Appendix H3

A life course approach to healthy ageing: the HALCyon programme

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There is a growing consensus from scientists, research funders and policy makers that ageing needs to be studied from an interdisciplinary and life course perspective, to inform strategies for maintaining a population that remains healthy and independent for longer. Healthy ageing is a term that is used a lot but rarely defined which inhibits both the research and policy agendas. In our research, we use the term biological ageing to capture the progressive generalised impairment of function ('senescence') that occurs post-maturity, caused by multiple factors, such as the growing dysregulation of homeostatic equilibrium, inflammation, oxidative stress, and loss of immune function. There is a growing consensus that molecular and cellular damage that underlies ageing starts *in utero* and accumulates across life. We defined *healthy biological ageing* as including three components: first, survival to old age; second, delay in the onset of chronic diseases or disorders (the compression of morbidity); and third, optimal functioning for the maximal period of time, both at the individual level (measured by self reports or objective tests of capacity to undertake the physical and mental tasks of daily living), and at the molecular, cellular & body system levels. Our research focuses on this third component of healthy ageing. Our preferred terms to describe functioning at the individual level are *physical and cognitive capability*, the capacity to undertake the physical and mental tasks of daily living; these terms emphasise the positive and are distinguished from the functioning of each of the many different body systems on which these tasks depend(*Cooper et al., Richards et al. OUP in press*).

Healthy ageing is also viewed, especially by older people themselves, as maintaining *psychological and social wellbeing,* namely how one feels and functions socially, as individuals grow older. Unlike physical and cognitive capability, there is little evidence for a decline in psychological and social wellbeing with age, except perhaps at the very oldest ages. However, it is important to study wellbeing because as evidence grows that most people age with some form of chronic disease or disorder, then finding ways to support wellbeing, despite health challenges, gain importance; either through supporting the individual or changing the environment.

A life course approach to healthy ageing

There is growing evidence from life course research in the population sciences that the ability to respond adaptively, either biologically, mentally or socially, is governed not only by current environmental challenges and genetic factors, but also by the response to earlier life challenges, especially at times of developmental plasticity. However most studies of healthy ageing to date are cross-sectional and define thresholds, based on one or more criteria, to distinguish healthy agers from others.

A growing research area is to harness the power of cohort studies to investigate functional ageing trajectories, their lifetime determinants and consequences. The UK has an enviable wealth of birth cohort studies as well as longitudinal studies starting later in life. The birth cohort studies are maturing into studies of ageing. Combining information from several cohorts maximises their value, by increasing power to detect associations, and testing whether these associations are robust and generalisable

across cohorts, or differ in response to changing societal conditions. This requires comparable data across studies, as well as the development of longitudinal methods to model ageing and risk factor trajectories and additional methods to combine data across cohorts. There are a growing number of collaborative networks of cohort studies of ageing, of which Healthy Ageing across the Life Course (HALCyon: www.halcyon.ac.uk) is one, and IALSA (Integrative Analysis of Longitudinal Studies of Aging: www.ialsa.org) is another.

Outline of the HALCyon research programme

HALCyon, funded by the New Dynamics of Ageing cross council research programme 2008-2013, brought together investigators on nine cohort studies covering 30,000 participants born between 1921 and 1958, to investigate how healthy ageing is affected by factors operating across the whole of life. Our focus is on three domains of healthy ageing: (1) physical and cognitive capability (2) psychological and social wellbeing, and (3) biological ageing at the cellular and physiological system levels. As well as looking at their inter-relationships, the factors chosen for investigation included: lifetime socioeconomic factors, childhood cognitive ability and education; diet and body size. This choice partly was based on scientific evidence, at least from single studies, that these life course factors are important in healthy ageing; the aim of HALCyon therefore was to supply more robust cross cohort evidence. The choice was also pragmatic as these factors were available in several of the cohorts.

