Nutrition and ageing: knowledge, gaps and research priorities

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Over the past two centuries human life expectancy has increased by nearly 50 years. Genetic factors account for about one-third of the variation in life expectancy so that most of the inter-individual variation in lifespan is explained by stochastic and environmental factors, including diet. In some model organisms, dietary (energy) restriction is a potent, and highly reproducible, means of increasing lifespan and of reducing the risk of age-related dysfunction although whether this strategy is effective in human subjects is unknown. This is ample evidence that the ageing process is plastic and research demonstrates that ageing is driven by the accumulation of molecular damage, which causes the changes in cell and tissue function that characterise the ageing phenotype. This cellular, tissue and organ damage results in the development of age-related frailty, disabilities and diseases. There are compelling observational data showing links between eating patterns, e.g. the Mediterranean dietary pattern, and ageing. In contrast, there is little empirical evidence that dietary changes can prolong healthy lifespan and there is even less information about the intervention modalities that can produce such sustainable dietary behaviour changes. In conclusion, current research needs include (1) a better understanding of the causal biological pathways linking diet with the ageing trajectory, (2) the development of lifestyle-based interventions, including dietary changes, which are effective in preventing age-related disease and disability and (3) the development of robust markers of healthy ageing, which can be used as surrogate outcome measures in the development and testing of dietary interventions designed to enhance health and well-being long into old age.

Biology of ageing: Intervention studies: Healthy ageing phenotype

Over the past 200 years, one of the most remarkable human achievements has been the apparently inexorable increase in life expectancy. Using data for the country with the greatest life expectancy in any year, this increase equates to a gain in life expectancy of 24 years per century\(^{3}\) or 5–6 h for every day that passes. As yet, there is no evidence of an upper limit to life expectancy and improvements have been seen in both low- and high-income countries\(^{2}\). For most high-income countries, and for some emerging economies including China, a fall in the birth rate combined with increased lifespan means that the population distribution is shifting so that a progressively greater proportion of people are aged 65+ years. This demographic shift is seen most dramatically in the numbers of the ‘extremely old’. Before the middle of the last century, very few people reached the age of 100+ years, but among the longest lived nations, e.g. Japan and Sweden, the numbers of such ‘extremely old’ people have grown very rapidly in the last few decades\(^{3}\). However, some countries have not shared this benefit and notable examples are the former communist countries of Eastern Europe where there was stagnation, or decline, in life expectancy over the last 30 years of the twentieth century\(^{4}\). Within the UK, there is a distinct north–south divide in life expectancy with those in Scotland dying younger than in England and in other European countries\(^{5}\) and there is a strong socio-economic gradient in both total life years and years of good health\(^{6}\).
The biology of ageing

Although there is no convincing evidence that lifespan is 'programmed' genetically, about one-third of variation in life expectancy can be explained by genetic factors. There is growing evidence about the specific genetic variants that contribute to inter-individual differences in lifespan(7,8). For example, those carrying the e4 variant of the APOE gene (rs2075650) die younger(9,10) and have increased risk of some age-related diseases including Alzheimer’s disease (AD)(11). In contrast, there is good evidence to support the idea that ageing is a lifelong process which is driven by the accumulation of random molecular damage(12,13). Many factors, both exogenous and endogenous, contribute to this damage but in most cases molecular damage results from a small set of chronic stresses due to inflammation, oxidative stress/redox changes and metabolic stress. This damage occurs in all the cell’s macromolecules, including DNA, proteins and lipids, and is responsible for the age-dependent increase in cellular defects which manifest as age-related frailty, disability and disease(12). Although the cell has multiple DNA repair systems which recognise and repair many types of DNA damage, some mutations escape this system and accumulate with age(14) in part because the DNA repair machinery appears to become less effective(15,16). In addition to somatic mutations in nuclear DNA, progressively greater numbers of mutations appear in the mitochondrial genome as we have shown for the ageing human colorectal mucosa(17). Because of the mitochondrion’s central role in energy transduction and in the regulation of many cellular processes, including apoptosis, age-related mutations in mitochondrial DNA may have important functional consequences(18) that contribute to the ageing phenotype. Misfolded and damaged proteins are removed from cells largely via the autophagy–lysosome pathways which operate in the cytoplasm(19). However, the effectiveness of these pathways falls with age, resulting in the intracellular accumulation of altered and misfolded proteins which become organised into toxic multimeric complexes. In the brain, such complexes promote neuronal death and are the basis of most neurodegenerative disorders(20) including AD.

