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The Ageing Process and Health

Biological ageing results from the accumulation of damage within cells, leading to a loss of function and, ultimately, cell death. The underlying mechanisms of ageing are also risk factors in the onset of frailty, disability and long-term diseases. This POST note examines the biological basis of ageing, the potential to manipulate the ageing process and to use such knowledge to promote better health later in life.

Overview

- Increased life expectancy has contributed to a rise in the number of people living with multiple, age-related long-term conditions.
- Research is beginning to identify the processes that cause biological ageing and the potential to intervene to improve health in old age.
- Drug based interventions and novel therapies are being developed to target the processes of ageing. However, there are barriers facing their implementation due to clinical trial regulations.
- Factors across the life-course contribute to ageing processes. Focusing on improving health at all stages of life may prevent or delay the onset of age-related illnesses such as dementia.

Background

Average UK life expectancy at birth has doubled since 1841 and is now 79.2 years (males) and 82.0 (females).[1] An increasing number of older people is resulting in a growing prevalence of long-term (chronic) age-related conditions and disabilities towards the end of life. For example, more than 25% of people over 60 currently report having two or more chronic conditions (multi-morbidity).[2] Moreover, the number of UK cases of dementia is projected to increase from 850,000 to 2 million by 2051, often co-occurring with other conditions.[3] Such conditions put pressure on health and social services and can have additional economic consequences such as people leaving employment to provide unpaid care to others. In 2017, the annual cost of unpaid care provided by 16-65 year olds in England was estimated to be £2.9 billion, due to social security benefits claimed by carers and foregone income tax.[4] This figure is projected to rise as an additional one million people over 65 may require unpaid care by 2035.[5] Over the same period, the number of carers available is expected to fall.[6]

Ageing is not a genetically predetermined set of events and many biological and environmental factors can influence the rate at which it occurs.[7] These factors also influence the onset of age-related diseases such as some neuro-degenerative disorders and cancer, as well as symptoms such as frailty.[8] An increased understanding of the basis for ageing could potentially lead to interventions that delay or prevent the onset of age-related chronic illness, increase the quality of life of older individuals and reduce dependencies and economic pressure on health services and care providers.

The biological basis of ageing

Life depends on a number of basic biological processes. For example, cells need to be able to break down food to produce energy, and to use that energy to make new cellular components (such as DNA and proteins) and to breakdown waste products. Collectively these processes are known as the cellular metabolism. They also need to be able to produce new cells to develop and regenerate tissues and organs, a process that involves cell division and DNA replication. Research suggests that these fundamental processes may become less efficient with age, causing a range of secondary consequences. These interact with the primary factors and influence the ageing process.[8] The next sections examine the primary factors and their secondary consequences that have been associated with ageing.

Primary factors

Key primary factors linked to ageing include:

- **Accumulation of damage in DNA (mutations) -** mutations can result from exposure to harmful chemicals or radiation in the environment, or from a

decline in the body's DNA repair mechanisms. Mutations over the lifespan can lead to loss of gene and cell function (Box 1). Premature ageing syndromes are often associated with deficiencies in DNA repair.[8]

- **Chromosome shortening** - incomplete replication of chromosomes (Box 1) means that the end sections (telomeres) can be lost or damaged with each round of cell division. This happens faster when cells are under stress and can halt cell division (cell senescence).[9,10]
- **Factors that bind to DNA** - ageing is associated with changes to epigenetic regulation across the genome (Box 1) which are linked to diseases such as Alzheimer's.[11,12] Epigenetic changes also accumulate predictably across the genome with age (the 'epigenetic clock', see Box 1). Its role in ageing is unclear.[13,17]
- **Mis-folded proteins** - cell function depends on proteins being folded into a particular shape. Mechanisms that mediate correct protein folding decline with age, as do those which degrade incorrectly folded proteins. Accumulation of misfolded proteins can be toxic to cells and is linked to age-related conditions such as Parkinson's and cataracts.[8]

