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Early determinants of the ageing trajectory

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Over the past 250 years, human life expectancy has increased dramatically and continues to do so in most countries worldwide. Genetic factors account for about one third of variation in life expectancy so that most inter-individual variation in lifespan is explained by stochastic and environmental factors. The ageing process is plastic and is driven by the accumulation of molecular damage causing the changes in cell and tissue function which characterise the ageing phenotype. Early life exposures mark the developing embryo, foetus and child with potentially profound implications for the individual's ageing trajectory.

Maternal factors including age, smoking, socioeconomic status, infections, nutritional status and season of birth influence offspring life expectancy and the development of age-related diseases. Although the mechanistic processes responsible are poorly understood, many of these factors appear to affect foetal growth directly or via effects on placental development. Those born relatively small i.e. which did not achieve their genetic potential *in utero*, appear to be at greatest disadvantage especially if they become overweight or obese in childhood.

Early life events and exposures which enhance ageing are likely to contribute to molecular damage and/or reduce the repair of such

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damage. Such molecular damage may produce immediate defects in cellular or tissue function that are retained into later life. In addition, there is growing evidence that early life exposures produce aberrant patterns of epigenetic marks that are sustained across the life-course and result in down-regulation of cell defence mechanisms.

Introduction

Over the past 250 years, average human lifespan has doubled from pre-industrial values of 35–40 years. Until the mid 19th century, much of this enhancement in life expectancy was driven by dramatic improvements in childhood mortality but in the last 50–60 years most of the increased lifespan is attributable to reduced morality in adulthood. Globally, in 1955 average life expectancy at birth was only 48 years but, by 2000, this had increased to 66 years and it is anticipated to be 73 years by 2025. Over the past 10 years, average life expectancy at birth has increased by approximately 2 years in both low- and high-income countries.[1] This postponement of mortality has resulted in the rapid growth of the very old (those >85 years) and in the emergence of substantial numbers of the extremely old (>100 years).[2] However, not all societies have benefited from this worldwide phenomenon and the stagnation, or decline, in life expectancy over the final 3 decades of the 20th century in the former communist countries of Eastern Europe is particularly noteworthy.[3]

The importance of genetics as a determinant of lifespan is evident from the greater concordance of length of life among monozygotic twin than among same sex dizygotic twin pairs and such studies suggest that the heritability of lifespan is approximately 0.23–0.33.[4] Candidate gene approaches have confirmed the association of variants in the *APOE* and *FOXO3A* genes with longevity in studies of centenarians[4] whilst the deleterious effect of the *APOE 4* variant on survival to advanced age has been reported recently in independent studies of Danish[5] and Dutch cohorts – the latter using a genome-wide association study (GWAS) approach.[6] Although its function remains unknown, the age-related decline in the concentration of dehydroepiandrostonesulphate (DHEAS) – the most abundant circulating adrenal steroid – is associated with increased risk of disease and may contribute to diminished longevity.[7] A recent meta-analysis of GWAS involving almost 15,000 individuals identified 8 independent common single nucleotide polymorphisms (SNPs) associated with DHEAS concentration and may help explain the link between DHEAS and ageing.[7] Results from other GWAS are likely to lead to the discovery of more genetic loci which explain the heritable fraction of longevity but the spectacular gains in human lifespan over the last few generations is potent evidence that the plasticity of human ageing is largely environmentally determined.

Maternal factors acting *in utero* can have a profound effect on life expectancy. For example, in 3 rural Gambian villages where there was marked seasonality in dietary adequacy and in prevalence of infectious disease, the likelihood of early death in adulthood was nearly 3 times greater for those born in the nutritionally debilitating "hungry season" compared with the "harvest season".[8,9] This effect was attributed to impaired development of the immune function in those who were nutritionally compromised *in utero* or in early post-natal life[9] – an hypothesis which is supported by the finding that thymic function may be programmed adversely by prenatal under-nutrition.[10] In addition, maternal exposure to severe infection may influence health in later life as demonstrated by the negative effects on self-reported health of adults aged >50 years[11] and on risk of death from cardiovascular (CVD) and respiratory diseases[12] in those who were exposed *in utero* to the 1918 influenza pandemic.

There is ample evidence that ageing and risk of mortality are socio-economically patterned with higher rates of mortality among the more socio-economically disadvantaged. Preston et al[13] have argued that such findings are unsurprising because healthiness and longevity are nearly universal goals and those with greater economic and social resources are more able to achieve these goals. In their investigation of the childhood social and economic circumstances which predicted survival to age 85 years among African–Americans, Preston et al[13] discovered that longer life was associated with having a farm background and literate parents and living in a two-parent household. In addition, childhood and adult mortality were positively correlated[13] indicating that i) factors which operated on mortality