HALCyon's analytical strategy is threefold: to undertake (1) systematic reviews and, where appropriate, meta-analyses of all available studies; (2) new cross cohort research with harmonised data, consistent analysis, and investigation of confounding variables, and (3) exploit special features of single cohorts for in depth analysis.

By January 2013 results from the HALCyon research programme had been disseminated via the publication of 31 papers, with a further 10 in press or submitted for publication. There is also a book due to be published at the end of 2013 with Oxford University Press on '*A life course approach to healthy ageing*.' Please see appendix for a list of HALCyon publications.

The results from HALCyon do not directly map on to the questions posed by the Commission. I have therefore attempted to provide some answers to these questions, using HALCyon research where relevant.

1. How does healthy ageing differ for current older people compared to previous generations?

In regards to disease trends, Christensen and colleagues provided evidence from high income countries suggesting a rise in chronic diseases among older people. This is likely to reflect increased duration of time living with disease because of earlier diagnosis, improved medical care resulting in reduced case fatality, and the ever-widening boundaries of definitions of diseases or disorders that are seen to require medical intervention. A recent publication from the MRC National Survey of Health and Development (*Pierce et al 2012*) showed that for this early post war British cohort just reaching retirement age, individuals, on average, had two out of a possible 15 clinical disorders that medical consensus would indicate require monitoring or treatment by 60-64 years and only one in six was disorder free. Thus most individuals age with a chronic condition.

In terms of disability or reports of functional limitations, the data are inconsistent and limited over time and across countries; however, a decline in the prevalence of severe disability is observed against a background of increasing prevalence of mild disability. UK data are no exception in being inconsistent and limited. Robine and colleagues concluded that as of 2009 there was no strong evidence of compression of morbidity or disability in high income countries with the lowest mortality; the three countries where there was evidence of a compression of disability in recent decades, Denmark, the

Netherlands, and the US, had all lagged behind the low mortality countries in terms of life expectancy at age 65.

Within country trends Deeg and other have revealed striking social inequalities, with more educated and socially advantaged groups being more likely to experience a compression of morbidity or disability than less educated or socially disadvantaged groups

There is a need to investigate possible birth cohort effects. For example, in the UK there is the golden generation, centred on the 1931 cohort that has had lower mortality rates at each age compared to earlier or later born cohorts (Murphy). However, we do not have good evidence about whether their health was also better at each age. Trends in mortality and morbidity do not necessarily go together.

HALCyon contribution: Studies investigating the evidence for trends in disability or functional limitations usually rely on self-reported responses to rather limited questions. What is needed is to study trends in objective measures of physical and cognitive capability for which there is growing evidence from HALCyon and elsewhere that these are reliable indicators of ageing. Two systematic reviews showed that reduced performance on grip strength, walking speed and chair rise time was consistently associated with subsequent mortality and morbidity (*Cooper et al. BMJ 2011, Cooper et al. Age and Ageing 2011).* With harmonised HALCyon datasets we have shown that performance on all these measures declines with age, and that gender differences in grip strength diminish with increasing age (*Cooper et al. PLOS One, 2011).* Using the Warwick and Edinburgh Mental Wellbeing Scale (WEMWBS), Gale and colleagues have shown no evidence of change in the mean wellbeing score by age across the HALCyon cohorts (*Gale et al, PLOS One 2012*). However HALCyon is unable to contribute to the question of cohort changes at the current time because, despite the large sample size and number of cohorts, there was insufficient variation in birth year at any given age to explore cohort differences. We need to encourage other cohort studies to include these measures using standardised protocols. The US toolbox (www.nihtoolbox.org) and forthcoming MRC guidance on healthy ageing indicators promote the use of such measures.

2. Can and should we maintain our expectations and views of health in older age compared to young age?

This question is a little ambiguous. If it means 'should we expect not to have any changes in our health as we get older' then that would seem unrealistic. However there is variability in age at onset and rates of functional decline, and the striking differences between social groups suggests that there are opportunities for improving the health in later life of those living in more adverse socioeconomic circumstances. Evidence that inequalities in wealth and income have widened since the 1980s strongly suggest there are grounds for increasing concern.