Secondary consequences

The secondary consequences of the factors above include:

- **Problems with energy production -** mitochondria are responsible for cell energy production. Mutations accumulate in mitochondrial DNA with age and can spread when mitochondria replicate. This can lead to inefficient energy production and cell damage.[8]
- **Decline in cellular metabolism** - many of the sensors, and cellular components that coordinate cell energy production with fuel availability lose function with age, leading to deregulated cellular metabolism. Metabolic decline with age is associated with insulin insensitivity, diabetes and a rise in abdominal fat mass.[8]
- **Decline in cell division and tissue regeneration** - as cells age, cell division is arrested (senescence). This is important to prevent, for example, tumours developing. However, cell senescence can exacerbate ageing due to a loss of regenerative capacity (if it affects the stem cells that replenish cells in tissues) or via tissue damage (senescent cells secrete harmful molecules and can cause chronic inflammation). [13]
- **Altered communication between cells** - loss of function of individual cells can lead to defective signalling and coordination between cells at the whole body level. For example, the immune system is less effective at removing senescent cells with age.[13]

Rates of functional decline vary between individuals. Thus, those with a similar chronological age can have different biological ages and levels of good health in old age (Box 1).

Box 1. Genetic factors and biological ageing

Biological age is a measure of cell functionality. Individuals with the same chronological age can have tissues of widely differing biological age. This may reflect different environmental exposures that can influence the mechanisms of ageing, but is also affected by variations in genetic factors that control the maintenance of cells.[14, 15] These factors operate at different scales including:

- **Genes** – units of genetic code (DNA) that contain the instructions to make a biological molecule (usually a protein).
- **Chromosomes** – long linear molecules consisting of proteins bound to DNA that contains multiple genes.
- **The genome** – the complete collection of an organism's DNA (the human genome consists of approximately 20,000 genes split across 23 pairs of chromosomes).
- **Epigenetic factors** – a range of molecules that regulate gene function by interacting with DNA (for example by binding to it which can switch genes on or off).

Variations in the factors that influence biological ageing can have health implications later in life.[15] This means that measures (biomarkers) of biological age may be a better predictor an individual's risk of developing age-related disease than their chronological age. Physical measures such as grip strength, and cellular measures such as chromosome length have been suggested as potential biomarkers for ageing.[16] The epigenetic clock (a predictable accumulation of epigenetic modifications in cells with age) also correlates closely with biological ageing and (all causes of) death in humans,[17] but it is yet to be validated as a good predictor of different age-related diseases.

Ageing interventions

Interventions that target the primary factors and secondary consequences that lead to biological ageing can increase both the life and health span of many laboratory animals.[8] Human ageing is also known to be affected by external factors; for example life expectancy differs between the least and most deprived parts of England.[18] Such variability suggests there may be opportunities to intervene to slow down biological ageing (Box1) and improve health in old age. In practice there are two main approaches: developing drugs and other therapies that target ageing, or taking a life course approach to managing ageing. These are examined in the following sections.

Developing drugs and other therapies

Repurposing of licensed drugs

Several drugs that are used to treat other illnesses have been shown to increase the life span and health of laboratory animals by targeting the molecular mechanisms of ageing. For example the large-scale US Interventions Testing Program routinely screens licenced drugs for their effects on the lifespan and health of ageing mice.[19] Some of these are now being investigated for their effect on human ageing (Box 2). In the UK, the Alzheimer's Society is funding clinical trials of a drug (liraglutide) normally used to treat diabetes for the treatment of the early stages of Alzheimer's disease.[20] Further research may allow these drugs to be repurposed to treat or delay the onset of age-related conditions. Repurposing is seen as a cost-effective way to develop potential new therapies.[21]

New therapies

Novel therapies are being developed to target aspects of the ageing process.[8,22] As well as removing senescent cells (Box 2), scientists are investigating the potential to reverse cell senescence and/or epigenetic changes within cells.[23,22] Studies suggest stem cell populations may also be re-activated (for example using compounds found in younger organisms [24]) or replenished via stem cell transplantation.[23]

