# Impact of nutrition on the ageing process ☆

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## Abstract

Human life expectancy has been increasing steadily for almost two centuries and is now approximately double what it was at the beginning of the Victorian era. This remarkable demographic change has been accompanied by a shift in disease prevalence so that age is now the major determinant of most common diseases. The challenge is to enhance healthy ageing and to reduce the financial and social burdens associated with chronic ill health in later life. Studies in model organisms have demonstrated that the ageing phenotype arises because of the accumulation of macromolecular damage within the cell and that the ageing process is plastic. Nutritional interventions that reduce such damage, or which enhance the organism's capacity to repair damage, lead to greater longevity and to reduced risk of age-related diseases. Dietary (energy) restriction increases lifespan in several model organisms, but it is uncertain whether it is effective in primates, including humans. However, excess energy storage leading to increased adiposity is a risk factor for premature mortality and for age-related diseases so that obesity prevention is likely to be a major public health route to healthy ageing. In addition, adherence to healthy eating patterns, such as the Mediterranean dietary pattern, is associated with longevity and reduced risk of age-related diseases.

**Key words: Hallmarks of ageing: Molecular damage: Dietary patterns: Healthy Ageing Phenotype**

For nearly 200 years, human life expectancy has been increasing at approximately 2 years per decade and shows little indication of reaching a plateau[1]. Much of the early benefit was derived from reduced childhood mortality from infectious diseases, but, since the mid-twentieth century, the gains have been due mainly to reduced mortality in later life. The latter can be attributed not only to better health care but also to the effects of economic growth and to public health policies including those that have restricted tobacco use and improved road traffic safety[2]. Despite these improvements, globally, there are large inequalities with countries in sub-Saharan Africa, notably Swaziland, Chad, Guinea-Bissau and South Africa, having life expectancy at birth which is little over half of that in the most favoured countries including Monaco, Macau, Japan and Singapore[3]. Within Europe, improvements in life expectancy in Western Europe over the past four decades have not been achieved in Eastern Europe because of political and macro-economic issues and of a failure to implement effective health policies[2]. Similar socio-economic gradients in life expectancy have also been observed within countries, and Marmot[4] has estimated that 2·5 million years of life are potentially lost annually to premature mortality in England through the effects of inequalities in health.

Ageing is the major risk factor for most common chronic diseases[5] including cancers[6], CVD and stroke[7] and dementia[8]. As a consequence, the gain in years of life over the past few decades has been accompanied by additional years of chronic poor health so that the greatest proportion of total expenditure on health care is now concentrated in the last few years of life. Interventions that reduce morbidity in later life are likely to have significant financial and social benefits, in addition to gains in individual well-being.

## Biology of ageing

Ageing is characterised by progressive, time-dependent loss of function and increased likelihood of death. This loss of function includes widely recognised, relatively rapid processes such as the loss of female fertility following the menopause and much more insidious declines in brain volume and in skeletal muscle mass that can lead to cognitive and physical frailty, respectively. There is no evidence that ageing *per se* is genetically determined (or programmed)[9], and the ageing phenotype appears to result from the gradual accumulation of damage to all the cell's macromolecules, such as
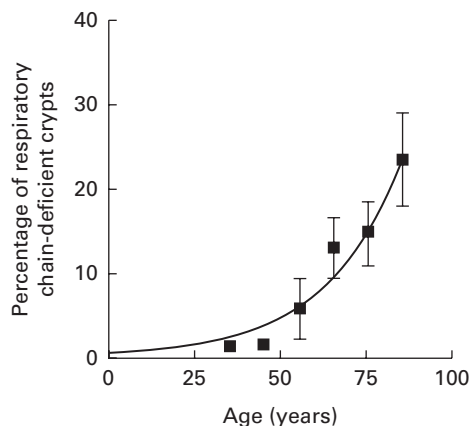
**Fig. 1.** Accumulation with age of mutations in mitochondrial DNA shown as % crypts with respiratory chain defects in biopsies of colorectal mucosa from healthy humans. From Greaves *et al.* (2010)[13]. $R^2 = 0.951$.

