaps via the combination of low skeletal muscle mass with high intra-abdominal fat mass, a phenotype particularly prevalent in some Asian populations (Yajnik, 2004). There is a relationship between low birth weight and plasma lipids in adulthood, affected by sex, although the effects of later BMI and lifestyle are greater in adulthood (Lawlor *et al.* 2006; Pereira & Power, 2012).

A U-shaped association has been shown between birth weight and later risk, with rates increasing at both the highest and lowest birth weights (Curhan *et al.* 1996*a*,*b*; Kyle & Pichard, 2006; Gamborg *et al.* 2007; Painter *et al.* 2008; Veenendaal *et al.* 2013). This may be the result of maternal obesity, high gestational weight gain or gestational diabetes, which have been shown to be associated with high birth weight. Excessive maternal weight gain in pregnancy may be associated with elevated offspring blood pressure and adiposity, although there appear to be subtle differences in the impact of maternal obesity and gestational weight gain as, in the Finnish cohort, young adults born large for gestational age at term did not show impaired FMD or other cardiovascular risk factors, although they did show an increase in carotid intimal medial thickness, a marker of subclinical atherosclerosis (Skilton *et al.* 2014). They were also more likely to be obese. However, birth weight is only a crude indicator of adverse environmental conditions such as suboptimal nutrition.

A major age-related vascular phenotype and an early change responsible for the development of CVD is endothelial dysfunction (Ozaki *et al.* 2001; Khan *et al.*

2005; Seals *et al.* 2011; Donato *et al.* 2015). Endothelial dysfunction is manifest through a number of processes including a reduced angiogenic capacity, increased cell senescence (Hayashi *et al.* 2008), enhanced inflammatory state and impaired vasodilator capacity. Amongst the possible mechanisms that contribute to age-dependent and CVD risk-associated endothelial dysfunction is a reduced bioavailability of the endothelium-synthesized dilating molecule nitric oxide (NO) augmented by NO scavenging due to oxidative stress. Implicated in this endothelial redox change is an increase in NADPH oxidase activity and in mitochondrial respiration (Bachschmid *et al.* 2013), in the absence of augmented antioxidant defences (Lesniewski *et al.* 2009). Circulating markers of antioxidants are either reduced or unchanged with ageing in humans (Seals *et al.* 2011). The transcription factor nuclear erythroid 2-related factor 2 (Nrf2) regulates gene expression to counteract oxidative stress. In vascular models, activators of the Nrf2 pathway have been shown to restore redox homeostasis (Chapple *et al.* 2012). *In utero* exposure to increased expression of Nrf2 may also have a persistent effect on antioxidant capacity to limit oxidative stress-induced DNA damage (Vanhees *et al.* 2013) and to improve endothelial function and afford cardiovascular protection in older age (Bonacasa *et al.* 2011).

Pregnancy-related disruption of redox balance impacts on the germ cell, embryo and fetus with long-term consequences on the mature organism, depending on the timing of these events (Dennery, 2010). For example, pre-eclampsia remodelling of the uteroplacental circulation is associated with increased markers of oxidative stress (protein carbonyls and nitrotyrosine residues) and placental vascular dysfunction in humans (Redman & Sargent, 2000). The consequences to the offspring are both short- and long-term and include adult hypertension, stroke, diabetes and obesity (Fernandez-Twinn & Ozanne, 2006; Kajantie *et al.* 2009). Maternal obesity and overfeeding can also alter fetal oxidant status. In the rodent, maternal cafeteria feeding diminishes fetal plasma total antioxidant status and offspring exhibit a disrupted redox balance with long-term cardiovascular effects (Bouanane *et al.* 2009; Torrens *et al.* 2012). In humans, increased levels of reactive oxygen species in the placenta may be linked to neonatal insulin resistance and obesity in response to maternal obesity or gestational diabetes (Coughlan *et al.* 2004; Roberts *et al.* 2009). Reduced levels of superoxide dismutase, catalase, glutathione and serum malondialdehyde have been observed in cord blood from babies born small for gestational age compared to infants born appropriate for gestational age (Gupta *et al.* 2004) and raised levels of biomarkers of oxidative stress in addition to insulin resistance persist in pre-pubescent life (Franco *et al.* 2007; Chiavaroli *et al.* 2009).