Box 2. Intervention trials

Metformin

Metformin is a first line drug for the treatment of type 2 diabetes in the UK. Clinical data suggests metformin can increase healthy lifespan in laboratory animals.[8] Targeting Ageing with Metformin (TAME) is a US based human clinical trial of metformin, overseen by the Food and Drug Administration. It includes 3,000 individuals aged over 60 and will measure the time to occurrence of several age-related diseases.[25] TAME is the first time that a regulatory body will consider using mixed age-related diseases as outcomes in a clinical trial.

Rapamycin

Rapamycin is approved as a treatment for cancer and to prevent the rejection of organ transplants. It promotes cellular processes such as metabolic stability and the removal of damaged cellular components.[8] An analogue of rapamycin, (everolimus) improved the efficacy of flu vaccinations in human individuals aged over 65.[26] The exact mechanisms remain unclear, but may involve replenishing the aged immune system. Researchers aim to test rapamycin, or safer analogues, against a range of ageing-related outcomes.

Senolytics

Research groups and commercial companies[27,28] are developing drugs (senolytics) that eliminate senescent cells.[29,30] Some cancer therapies (such as dasatinib and navitoclax) and food supplements (quercetin) have shown success in preclinical trials, removing senescent cells in different tissues and improving the health of ageing mice.[31,32] Researchers hope to begin clinical trials in humans soon.

Challenges to implementation

Marketing pharmacological interventions against ageing will require clinical trials. These present a number of challenges:

- **Complex trial populations** – older populations show large variations in the cellular processes causing ageing, the number of illnesses suffered and the drugs taken to manage them so clinical trials need to be larger (and more costly) in order to detect effects.[33]
- **Trial outcomes** – ageing-related indicators, such as disease-free survival or a reduction in multi-morbidity, are not recognised as primary outcomes in trials under current UK regulations.[19] Neither are surrogate biomarkers for ageing (Box 1). Instead there is a focus on treating single diseases.[19] The first clinical trial to target ageing is underway in the US (Box 2). Regulatory changes may be required to allow such trials in the UK.
- **Preventative medicines** – many anti-ageing interventions will involve preventative medicines which require longer-term studies and extensive safety checks, as individuals tend to take such drugs for longer and in the absence of any disease.[33]

A life course approach to ageing

A life course approach is recognised as a key component of healthy ageing and is strongly advocated by the World Health Organisation (WHO).[34] The WHO recognises that factors experienced across the life course affect the ability of tissues to attain an optimal level of functioning and impact on the risk of chronic diseases and disabilities.

Prenatal development and ageing

Research shows that maternal factors both before and during pregnancy can influence ageing in offspring later in life. For example, maternal obesity, smoking and a lack of essential nutrients correlate with an increased risk of age-related diseases developing in the infant later in life.[14,35,36] Among the possible mechanisms by which maternal factors may influence offspring ageing are:

- Poor male and female pre-conception health can alter epigenetic factors (Box 1) and cause damage in egg and sperm cells, increasing the risk of early biological ageing in the offspring.[14]
- The in utero environment may cause damage to foetal cells through DNA and epigenetic changes. This could potentially lead to developmental problems and may influence processes such as brain development, appetite regulation, immune function and fat deposition in the offspring.[35,37,38] Factors such as maternal obesity, malnutrition, smoking, stress and a high alcohol intake are thought to influence these risks.[36,37,38,39]

Some of these effects are permanent, particularly if they occur in tissues that are fully developed by birth, such as cardiac muscle tissue. Others, such as epigenetic changes, may be reversed through lifestyle interventions later in life.[14]

Child and adult influences on ageing

Longitudinal studies, such as the MRC National Survey of Health and Development, have linked many social and biomedical factors across life to measures of biological ageing.[40] For example, socioeconomic disadvantage during childhood is strongly related to poorer physical, cardiovascular and metabolic function later in life.[41] This is partially linked to an increased exposure to unhealthy lifestyle factors.[42] A healthy adult lifestyle involving physical activity, a healthy diet and an absence of smoking has been associated with the maintenance of higher physical and cognitive functioning in 60 year olds in the Survey.[43]

