Changing course in ageing research: The Healthy Ageing Phenotype

Oscar H. Franco, Kavita Karnik, Gabrielle Osborne, Jose M. Ordoval, Michael Catta, Frans van der Ouderaa

1. Introduction ............................................................................................................................... 14
2. The world is ageing .................................................................................................................. 14
3. The malleability of the ageing process .................................................................................... 14
4. Yin and Yang: vulnerability and resilience ............................................................................ 14
5. Ageing and the “Healthy Ageing Phenotype” ....................................................................... 15
6. Once ill always ill? Once frail? .............................................................................................. 15
7. Multiple tissues but common pathways: mechanisms and biomarkers of the HAP .......... 15
8. A healthy lifestyle the key to healthy senescence ................................................................. 15

© 2009 Elsevier Ireland Ltd. All rights reserved.
1. Introduction

“Prevention is better than cure”
Desiderius Erasmus (1466–1536)

The age distribution of the world’s population is dramatically shifting; longevity continues to rise and there are steady improvements in healthcare, but there is not an accompanying increase in fertility rates [1,2]. In total, the global proportion of people aged above 60 years is expected to increase from 10% to 21% in the next 5 decades [3]. However, research into how to achieve healthy ageing and which life-time trajectories are associated with positive health and wellbeing in older age, is still relatively under-researched. Hence, to identify alternative perspectives in ageing research, Unilever and the Medical Research Council (MRC) of UK convened a Spark workshop entitled ‘The Healthy Ageing Phenotype’ [4]. Spark workshops are strategic meetings in which scientists from different disciplines and perspectives, share knowledge, build novel concepts, and assess options for future research activities. In this particular meeting, international specialists from complementary fields gathered to:

(i) find clear attributes and definitions of the ‘Healthy Ageing Phenotype’;
(ii) identify potential mechanisms and interventions to improve healthy life expectancy of the population;
(iii) highlight areas on ageing research that should be prioritised for the future.

2. The world is ageing

Global life expectancy in the last two centuries has been increasing linearly and does not appear to be approaching a plateau [2]. Longevity in best in class countries has risen by approximately 3 months per year for the past 170 years and average mean life expectancy is forecasted to be 96.4 years in 2050 [2]. Incessant progress in the prevention of mortality as a result of advances in income, hygiene, sanitation and infection control, nutrition, education, and medicine, is generally believed to account for the increases in longevity [2]. Concomitantly, fertility rates are falling, leading to an unprecedented shift in demographics [1–3]. Nevertheless, increases in life expectancy and in the proportion of individuals living longer do not necessarily translate into improvements of health and wellbeing [5,6]. Indeed, many countries, although experiencing steady increases in longevity, are suffering from stagnation of healthy life expectancy and a greater burden caused by chronic conditions and disability [5,6]. For example, in the UK between 1991 and 2001, life expectancy increased by 2.2 years but only 0.6 years were healthy years [5,7]. Disparities in life expectancy between the best and worst (electoral) wards in the U.K. exceed twenty years [8] and increasing healthy life expectancy across the world has been identified as a key objective for research [5,7].

3. The malleability of the ageing process

The recent history of human longevity demonstrates that the ageing process is malleable to a significant degree, but the extent of this has not yet been fully explored in humans as the majority of research on this area has been conducted in lower animal models (e.g., nematodes, flies) with a limited degree of extrapolation [4,9]. Ageing is a multi-factorial process and it is vital to understand the mechanisms associated with ageing and that determine healthy life trajectories [10,11]. Aberrant gene expression, for example, is strongly involved in processes leading to the development of diseases that restrict lifespan and some have suggested that genetic factors may also underlie the ageing process itself [12,13]. However, the ageing process seems to occur at different rates in different tissues and appears to have a considerable stochastic element [11,14]. Although twin studies suggest that genotype explains roughly 25% of differences in life expectancy, the role of environmental and lifestyle factors (such as pollution, infections, stress, physical inactivity, psychological wellbeing, health infrastructure and financial security), combined with an element of chance, are also important and could account for the remaining variance [12,15,16]. It has been claimed that the influence of the environment is permanent and starts immediately after fecundation [17]. For example, several studies, have reported that the intrauterine environment has short-term influences on health outcomes as well as long-term influences on the development of diseases during adulthood [17–19]. Low birth weight and being born small for gestational age have also repeatedly been associated with development of diabetes, hypertension and cardiovascular disease (CVD) at middle age [17–19].