The ageing phenotype

In addition to cellular dysfunction as a result of molecular damage (outlined earlier), ageing is characterised by reduced function at the tissue level. This reduced tissue function may be due to:

1. Fewer cells in the tissue: There is very good evidence that brain volume decreases during ageing although neuronal loss appears to account for only a modest proportion of this decrease(21). The function and mass of the neuromuscular system decrease gradually from about 30 years of age(22) and these decreases contribute to the development of sarcopenia and other features of physical frailty.

2. Fewer viable, or functional, cells in the tissue: During ageing, the proportion of senescent cells in mitotic tissues increases(23). Although this loss of proliferative capacity has been proposed as an anti-neoplastic process, recent discoveries that senescent cells secrete growth factors, proteases and cytokines suggest that the presence of senescent cells may exacerbate tissue ageing(24) and might therefore be a contributing factor to age-related pathology(23).

3. Cellular heterogeneity within tissues: Studies of individual cardiomyocytes from young (6 months) and old (27 months) mice showed greater cell-to-cell variation in gene expression in the older tissues and this variation appeared to be random(25). This increase in cell-to-cell variation in gene expression could cause age-dependent loss of tissue function (Fig. 1) and we have hypothesised that this may relate to the changes in patterns of DNA methylation which occur during ageing(26). DNA methylation is one component of the epigenetic machinery that plays an important role in regulating gene expression at all stages of the life course and which is modulated by dietary and other exposures(27,28). Chronic stresses (which contribute to the ageing process) may increase cellular heterogeneity within tissues because of repeated cycles of tissue repair and this may be mediated, at least in part, by epigenetic mechanisms(29).

Nutritional modulation of the ageing process

As noted earlier, only about one-third of the variation in longevity appears to be heritable so that most of the inter-individual variation in lifespan is explained by stochastic and environmental factors, including diet. For more than 80 years, it has been known that dietary energy restriction (DR, restriction in energy supply while ensuring adequate intake of all nutrients) can extend the lifespan in rodents and a similar effect has been demonstrated in several other model organisms including yeast, worms, flies, fish and spiders. The DR paradigm has been invaluable in elucidating the molecular pathways that modulate ageing including the insulin-like growth factor-1/insulin signalling pathway, the sirtuin pathway, the AMP activated protein kinase pathway and the mammalian target of rapamycin pathway all of which interact(30,31). However, a recent meta-analysis of the effects of DR on lifespan in rats and mice found great heterogeneity in response with, in...
general, bigger responses in rats than in mice but also evidence that DR may have no, or adverse, effects on lifespan in some mouse strains(32).

The effect, if any, of DR on lifespan in primates and especially human subjects remains controversial. Ethical and practical considerations preclude a direct test of the DR hypothesis in human subjects but attempts have been made to test the hypothesis in non-human primates. In 2009, Colman et al. reported that energy restriction, by about 30%, during adulthood may reduce ageing and increase lifespan in rhesus monkeys(33). More recently, Mattison et al. observed no effects on survival in rhesus monkeys of a similar 30% DR regime initiated at various stages in the life course(34). Despite the marked contrast between studies of the effects of DR on mortality, both studies reported that DR monkeys remained healthier for longer, i.e. there were reductions in age-related diseases which were associated with reduced body fatness(33,34). These studies provide experimental support for the hypothesis that excess body fatness (obesity) accelerates the ageing process (perhaps through the damage caused by greater inflammatory and metabolic stress) which is exemplified by the observational data that BMI greater than about 25 is associated with progressively increased mortality(35) and that weight gain in middle age is associated with reduced likelihood of healthy survival after the age of 70 years in women(36).

There is considerable interest in the development of drugs or other agents which can mimic the beneficial effects of DR. Among these agents, the plant stilbenoid, resveratrol, is of particular interest because it inhibits inflammatory responses via the mammalian target of rapamycin pathway(37), perhaps by activating sirtuin 1(38) with effects on epigenetic regulation of gene expression. However, a recent meta-analysis of outcomes from nineteen studies of the effects of resveratrol on lifespan in several model organisms showed strong, consistent effects in lifespan extension in yeast, worms and the tropical fish Nothobranchius furzeri, but no evidence of any benefit for fruitflies or mice(39), so a beneficial effect on human ageing appears uncertain.