Many unhealthy lifestyle factors increase cellular damage accumulation. For example, obesity, coupled with inactivity, can result in long-term inflammation, causing damage to cells and tissues.[44] A high body mass index has also been linked to reduced expression of DNA repair genes in brain cells resulting in more rapid brain ageing, and a greater risk of dementia.[38] Other lifestyle factors can prevent tissues reaching a peak level of functioning. For example, smoking and low levels of physical activity prevent bone and muscle from reaching an optimal mass during adolescence, increasing the risk of conditions such as bone loss and osteoporosis later in life.[45]

Implications for public health policy

The life course approach suggests that, to achieve healthy ageing, interventions must start early (pre-conception) and continue throughout life. Interventions may vary through the life course. For example, those that enable the body to build to optimal capacity are required during development, whereas a focus on delaying decline is needed later in life.[14]

Preconception health

Promoting maternal health may improve the ageing trajectories of offspring and reduce inequalities in healthy ageing at the start of life. The UK Chief Medical Officer

(CMO) suggests that more could be done to target pre-conception health.[46] Opportunities for giving women advice on preconception health include, for example, when individuals come into contact with health services to plan a pregnancy or obtain contraception.[46] Additionally 1 in 5 women are likely to be planning another pregnancy following the birth of a child; the CMO suggests that health checks for the mother and child could incorporate advice.[46] Greater levels of pre-conception health education in the curriculum may also be beneficial and reach many individuals over a wide-scale.[46]

Health during pregnancy

Pregnancy is a time when women come into contact with health practitioners and promoting health at this time has the further benefit that two generations are targeted.[46] The government issues advice on diet, smoking cessation, alcohol intake and physical activity during pregnancy (see POSTnote 551). Despite this, many women experience excessive gestational weight gain[47] and 10.7% of pregnant women smoke.[47] Monitoring weight throughout pregnancy is not routine in the UK but some academics suggest this could help to identify women requiring greater support.[48,49] The 2017 Tobacco Control Plan for England aims to further reduce the number of women smoking during pregnancy to 6% by 2022.[47]

Childhood health

Improving childhood health for example through tackling obesity and promoting physical activity are key targets for improving healthy ageing. Support is available through government programmes in England[50] such as the National Healthy Child Programme,[51] the Healthy Start Programme[52] and the Change4Life programme[53]. Despite this, around one third of children aged 2-15 are currently overweight or obese.[54] The national diet and nutritional survey reported that only 8% of children aged 11-18 met the recommended 5 daily portions of fruit and vegetables and that the mean intake of saturated fat exceeded recommendations in all age groups.[55] This suggests advice may not be motivating wide-scale behavioural change. To reduce children's exposure to unhealthy choices, the School Food Plan has published new school food standards which are addressed by Ofsted.[56] Additionally, the Universal Infant Free School Meals plan, requires all government funded schools to offer a free daily meal to infant school pupils.[57] Despite this, uptake of school meals is 43%[566] and many children are thought to revert to unhealthy diets out of term time.[58] The lack of success of schemes targeting behavioural change to reduce obesity has led to the introduction of policies directed at the food industry, including the soft drinks industry levy and the sugar reduction programme (see POSTnote 530).

Healthier lifestyles in adulthood

Early diagnosis, personalised advice and recognising the link between biological ageing and mental health are widely acknowledged to be important for maintaining function in older individuals. These are discussed below.