Supplementation with L-arginine to increase NO bioavailability or antioxidant levels during gestation and early postnatal life lowers blood pressure and improves vascular endothelial function in an animal model of hypertension (Alexander *et al.* 2004); however, randomized controlled trials of combined vitamin C and E supplementation during pregnancy have yet to show usefulness in preventing pre-eclampsia (Rumbold & Crowther, 2005; Poston *et al.* 2006). Low levels of folate, an essential cofactor for epigenetic methylation, are strongly correlated with pre-eclampsia in mothers and small for gestational age infants (Darnton-Hill *et al.* 2015) and maternal supplementation with mixed antioxidant vitamins and essential minerals to prevent the later elevation of offspring blood pressure and vascular and renal dysfunction associated with poor maternal nutrition (Torrens *et al.* 2006; Franco *et al.* 2009).

Ageing-associated damage to the endothelium may also result from a deterioration in endogenous endothelial progenitor cell levels and function, decreasing capacity for neovascularization and reducing re-endothelialization following vascular lesions (Williamson *et al.* 2012).

Bone health

Ageing is associated with bone loss and osteoporosis, which increases the risk of age-related fracture, typically of the hip, spine and distal forearm, which is associated with substantial morbidity and mortality (Harvey *et al.* 2010). Incidence of such fractures increases with age and is related to declining bone strength. These depend upon the peak attained during skeletal growth and the subsequent rate of bone loss. Bone mass is partly a heritable characteristic, although current fixed genetic factors do not explain more than a small proportion of the variance in bone mass at the population level. However, there is increasing evidence that early environmental influences modulate the attainment of peak bone mass.

Epidemiological studies show links between birth weight, weight in infancy, and adult bone mass (Baird *et al.* 2011). Initially associations were shown between weight at 1 year and bone mineral content, although not density, at the lumbar spine and femoral neck at age 21 years independent of adult BMI (Cooper *et al.* 1995). This relationship was replicated in men and women aged 60–75 years in Hertfordshire (Cooper *et al.* 1997), and persisted after adjustment for later environmental influences on bone loss including level of physical activity, dietary calcium intake, smoking, alcohol consumption and age at menopause. In these studies, there is evidence for effects of the early environment (Harvey *et al.* 2014) and for a gene–environment interaction: a polymorphism in the vitamin D receptor gene relates to bone mineral density in a direction that depends on birth

weight (Dennison *et al.* 2001), indicating that the genetic processes influencing adult bone size and mineral density may be modified by undernutrition *in utero*, probably by epigenetic influences (Harvey *et al.* 2014).

Further observations in a range of countries have confirmed the association between growth in infancy and adult bone mass (Baird *et al.* 2011). Clinically, recent studies have shown links between childhood and adolescence growth and risk of later hip fracture (Javaid *et al.* 2011) and greater maternal height and low rate of weight gain between 7 and 15 years in the child (Cooper *et al.* 2001). In addition, adults suffering fracture were shorter at birth but of average height by 7 years, perhaps because accelerated childhood growth in the absence of adequate skeletal mineralization was associated with greater fracture risk later, another instance of the importance of a match between pre- and postnatal environments in influencing later risk of disease. These epidemiological studies, however, indicate that effects on bone mass alone are not sufficient to explain hip fracture risk. It is likely that skeletal muscle size and function (see below) contributes to frailty in individuals born light and thereby adds to the risk of fracture conferred by reduced bone mass.