HALCyon contribution: HALCyon research has provided robust evidence that we should take socioeconomic circumstances in childhood as well adulthood into account if we are trying to improve capability at older ages. A HALCyon systematic review and meta-analysis showed modest associations between childhood SEP and walking speed and chair rise time that remained after adjustment for adult risk factors; this translates into an 11% increase in mortality for those who were most deprived compared with those who were least deprived. *Birnie, Cooper et al. PLOS One 2011.* In a HALCyon in depth study in NSHD, Murray et al. (*AJE, in press*) showed that lifetime area level characteristics, as well as individual level characteristics, influence physical capability. Early experience is also important for adult cognitive capability: a HALCyon and IALSA study across three cohorts showed that midlife fluid cognition was associated with childhood cognition and level of educational qualifications (*Clouston et al. IJE 2012*). Gale and colleagues have also shown in the HALCyon cohorts links between factors childhood cognitive ability and other earlier life factors and adult anxiety and depression (*Gale et al Psychological Medicine 2011*) building on an established field of research usually based on single cohort studies. They have shown similar and more novel findings in relation to adult wellbeing (*Gale et al PLoS One 2012*),

One question commonly asked is whether 'it all goes together when it goes'. While strong cross sectional evidence shows that physical and cognitive capability are strongly correlated, far fewer longitudinal studies exist. A HALCyon/IALSA systematic review of the dynamic relationship between physical capability, lung function & cognition in longitudinal aging cohorts (*Clouston et al, Epidemiologic Reviews 2013*) identified 36 studies of interest, but only 7 had investigated *change* in fluid cognition with *change* in physical capability/lung function. Overall, findings were not sufficiently strong or consistent to support evidence of a common process of decline. Operationalisation and measurement challenges limited comparability, again identifying the need for common protocols and approaches.

Another relevant question is how capability is related to wellbeing. There is reasonable evidence that wellbeing may be protective of physical and cognitive capability, as well as being affected by functional decline (*Gale et al. OUP, in press*). A recent HALCyon cross cohort paper showed that higher levels of physical capability were associated with higher levels of subsequent mental wellbeing (as measured by the Warwick Edinburgh Mental Wellbeing Scale (WEMWBS)). However these associations were modest, and adjustment for potential confounders including age, gender, socioeconomic position, living alone, health status and neuroticism explained a large part of these associations (*Cooper et al., submitted*). The next step is to identify key factors that may modify the relationship between physical and cognitive capability and wellbeing.

3. Should 'ageing' itself be considered a disease or condition that requires remedy or should it be embraced as a positive stage of life?

There are different answers to this question for different aspects of the ageing process. Getter older is inevitable and improving opportunities for older people and encouraging a positive assessment of growing older, by individuals and by society, would clearly be a good thing. Being valued, and valuing oneself, for the experience, wisdom and expertise that can come with growing older is something to strive for. Having said that, identifying effective ways to maintain physiological resilience in order to slow down the onset of chronic disease or the rate of functional decline is also a goal worth striving for so that people can choose to stay active and independent for longer. And we also need to find effective ways (via the environment or personal characteristics) of social and psychological adaptation so that individuals can remain active and maintain wellbeing in the face of biological ageing.

4. What needs to be done to ensure that we remain healthy for as long as possible as we age?

<u>HALCyon contribution</u>

This seems a simple question but is deceptively complex. Clearly from a life course perspective we should aim to maximise the level of peak function achieved at maturity as well as modifying the age at onset and rate of functional decline.

Modifiable factors, such as diet are thought to be important for physical and cognitive capability at all stages of life but robust evidence from cross cohort studies has been inconsistent and limited (*Mishra et al., OUP in press*), and not supported by trial evidence. The lack of harmonised measures across cohorts limits comparisons. For example, creating harmonised dietary measures from food frequencies questionnaires and dietary diaries in the HALCyon cohorts was very challenging and limited cross cohort comparisons; studies in single cohorts were thus undertaken, for example showing small associations between diet and physical capability (*Mulla et al. Age and Ageing 2012)*. There is more robust evidence from observational studies, randomised control trials and experimental studies of the importance of physical activity. Various HALCyon cohorts have contributed to this evidence (e.g. *Cooper AJPM 2011*) but cross cohort comparisons were not possible because of the different methods used to measure activity.