The importance of early diagnosis

The National Dementia Strategy recognises that early diagnosis of age-related diseases is critical for enabling older individuals to engage in drug-based and lifestyle interventions that delay symptoms and allow them to remain independent.[59] A free NHS health check is offered every 5 years to individuals aged 40-74 years. Patients are given a risk score for conditions such as stroke, heart disease or dementia.[60] This has resulted in a small increase in disease detection above routine practice, but only 43.2% of invitees attended a check in the first quarter of 2017.[61] Public Health England (PHE) advises that initiating health checks by phone and sending reminders can improve uptake.[62] Academics suggest that health checks could include other biomarkers of healthy ageing (Box 1) such as grip strength and working memory to identify functional decline.[16] Access to health checks is an issue facing many older people. In 2011, less than 50% of people over 80 found it easy to travel to a hospital.[63] Initiatives such as the Hospital at Home scheme in Scotland and Integrated Community Ageing teams in Islington address patient isolation.[64] In the Islington scheme, assigning groups of health practitioners to individual care homes has helped to reduce the number of hospital admissions by 26% since 2014.[64]

Personalised health advice

Health assessments are coupled with personalised advice in several regions of the UK.[64] In Southampton, geriatric assessments provide person-specific management plans, incorporating local services. This reduced injuries from falls by 6% and hospital admissions by 7%, between 2013 and 2014.[6464] Malnutrition can exacerbate age-related conditions and slow recovery in older people.[65] It results from a complexity of social, medical and psychological factors. PHE suggest such factors should be considered when providing nutritional advice and be addressed in hospitals and future services.[66]

Ageing and mental health

Age-related conditions can limit social connectivity, increase loneliness and lead to a decline in mental health. It is estimated that depression affects 22% of men and 28% of women over 65 in the UK.[67] Only 6% of cases are referred to mental health services despite a high reported efficacy of treatment.[67] Depression can exacerbate ageing processes, complicate treatments and reduce quality of life.[67,68] Several groups call for a greater recognition of poor mental health in older people and a combined approach to treating multiple physical and mental health conditions.[67,68,69] Employment and life-long skill development are also associated with increased physical and social activity.[5,70] Reducing discrimination, providing training and offering flexible hours could enable older people to stay in work for longer,[70] allowing employers to benefit from their experience.[70]