Skeletal muscle

The relationship between birth weight and muscle strength in later life, first described in the Hertfordshire Ageing Study, has been replicated using a prospective national birth cohort of men and women aged 53 years (Kuh *et al.* 2002). This study also investigated the effect of childhood growth on adult muscle function and demonstrated that there was no interaction between birth weight and later body size. A potential underlying mechanism is that birth weight is related to an individual's muscle fibre number and types, established by birth, and that even in middle age, compensating hypertrophy may be inadequate. The relationship between birth weight and muscle strength may reflect a common genetic mechanism but this has been little explored. One study investigated the role of polymorphism in the insulin-like growth factor 2 gene (*IGF2*) (Sayer *et al.* 2002). The product of this gene, insulin-like growth factor II, is central to fetal growth and has a proliferative action in adult muscle. However, the study showed that birth weight and the polymorphism of the *IGF2* gene had independent effects on grip strength in men suggesting that this polymorphism did not explain the observed association between early growth and grip. Adult muscle mass, as estimated by urinary creatinine excretion, is also related to early size independent of adult size (Phillips, 1995). A study of men and women aged 50 years showed that muscle mass was related to low birth weight and small head circumference, but not to thinness at birth (Phillips, 1995). A study of adult body composition in people aged 65–75 years using whole body dual X-ray absorptiometry confirmed that low birth weight was associated with lower adult lean mass in both men and women (Sayer *et al.* 2004*a*). From a clinical point of view, measures of muscle mass and function are not only relevant to bone health and frailty but also predict cardiovascular risk in diabetic patients (Lopes-Jaramillo *et al.* 2014).

Epigenetic mechanisms as an underlying process

There is currently considerable interest in the role of epigenetic processes induced during development in later risk of non-communicable diseases (NCDs) (e.g. Hanson & Gluckman, 2014). The mechanisms include changes in DNA methylation, histone modification and small non-coding RNAs. A range of maternal dietary, body composition, metabolic and endocrine factors can initiate such changes in specific tissues of the developing fetus (Godfrey *et al.* 2007), or potentially in all tissues if the process was initiated in the early embryo (Fleming *et al.* 2004). The resulting epigenetic effects can affect gene transcription in the presence of the appropriate transcription factors. Thus, whilst measurable at birth, the epigenetic changes may not be manifest in the phenotype until later in the life course, affecting for example the responses to later nutritional or metabolic challenges (Hanson & Gluckman, 2014). Such changes have been shown to be reversible in fetal and early postnatal life (Lillycrop *et al.* 2005; Burdge *et al.* 2009), although this is not necessarily universally the case. In addition, because some epigenetic changes can be induced in the germ cells, they can potentially be passed across generations via the egg and sperm (Skinner *et al.* 2010).

Epigenetic changes are established to play a role in ageing via effects on telomere stability (Blasco, 2007), antioxidant protection, metabolic homeostasis and effects on specific genes (Fraga & Estellar, 2007). NCDs associated with ageing, such as some forms of cancer, atherosclerosis, obesity, osteoporosis and sarcopenia, involve epigenetic processes but it is not yet known whether these processes are accelerated by epigenetic changes induced during development.

Immune function as an underlying process

Immune cells are strongly affected by ageing, which results in, among other effects, an increase in the number of memory cells at the expense of immunologically naive cells, termed immunosenescence, which is associated with reduction of the T-cell repertoire and the 'immunological space' (Franceschi *et al.* 1999; McElhaney & Effros, 2009; Freund *et al.* 2010). However, both in individuals who successfully age and in those who do not, an increase in pro-inflammatory status is observed

(Baggio, 1998; Mari *et al.* 1995, 1996; Freund *et al.* 2010) and inter-individual pro-inflammatory thresholds are hypothesized to exist, depending on the age and coping mechanisms available within the individual: beyond this, ageing-related disorders may develop (Franceschi *et al.* 2000).

Both fetal and childhood conditions, such as fetal nutrition, childhood maltreatment and the socioeconomic status of the family may contribute to the pro-inflammatory trajectory and thereby to the development of ageing-related disorders in later life (Surtees *et al.* 2003; Danese *et al.* 2007; Pollitt *et al.* 2007; West *et al.* 2010; Amarasekera *et al.* 2013). The induction of inflammatory responses across the life course may also contribute to the pro-inflammatory trajectory of an individual (Franceschi *et al.* 2000).