4. Yin and Yang: vulnerability and resilience

It is important to note that ageing over the life course is not necessarily a steady decline from optimal physiological performance in early adulthood to poor functioning in late adulthood. To a large extent, remarkable physiological resilience in early stages of the ageing process reduces the negative effects of external stressors such as smoking, infections, psychological stress, sedentarism and poor dietary habits and these stressors do not visibly induce morbidities at a young age. By resilience, we mean the capacity to maintain adequate function and structure at molecular and cellular levels by adapting or changing to specific challenges [20,21]. This process relies on the interaction of multiple mechanisms that aim to preserve physical and psychological stability and homeostasis to ensure that the individual remains outside the realms of disease. The integrity of these homeostatic mechanisms determines the deviation from normality; deviation can be generalised or tissue-specific and is not necessarily clinically manifested [20,21]. An adequate detection and measure of the level of resilience/vulnerability is key to identify the processes that lead from health to frailty and ultimately to the appearance of disease and death [20,21]. A further exploration of the nature of resilience and the way we can prevent permanent dysregulation would provide significant insights into the healthy ageing process.
5. Ageing and the “Healthy Ageing Phenotype”

Ageing is often defined as the progressive loss of function accompanied by increasing morbidity and decreasing fertility with advancing age [10,11,14]. However, although ageing is the most significant risk factor for the appearance of morbidities, the ageing process starts in-utero and is not necessarily accompanied by the presence of disease and poor quality of life. Life and ageing are practically synonymous and one cannot occur without the other. Unlike ageing, poor health is not a sine qua non-condition of life. As life starts so does the chance of departing from health. This chance increases with ageing and is determined by an intricate network of mechanisms that aim to maintain or recover corporal and mental homeostasis [10,11,14]. The ‘Healthy Ageing Phenotype’ (HAP) can be defined as the condition of being alive, while having highly preserved functioning metabolic, hormonal and neuro-endocrine control systems at the organ, tissue and molecular levels. It is further characterised by having a higher degree of physiological complexity in aspects of functioning such as heart rate variability, neuronal structure and bone architecture, which is associated with a biologically younger body. The HAP represents optimal reserve and biological resilience to respond to and accommodate daily environmental stressors, which translates into the absence of debilitating conditions (e.g., CVD, dementia, cancer) and the presence or maintenance of other important aspects of human functioning (e.g., cognitive and physical function). The HAP is multi-dimensional, age and gender-dependent and determined by the interaction between our genes, acquired epi-genetic imprinting and environmental factors.

6. Once ill always ill? Once frail... 

To some extent frailty is the inverse of the Healthy Ageing Phenotype, but the precise extent to which they are two sides of the same coin is as yet unclear. There is no universal definition of frailty, but it is thought to be a multi-factorial dynamic state which occurs as a result of deleterious changes in the homeostatic network [20–24]. Cumulative defects alter the homeostatic network and lead to multi-system dysregulation and a decline in the adaptive capability to respond appropriately to stressors (the effect of stressors is likely exacerbated by poor lifestyle choices). Thus, frailty presents as a complex set of conditions including sarcopenia, osteoporosis, poor motor function, impaired energy metabolism, extreme values of BMI, poor nutritional status, blood pressure instability and vulnerability to infection [20–24]. Although frailty is not a disease and it can occur independently, its presence increases the risk of development of disease, disability and death, and can occur subsequent to disease [22,24]. For example, the occurrence of frailty (as measured by a 1 category increment in the Clinical Frailty Scale) has been independently associated with a 20% increase in the risk of death and with increased risk of developing CVD [25,26]. Furthermore, different pre-disease states such as insulin resistance and atherosclerosis have been associated with the development of frailty [20–22,24]. Nonetheless, frailty is to a large extent a reversible state that could be adverted or ceased by restoring resilience and homeostasis [20–22,24]. One way to tackle frailty is through the use of pharmacological interventions. An alternative approach is to focus on lifestyle changes such as increased physical activity, smoking cessation and adequate dietary and sleep patterns as they may hold the key to improvement and/or reversal of frailty. It is also worthwhile to explore interventions and preventive strategies that combine pharmacology and lifestyle interventions as this may be the most fruitful way to achieve absence of frailty and disease.

7. Multiple tissues but common pathways: mechanisms and biomarkers of the HAP

Many chronic conditions share common underlying pathways and are lifestyle and age dependent (Fig. 1). For example, high-energy intake (diet) with low energy expenditure (physical activity) results in increased visceral obesity, insulin resistance and vascular inflammation. These conditions are associated with loss of metabolic flexibility (i.e., dysregulation of lipid and glucose fluxes), which may lead to CVD, diabetes and neuro-degenerative disease. This metabolic dysregulation is also associated with age-related cognitive decline and several mechanisms have been suggested to underlie this relation including microvascular and macrovascular disease, inflammation, adiposity, and insulin resistance [27]. Age-related hormonal changes, such as menopause, may contribute to this situation as a decline in circulating estrogen levels affects adiposity, lipid metabolism, and prothrombotic states which are associated with an increased risk of CVD [28,29]. To prevent the accumulation of damage to the homeostatic balance, early identification of incipient dysregulation, before levels of vulnerability progress to a pathological level, is essential [20,21]. This will allow the development of interventions to target specific pathways associated with multiple chronic conditions and morbidities and deliver effective prevention strategies. Due to the complexity of conditions such as frailty and metabolic dysregulation, an ‘integrated physiology’ (systems) approach is appropriate. This will allow a comprehensive understanding of these conditions and it will enable the identification of common pathways associated with dysregulation and how to preserve or reverse them.