DNA, proteins and lipids[1]. Damage to DNA is not confined to the nuclear genome and there is good evidence of increasing burden of mitochondrial DNA mutations with increasing age in humans (Fig. 1)[10,11]. Damaged (unfolded) proteins also accumulate with age[12], and it seems likely that long-lived proteins, i.e. those that turnover slowly, if at all, may be at the greatest risk of acquiring damage with age[13]. For example, the accumulation of damaged crystallin in the human lens with age leads to cataract[13], which is the most common cause of blindness. The structure and function of cells and of organelles depend on the composition and integrity of membrane phospholipids. These phospholipids are rich in PUFA that are susceptible to oxidative damage, and peroxidation of membrane phospholipid acyl chains is hypothesised to play a causal role in the ageing process[14]. As one would expect, age-related macromolecular damage has profound effects on cell function, and such dysfunction is likely to be most pervasive when it affects stem cells that are essential for the normal maintenance of mitotic tissues and for tissue repair following disease, surgery or other trauma. During ageing, stem cells may (1) become depleted through loss of capacity for self-renewal, (2) lose their ability to generate appropriately differentiated cell lineages, (3) become moribund because of senescence or (4) acquire genetic and epigenetic damage that initiates tumorigenesis[15].

In a recent review, Lopez-Otin *et al.*[12] proposed nine tentative hallmarks of ageing that are common to many organisms, including mammals. These hallmarks include the following factors: genomic instability; telomere attrition; epigenetic alterations; loss of proteostasis; deregulated nutrient sensing; mitochondrial dysfunction; cellular senescence; stem cell exhaustion; altered intercellular communication (Fig. 2)[12]. In selecting these hallmarks, Lopez-Otin *et al.*[12] searched for factors that met the following criteria: (1) it occurs during ageing; (2) experimental enhancement of the factor accelerates ageing; (3) experimental amelioration of the factor slows ageing and so increases healthy lifespan. Lopez-Otin *et al.*[12] recognised that evidence for the third criterion was often limited.

Although there is no 'death gene', population genetics studies have shown that about 25 % of the inter-individual variation in lifespan can be accounted for by heredity, and it seems likely that the underlying genetic factors influence ageing through effects on somatic maintenance[1]. The remaining 75 % of the variation is due to environmental factors and stochastic events. In other words, the ageing process is plastic and interventions that increase longevity, and which reduce susceptibility to age-related diseases, are those that reduce macromolecular damage and/or which enhance the cell's ability to repair such damage. The ubiquitous causes of molecular damage include inflammation, metabolic stress and oxidative stress/redox changes. Some inter-individual differences in capacity to cope with macromolecular damage are genetically encoded. For example, the 50-fold difference in lifespan between the Atlantic bay scallop (*Argopecten irradians*) and the sessile giant clam (*Tridacna derasa*) appears to be due, at least in part, to more effective somatic maintenance in the giant clam[16]. In humans, diseases characterised by accelerated ageing such as Werner's syndrome, Cockayne's syndrome and xeroderma pigmentosum are caused by inherited defects in the machinery responsible for DNA repair.

## Nutritional modulation of the ageing process

Since the ageing phenotype results from the accumulation of damage to the cell's macromolecules, nutritional interventions that reduce ageing must do so because they reduce the amount of damage sustained by the cell and/or because they enhance the capacity of the cell, tissue or organism to repair, or to cope with, that damage. Genetics-based studies[17,18], and intervention studies with pharmaceutical agents such as rapamycin[19], have strengthened the evidence for the plasticity of the ageing process, and it is apparent that modulation of a relatively small number of pathways central to energy and nutrient sensing and to cellular defence is key to the ageing process. Investigation of these same processes is likely to reveal how nutrition influences ageing.