Inflammatory responses constitute secondary responses to a stressor, when primary homeostatic mechanisms, such as the endocrine axes, are unsuccessful. As a consequence, allocation of metabolic resources will be shifted to the immune system to benefit the immediate survival of the individual. However, when inflammatory responses are chronically induced, the set point for metabolic parameters can be permanently shifted contributing to, amongst other conditions, increased insulin resistance (Kotas & Medzhitov, 2015). There is therefore an interaction between infectious and auto-immune effects on the immune system and NCDs. The possible interaction may underlie early life effects on longevity associated with season of birth reported in The Gambia (Moore *et al.* 1997), effects which have both nutritional and epigenetic components.

Hence, by overriding homeostatic mechanisms such as endocrine responses, and by shifting the set point for metabolic parameters, inflammatory responses might have a strong impact on the developmental plasticity of an individual, which, depending upon the life course history, the environment and the socioeconomic resources available, may predispose individuals towards chronic disorders in later life.

Wider social and global issues

Increasing longevity in many populations around the world creates problems as well as benefits. Ageing populations can be expected to experience greater prevalence of chronic disease, especially NCDs (Prince *et al.* 2015); the compression of morbidity may result in extended healthy lives for many individuals but this may require investment. The trade-offs between investments in health care for younger *versus* older members of the population raise complex issues (Fries, 1980), although, as this review explains, health at the two ends of life may be more related than previously thought.

The balance between health over the life course and the need for health care can be viewed using the economic analogy of capital *versus* stock (Dasgupta & Serageldin, 2001). Whilst both individuals and populations may have to utilize stock to pay for health care or to make up for lost earnings or capabilities when they suffer acute health problems, a sustainable life course health care policy will allow health capital to be retained or even increased. In low socio-economic status groups in high income countries (HICs), and in low- to middle-income countries (LMICs) more widely, stock will soon be exhausted and capital growth will become negative.

Not all individuals commence the life course with the same resources (Hanson & Gluckman, 2011*a*). Individuals or groups who have a good start to life and healthy childhood development already have some health capital and achieve a higher peak intrinsic capacity for many functions: they may for example not have stunted growth and have a more extensive coronary vasculature. As life proceeds they are more likely to retain this inherited health capital and to build on it. Part of this inheritance may be in the form of genetic predisposition, but factors such as maternal nutrition, body composition and lifestyle are more important, as are prenatal care, immunization and promotion of breast feeding (Gluckman *et al.* 2008). Some of these effects are mediated by epigenetic processes in the offspring, which can alter the individual response to later challenges (Godfrey *et al.* 2007). They may even be established before conception. Whilst this has implications for the health of current and future parents, in reality a wider set of social factors and age groups influence the developmental environment of the next generation. The life course approach emphasizes that the health of one age group should not be considered in isolation from that of others, and raises broad social and environmental, as well as medical, considerations.

Turning to potential interventions, the life course approach indicates that a shift in trajectory may need to be produced at a time when an individual or population group is fundamentally healthy and not accessing health services voluntarily (Hanson & Gluckman, 2011*b*). This emphasizes the importance of a health literacy approach, for example in adolescents (Kleinert, 2007). It also raises questions of equity in access not only to health care, but also to education, family planning and other empowerment issues, especially for girls and young women. These are issues which resonate with the Sustainable Development Goals and which need support in the post-2015 era.

Lastly, the life course health trajectory concept provides a theoretical basis for instituting and measuring the efficacy of interventions at critical points (Fig. 1). The response of an individual to an additional challenge at a particular time point can be used to predict their future trajectory and likely health needs. Biomarkers of risk

trajectory can thus be highly informative, obviating the need to wait for later outcomes such as manifestation of disease and shortening the time frame of evaluation of intervention trials substantially. The discovery of such biomarkers of risk trajectory, which can be measured in early life, makes this argument even more powerful.

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Additional information

Competing interests

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