In addition it is crucial to shift from a strategy of solving complex multi-morbidities in old age to strategies that target the population earlier in life and aim to prevent complex dysregulation. Rather than approaching this from an ‘individual high risk’ strategy, it should be a ‘population based’ risk reduction strategy where people are encouraged early in the ageing process to be proactive and maintain homeostatic balance through methods such as adopting a healthy lifestyle.

8. A healthy lifestyle the key to healthy senescence

The activities of daily living and lifestyle are very important factors in the maintenance of the homeostatic network. Several studies have demonstrated the health benefits of physical activity and adequate cardio-respiratory fitness [30,31]. Physical activity has its effect through a variety of mechanisms (e.g., lowering the inflammatory response and positively attenuating several risk factors for CVD), and is associated with decreases in the risk of developing diabetes, CVD and mortality, as well as improvements in wellbeing [11,30,31]. In addition to physical activity, eating habits contribute to the delineation of our life course trajectories [32,33]. For example, experiments in rodents and lower animals have suggested caloric restriction is a potential route to healthy senescence, however, when this approach was applied to humans it was not fully suitable [34]. Nonetheless, diet and different dietary factors have been associated with positive health outcomes including reduction on mortality and of CVD and its risk factors [32,33,35]. Several studies have explored other aspects of a ‘healthy lifestyle’ and shown that in more than eighty thousand American nurses characteristics such as non-smoking, normal body mass index levels, moderate alcohol consumption, above moderate physical activity and a healthy diet was associated with a 83% reduction of coronary heart disease and 91% reduction on the risk of developing diabetes [36,37]. Supporting evidence on the additive effect of several interventions targeting lifestyle factors not only comes from observational studies but also from experimental analyses. For
instance, the DPS (Diabetes Prevention Study) and DPP (Diabetes Prevention Program) studies confirmed the potential benefit of multiple lifestyle changes on prevention of diabetes [38,39].

9. On Morpheus arms

Another aspect of a healthy lifestyle is sleep quality and quantity. Although almost one third of human existence is spent sleeping, there is limited evidence about the impact of sleep on ageing. With age, quantity and quality of sleep deteriorates and given that there has been a reduction in the population's total average sleep time over the past 100 years the relative impact of these changes could increase [40,41]. Among Americans, for example, the modal sleep duration has decreased 1 h (from 8 to 7) in the last four decades [40]. Recent studies have demonstrated that even relatively short periods of sleep restriction lead to increased visceral adipose tissue and cardio-metabolic risk [40,41]. Researchers have also started to explore the converse effects of sleep and shown that good sleep is related to positive psychological states [42], although the directionality (i.e., does good sleep lead to higher wellbeing or vice versa) and underlying mechanisms of this relationship remain unclear. The role of sleep in maintaining the healthy phenotype throughout the life course has been under-researched and further efforts are required to clarify the mechanisms that lead from sleep disturbances to metabolic abnormalities and deterioration of health, as well as research on potential interventions that could improve the characteristics of populations' sleep patterns.

10. A sound mind in a sound body: wellbeing and health

In addition to studying the physiological homeostasis of the body it is important to understand the psychological determinants that enable people to flourish (i.e., wellbeing) and how this relates to optimal mental and physical functioning. Wellbeing is a complex multi-dimensional concept and there are two main approaches to its study: the eudaimonic approach (also known as psychological wellbeing) centres on the fulfilment of personal potential and living a meaningful life and is concerned with having purpose in life, self-acceptance, personal growth and positive inter-personal relations. The hedonic approach (also known as subjective wellbeing or happiness) refers to personal satisfaction, happiness and contentment [43]. Researchers have shown that wellbeing has an important bearing on the trajectories of ageing [44–46]. Findings from the Whitehall II study, for example, have shown that high levels of wellbeing are associated with reduced neuro-endocrine, inflammatory, and cardiovascular activity [47]. In relation to lifestyle factors, high levels of wellbeing have been associated with a healthier lifestyle. Wellbeing can also be discussed in terms of psychological resilience (preservation of wellbeing in the face of adversity), which research has demonstrated to have a positive effect on health. For example, adequate management of stress has been associated with a 24% decrease risk of stroke [48]. This suggests that interventions should sustain both physiological and psychological homeostasis to maintain resilience and subsequently the absence of frailty and disease [49].