For at least 80 years, it has been apparent that nutrition modulates the ageing process. The earliest unequivocal evidence for the impact of nutrition on ageing came from studies in rodents showing that dietary restriction (DR) – providing animals with less food than they would eat under *ad libitum* conditions – increased lifespan and reduced (or delayed) the development of age-related diseases. DR (usually energy restriction while ensuring adequate nutrient supply) is now a very well-established experimental paradigm that extends lifespan and healthspan in many species[20,21]. However, note that the effects of DR on lifespan can be heterogeneous, even within the same species, and that there is evidence that DR can reduce lifespan in some inbred strains of mice[22]. The effect of DR in humans is not known, and both practical and ethical constraints mean that a direct test of the hypothesis is challenging; however, two recent studies have attempted to test the hypothesis in another primate – the rhesus monkey. One of these studies reported apparently greater longevity in rhesus monkeys exposed to 30 % DR throughout
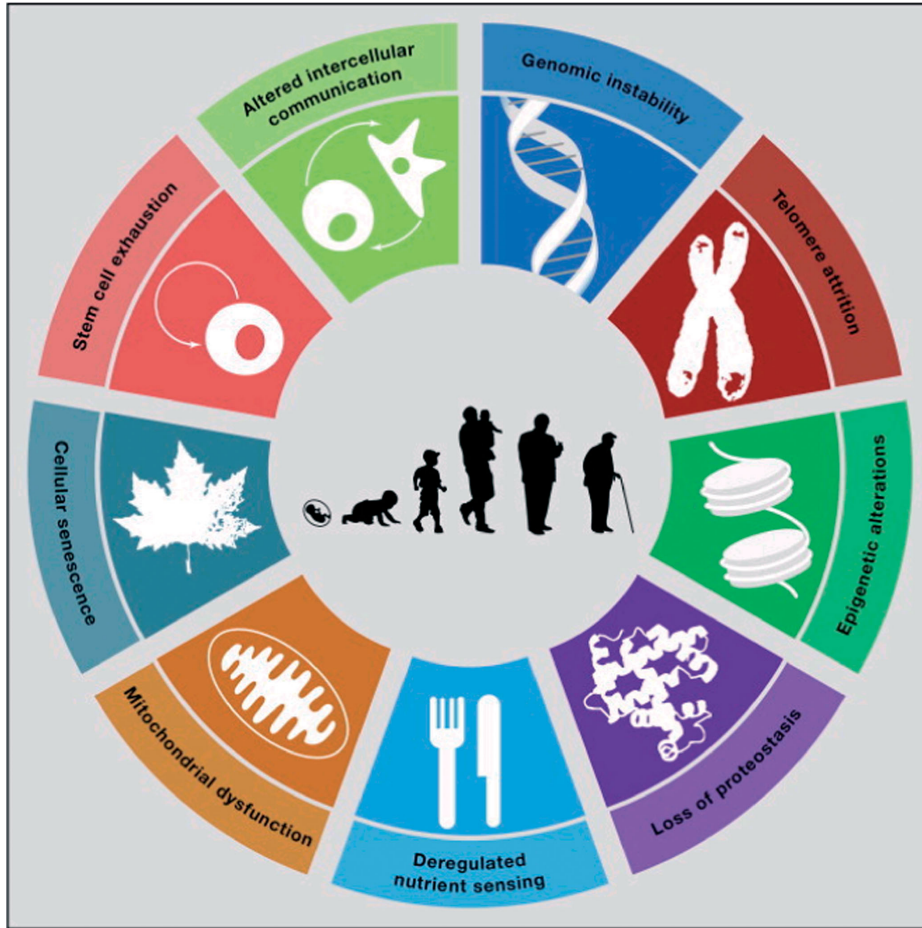
**Fig. 2.** Hallmarks of ageing proposed by Lopez-Otin *et al.* (2013)[12].

adulthood[23]. In contrast, the other study found no effect on lifespan regardless of the stage in the life course at which DR was introduced[24]. Several features of the studies, including differences in dietary regimen, might explain the divergent effects on lifespan, but none of these was conclusive[25]. However, in both studies, the dietary-restricted animals were leaner and had a lower burden of age-related diseases. Translating these outcomes to humans suggests that avoiding obesity may improve healthy ageing, and, indeed, there is strong evidence for greater risk of death when BMI is in the overweight and, especially, obese range[26].

## Obesity and ageing

The Prospective Studies Collaboration pooled data from fifty-seven human prospective studies involving approximately 900 000 adult participants to investigate the relationships between BMI at baseline and subsequent mortality[26]. Most studies were based in Western Europe or North America, and to minimise potential confounding due to current ill health, deaths in the first 5 years of follow-up were excluded. For most of the common causes of death, including CVD, there was strong evidence of progressively greater risk of death with increasing BMI above the minimum in the range

of 22·5–25 kg/m$^2$. For some cause-specific mortality, e.g. cancer, there was greater risk with BMI < 20 kg/m$^{2[26]}$. In addition, there is evidence that increased adiposity in adulthood has adverse effects on long-term health. Compared with women who were lean (BMI 18·5–22·9 kg/m$^2$) at age 18 years of age and who remained weight stable in adult life, those who gained weight in midlife had reduced likelihood of healthy survival after the age of 70 years[27]. In this case, 'healthy survival' was defined as having no history of major chronic diseases and no substantial cognitive, physical or mental limitation[27]. Women who were overweight at 18 years of age, regardless of subsequent weight change, had reduced healthy survival and those who were overweight at 18 years of age and gained at least 10 kg in midlife were five times less likely to enjoy healthy survival after 70 years of age[27].