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HALCyon research has shown that early life factors are associated with later life capability, either through maximising peak level of function at maturity or its rate of decline. For example, there is robust HALCyon evidence that birth weight is positively related to subsequent grip strength; in children, young adults and in those at older ages *(Dodds et al. JNHA 2012)*, suggesting that factors *in utero* or early postnatal life may leave long-term biological imprints on later life function. There is evidence from single cohorts (e.g. NSHD) that growth in the prepubertal and pubertal periods is also important.

There is evidence from eight of the HALCyon cohorts (*Hardy et al., PLoS One in press*) and other studies that adult adiposity has negative associations with physical capability. Greater adiposity was associated with worse physical performance on three tests; the detrimental impact was greatest in the highest two fifths of BMI, and generally stronger in women than men. Low grip strength was also associated with poorer performance: again, associations were generally stronger in women than men; and particularly poor performance was seen in those in the lowest fifth of grip strength. BMI and grip strength were independently associated with performance and no consistent evidence of effect modification.

Despite high estimates of heritability, the evidence of genetic effects on physical and cognitive capability is limited. Across the HALCyon cohorts and relevant studies, we showed no consistent evidence of associations between physical capability and common polymorphisms of: (1) *TERT*, a telomere maintenance gene (*Alfred et al., Aging Cell, 2011*); (2) *ACTN3*, a genotype related to athletic status (*Alfred et al., Human Mutation*, 2011); (3) Genetic variants on the growth hormone and IGF-1 axis (*Alfred et al., PLoS One, 2012*); and (4) Genetic markers of bone & joint health (*Alfred et al., Bone, 2013*). Davies et al. (*Davies et al, OUP, in press*) have also provided a plethora of genetic insights into ageing.

The HALCyon associations between change in telomere length and physical capability were also weak and inconsistent (*Gardner et al., under review*). Here we have contributed through the technical and methodological work undertaken. Measurement of telomere length in four of the HALCyon cohorts has resulted in the creation of one of the largest telomere datasets in the world (n=6,200) including repeat measures in a significant proportion (n=2,100). Work so far includes inter-lab comparisons of telomere measurements (*Zglinicki et al., forthcoming*), and a systematic review of gender differences in telomere length (*Gardner et al., forthcoming*). Telomere length is now thought unlikely to be a robust marker of biological ageing; a biomarker index may be more fruitful but the strongest contenders are biomarkers of physiological systems (e.g. lung function and grip strength) rather than markers at the molecular or cellular levels (*Zglinicki et al., OUP in press*).

Somewhat more positive were the results of the relationships between markers of the HPA axis and physical and cognitive capability. Across 4 HALCyon cohorts and 2 other studies a larger diurnal drop in cortisol was associated with faster walking and chair rise speed (*Gardner et al., Psychoneuroendocrinology, 2012*); however, there was little evidence of associations with grip strength or standing balance. These results were cross sectional. In a single cohort study (Caerphilly), higher cortisol levels measured twenty years earlier, were associated with walking speed, in ways that suggested that the ability to mount a good stress-induced response may be a marker of a more reactive and healthier HPA axis (*Gardner et al., IJE 2012, Ben-Shlomo et al., OUP in press*).

5. Are there cultural, ethnic or socioeconomic factors that help to promote or prevent healthy ageing?

The evidence referred to above is clear on the role of lifetime socioeconomic conditions affecting physical and cognitive capability, and indeed their role in other aspects of healthy ageing have been well described. HALCyon has not contributed to the study of ethnic or cultural differences in healthy ageing because few of the HALCyon cohorts are ethnically diverse.

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