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Endnotes

1 *National life tables, UK: 2014 to 2016*, ONS, 2017
2 Long Term Conditions Compendium of Information: Third Edition, DH, 2012
3 *Dementia UK repor*t, Alzheimer's Society, 2014
4 Pickard L et al, *Health Soc. Care Community*, 00:1–11, 2017
5 Future of an ageing population. GOS, 2016
6 Pickard L, *Ageing Soc*, 35(1), 96-123, 2013
7 Kirkwood T, *Cell*, 120(4), 437-447, 2005
8 Lopez-Otin C et al, *Cell* 153(6), 1194-1217, 2013
9 Blackburn E et al, *Nature Medicine* 12, 1133–1138, 2006
10 Von Zglinicki T, *Trends in Biochem Sci*, 27(7), 339-334, 2002
11 Pal S & Tyler J, *Science Advances*, 2 (7), e1600584, 2016
12 Brunet A & Berger S, *J. Gerontol*, 69 (Suppl_1), S17–S20, 2014
13 Childs B *Nature Medicine*, 21, 1424-1435, 2015
14 Hanson M et al, *J. Physiol*, 594(8), 2147–2160, 2016
15 Belsky, D et al, *PNAS*, 112 (30), E4104-E4110, 2015
16 Lara J et al, *BMC Medicine*, 13:222, 2015
17 Marioni R et al, *Genome Biol*, 16:25, 2015
18 *Inequality in Health and Life Expectancies within Upper Tier Local Authorities: 2009 to 2013*, ONS, 2015
19 www.nia.nih.gov/research/dab/interventions-testing-program-itp
20 www.alzheimers.org.uk/info/20053/research_projects/656/testing_the_effect_of_the_diabetes_drug_liraglutide_in_alzheimers_disease
21 *Report on Rejuvenating Ageing Research*, AMS, 2009
22 Ogrodnik M et al, *Nat. Commun*, 8, 15691, 2017
23 www.nature.com/news/ageing-research-blood-to-blood-1.16762
24 Castellano J et al, *Nature*, 544, 488-492, 2017
25 www.clinicaltrials.gov/ct2/show/NCT02432287
26 Mannick J, *Sci. Transl. Med*, 6(268), 268ra179, 2014
27 www.unitybiotechnology.com/
28 www.oisinbio.com/
29 Baker D et al, *Nature*, 530, 184-189, 2016
30 Baker D et al, *Nature*, 479, 232-236, 2011
31 Zhu Y et al, *Ageing Cell*, 15(3), 428-435, 2016
32 Childs B et al, *Nat. Rev. Drug Discov*, 16, 718-735, 2017
33 Newman J et al, *J. Gerontol*, 71(11), 1424-1434, 2016
34 *World report on ageing and health*, WHO, 2015
35 Godfrey K et al, *Lancet Diabetes Endocrinol*, 5(1), 53-64, 2016
36 Poston et al, *Lancet Diabetes Endocrinol*, 5(12), 1025-1036, 2016
37 Ungerer M, *Alcohol Res*., 35(1), 37-46, 2013
38 Knopik S et al, *Dev. Psychopathol*. 24(4), 1377-1390, 2012
39 Send T et al, *Neuropsychopharmacology*, 42, 2407-2413, 2017
40 Kuh, D et al *A life course approach to healthy ageing*, OUP, 2014
41 Kuh D et al, *Proc. Nutr. Soc.* 73(2), 237-248, 204
42 www.instituteofhealthequity.org/resources-reports/fair-society-healthy-lives-the-marmot-review/fair-society-healthy-lives-exec-summary-pdf.pdf
43 Michel JP (Eds) *Healthy ageing: midlife prevention of age-related disability. Chapter 1,* Springer, 2018
44 Mathers J, *Br. J. Nutr.*, 133(S1), S18-S22, 2015
45 Weaver C, *JCEM*, 84(1), 1839-1843, 1999
46 The Health of the 51%: Women. CMO report, DH, 2014
47 Towards a smoke-free generation: tobacco control plan for England, DH, 2017
48 Ma R et al, *Lancet Diabetes Endocrinol.*, 4(12), 1037-1049, 2016
49 Allen-Walker V et al, *BJOG*, 123(6), 871-874, 2016
50 *Briefing Paper: Early intervention,* HoC Library, 2017
51 *Healthy child programme: rapid review to update evidence*, PHE, 2015
52 www.healthystart.nhs.uk/healthy-start-vouchers/
53 www.nhs.uk/change4life-beta/cards
54 www.gov.uk/government/publications/childhood-obesity-a-plan-for-action/childhood-obesity-a-plan-for-action
55 *NSNS: results from Year 5 and 6 (combined)*, FSA/PHE, 2016
56 www.schoolfoodplan.com/plan/
57 www.gov.uk/guidance/universal-infant-free-school-meals-guide-for-schools-and-local-authorities
58 *Hungry Holidays: A report on hunger amongst children during school holidays.* Appg Hunger, 2017
59 *Living Well With Dementia: a national dementia strategy*, DH, 2009
60 www.nhs.uk/Conditions/nhs-health-check/Pages/What-is-an-NHS-Health-Check-new.aspx
61 www.healthcheck.nhs.uk/commissioners_and_providers/data/
62 *Top tips for increasing the uptake of NHS Health Checks*, PHE, 2016
63 *The Future of Transport in an Ageing Society,* ILC-UK & Age UK (2015).
64 www.bgs.org.uk/pdfs/2016_rcgp_bgs_integration.pdf
65 *Nutrition for older persons,* WHO
66 *Helping older people maintain a healthy diet: A review of what works.* PHE, 2017
67 *Hidden in plain sight*, Age UK, 2016
68 www.who.int/mediacentre/factsheets/fs381/en/
69 *Public mental health*, CMO report, DH, 2013
70 *Fuller Working Lives: a partnership approach,* DWP, 2017