Being obese, or carrying the fat mass and obesity-associated protein encoding gene (*FTO*) risk allele for overweight and obesity, is associated with changes in brain structure, which are consistent with more rapid brain ageing[28]. Such results from imaging studies correlate positively with evidence from epidemiological studies showing that overweight and obesity in midlife are associated with a greater risk of dementia[29]. Obesity and sedentary behaviour (a potential causative

factor) are associated with an increased risk of molecular and cellular damage and, if sustained, with an increased risk of all common age-related diseases due, at least in part, to the damaging effects of chronic, low-level inflammation[30]. Given that obesity-related behaviours (diet and physical activity) track from childhood into adulthood[31], effective interventions that prevent obesity in childhood may have lifelong benefits.

## Dietary patterns and human ageing

Nutrition is critical for health and well-being at all stages in the life course, and, indeed, the nutrition of one generation may influence ageing in the next generation. While nutrition has immediate effects on metabolism and health, nutritional exposures can have very long legacies. This is exemplified by the impact of maternal nutrition during pregnancy and of nutrition in early postnatal life on ageing (reviewed by Langie et al.[32]). For example, we have shown recently that a nutritional insult during pregnancy and lactation (maternal folate insufficiency), especially when followed by a second nutritional insult (high fat feeding from weaning), may reduce genomic defence mechanisms in the adult offspring brain, i.e. expression of base excision repair genes (a DNA repair system that corrects the lesions caused by oxidative damage)[33].

It is probable that many dietary factors including total energy intake relative to energy needs (which determines the risk of obesity), specific nutrients and other non-nutrient bioactive constituents, individually and collectively, influence the accumulation of macromolecular damage within the cell and, therefore, the ageing process. For example, we have observed that the capacity for nucleotide excision repair (a DNA repair system that removes large DNA adducts) is reduced in those with a higher BMI, even among young, healthy adults[34]. More broadly, there is evidence that nutritional intake and nutritional status influences DNA repair[35], and these nutritional factors may explain some of the substantial inter-individual variation in DNA repair capacity in humans[36]. Investigation of such complex interrelationships is challenging especially in human epidemiology, with difficulties in exposure measurement[37,38] and with substantial risks of confounding. The more recent focus on dietary patterns offers promise not only in identifying associations with healthy ageing but also in providing the evidence base for the development of public health interventions. The strongest evidence for links between a dietary pattern and ageing is that for the Mediterranean diet – a dietary pattern which is characterised by high consumption of plant-based foods, moderate-to-high consumption of fish and low intakes of dairy foods and meats and meat products[39]. In addition, meta-analysis has shown that adherence to the Mediterranean diet is associated with substantial reductions in the risk of several major age-related diseases including CVD, cancers and neurodegenerative diseases[40]. Such observational evidence has been strengthened considerably by a recent human intervention study that has demonstrated primary prevention of CVD with Mediterranean diet-based interventions[41].

## Concluding comments

This is an exciting time for research on nutrition and ageing. It is now evident that the ageing phenotype is due to the accumulation of macromolecular damage and that the ageing trajectory is plastic and responds to dietary, and other, interventions. In addition, there is reason to hope that we will soon have a better understanding of the molecular mechanisms through which nutrition can enhance healthy ageing. At a public health level, we need effective interventions to improve dietary behaviours so that we can reap the rewards of greater health and well-being in later life[42]. To date, research on such interventions has been hampered by the lack of appropriate outcome measures since the biological complexity of the ageing process means that there is no single, simple and reliable measure of how healthily someone is ageing. To help address this research gap, we have proposed, tentatively, a panel of outcome measures based on the concept of the 'Healthy Ageing Phenotype'[43], which could be deployed in community-based, lifestyle interventions on healthy ageing[44].

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