### Nutrition and brain ageing

Of all the age-related diseases and disabilities, neurodegenerative diseases, including dementia and Parkinson’s disease, have the most profound effects on the sufferers and their families and friends. The prevalence of AD, the commonest form of dementia, is strongly age-dependent with age-specific prevalence almost doubling every 5 years after the age of 65 years. It is predicted that the worldwide prevalence of AD will quadruple by 2050 when it is anticipated that one in eighty-five persons worldwide will have the disease(40). It has long been known that carriage of the e4 variant of the APOE gene confers increased AD risk; however, until recently, little was known about genetically determined resistance to AD.

Using whole genome sequence data from 1795 Icelanders, Jonsson et al. have shown that the A673T SNP in the APP gene that encodes the amyloid-β precursor protein appears to protect against AD(41). Cognitive impairment, an early essential element of AD, shares many of the same risk factors as CVD including obesity and associated metabolic derangements(42). On this basis, it is reasonable to assume that obesity and sedentary behaviour are important predictors of AD risk as they are of the risk of other age-related diseases(43) and that interventions which address these risk factors may reduce AD risk.

Adherence to the Mediterranean dietary pattern is associated with reduced mortality risk, a benefit that appears to be independent of geography(44). A recent meta-analysis of nine observational studies in several parts of the world has confirmed lower all-cause mortality associated with adherence to the Mediterranean diet and also showed significantly lower risk of neurodegenerative disease(45). To date, there have been relatively few nutritional intervention studies which have attempted to delay, prevent or reverse the development of AD. Of interest is the recent trial that tested the effect of supplemental B vitamins (folic acid, vitamin B₆ and vitamin B₁₂) on the rate of brain atrophy in participants with mild cognitive impairment(46). The rate of brain atrophy with age is increased in those with mild cognitive impairment, and raised circulating concentration of homocysteine is a risk factor for both mild cognitive impairment and brain atrophy, so the authors hypothesised that lowering homocysteine with supplemental B vitamins would reduce the rate of brain atrophy(47). Using MRI to quantify the brain volume before and after the intervention, they showed that the extra B vitamins obliterated the relationship between baseline homocysteine and rate of brain atrophy and slowed brain atrophy in those with mild cognitive impairment(48).

### Dietary interventions to promote healthy ageing

There is compelling evidence from studies in animal models, and from experimental and observational studies in human subjects, to support the hypothesis that the ageing trajectory is plastic(12). On this basis, there is reason to hope that nutritional, and other lifestyle-based, interventions have potential to enhance healthy ageing and to reduce the burden of age-related frailty, disability and disease (see(47) for a review). However, there is little empirical evidence that dietary changes can prolong healthy lifespan and there is even less information about the intervention modalities that can be used to produce the necessary sustainable dietary behaviour changes. Within Newcastle University, we are conducting the LiveWell Programme that aims to develop and pilot lifestyle-based interventions to enhance healthy ageing with a focus on people in the retirement transition. In preparation for intervention development, we have undertaken a systematic review and meta-analysis of the effectiveness of interventions promoting the Mediterranean diet or any of its component foods in people aged 55–70 years; review registered with Prospero CRD4201100148(48). This review also aims to identify the most effective behaviour change techniques which will be applicable to study participants in the retirement transition. Although there are a large number of candidate biomarkers of ageing(49), a major
limitation for all intervention studies that aim to enhance healthy ageing is the lack of reliable markers of healthy ageing which could be used as outcome measures. In the LiveWell Programme, we are developing a panel of outcome measures which aim to characterise, and to capture, important features of the healthy ageing phenotype and for which robust tools can be identified for use in large-scale community-based intervention studies.

Research priorities in nutrition and healthy ageing

The recognition that the ageing of human societies is a worldwide phenomenon with profound implications for economies, and for social well-being, is the impetus for increasing investment in research on many aspects of ageing and of older people and societies. Such research has provided strong evidence that ageing is plastic and is a complex process driven by the accumulation of molecular damage and it is clear that nutrition modulates the ageing process and the risk of age-related pathology. To build on these advances, future research should aim to (i) produce a better understanding of the causal biological pathways linking diet with the ageing trajectory, (ii) support the development of lifestyle-based interventions, including dietary changes, which are effective in delaying or preventing age-related frailty, disease and disability and (iii) develop robust markers of healthy ageing which can be used as surrogate outcome measures in the development and testing of dietary interventions designed to enhance health and well-being long into old age. Such markers will also be useful for large-scale public health surveys of ageing populations.

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