Although the integrated study of the biology and psychology of optimal functioning and its relation to health is a relatively new area of research, and further research is required to understand these relations, it holds considerable promise and will contribute to our understanding of healthy mental and physical functioning across the lifecourse.

11. Multi-dimensional problems might need multi-dimensional solutions

The current paper has provided a brief overview of a variety of lifestyle, environmental, psychological and physiological factors that play a role in healthy ageing. What this highlights is that there is not necessarily a single mechanism that underlies healthy ageing, and although there may be common pathways it is important
to approach the preservation of the ‘Healthy Ageing Phenotype’ through the implementation of multi-factorial strategies. It may be that the best approach is a combination of single interventions with multiple and multi-systemic effects. However, current medical care and scientific research tend to be compartmentalised and performed in secluded silos, which means it is unlikely that integrated ‘solutions’ can be developed to improve healthy longevity. For example, the lack of success in preventing and halting current global epidemics of obesity, diabetes and CVD can be attributed in part to the lack of synergism of numerous isolated efforts dealing with these conditions. Wald and Law [50] commented on the inadequacy of this strategy in the BMJ: “current treatment to prevent heart disease… has generally been limited to single risk factors… a large preventive effect would require intervention in everyone at increased risk irrespective of the risk factor levels; intervention on several reversible causal risk factors together; and reducing these risk factors by as much as possible”. Consequently, to stop the current epidemic of CVD, Wald and Law proposed the Polypill—a theoretical combination of six pharmacological compounds (a statin, three antihypertensives, aspirin and folic acid) that could reduce CVD by over 80% [50]. However, the Polypill is a pharmacological solution to inherent consequences of our lifestyle and thus, cannot and should not constitute the long-term solution to our current ailments. Alternative approaches such as dietary modifications could play an essential role in the treatment and prevention of chronic disease. We argue that while the polypill approach is appropriate for high risk individuals, others would benefit from multi-dimensional interventions that aim to make overall lifestyle modifications including dietary improvements, increases in physical activity, smoking cessation and improvement of wellbeing and sleep habits. This multi-dimensional approach should not be the exception in prevention and healthcare but the rule, and in the footsteps of the Diabetes Prevention Study [39], it is vital that intervention studies address the potential of multi-dimensional interventions for extending healthy longevity.

Although both pharmacological and lifestyle interventions contribute to the prevention of major lifestyle chronic conditions (e.g., hypertension and diabetes), there has been a historical lack of resources into research on prevention. Now is the time to address this and invest in research on effective strategies for behaviour modification (whether it be through pharmacological and/or lifestyle means) to optimise lifestyle at different stages of the lifecourse. A more holistic, multi-disciplinary approach that is centred on biological resilience, its maintenance and how to reverse early deviations in the homeostatic balance before they become pathological trajectories is urgently required.

12. Exploring the other side of the moon: a new world demands a change of course

In conclusion, human life expectancy has been increasing linearly and is not expected to stop in the near future [2]. With increases in life expectancy the distribution of the population has changed dramatically and the chances of living to an old age are increasing, but so is the probability of time spent with disease and disability. A new society, with novel characterististics and new needs is emerging and research into healthy longevity requires an innovative approach: multi-factorial prevention and treatment of frailty, disability and disease seems the most appropriate way to steer the population to a healthier phenotype. This new strategy should be the focal point of scientific research and health care in the years to come. Although significant efforts may be required to implement the strategy, the potential rewards are tangible and of vast size, and the health expectations of the new generations demand it.

13. Recommendations

(i) Ageing over the lifecourse is not necessarily a steady decline from optimal physiological performance in early adulthood to poor functioning in late adulthood. To a large extent, remarkable physiological resilience along the ageing process reduces the negative effects of external stressors such as smoking, infections, psychological stress, sedentarism, poor dietary habits and alcohol misuse. Further research is required to understand the nature of this resilience and how to prevent permanent dysregulation as we age.

(ii) To more adequately identify reversible stages preliminary to disease and frailty it is important to differentiate between biomarkers appropriate for screening, diagnosis and prognosis and to develop new biomarkers that could provide a more effective early discrimination (discernment). This is important because an understanding of the onset of pre-disease/frailty conditions may lead to insights into how to delay or even reverse symptoms.

(iii) Cardiovascular fitness is a strong predictor of mortality in older populations. Improved physical fitness can lead to metabolic and muscular-skeletal benefits as well as improved brain function. Benefits are even observed for modest levels of physical activity and late onset of activity. Nonetheless, in the context of healthy ageing, the data on physical activity is sparse and largely qualitative. Physical activity is likely to be one of the key factors in determining maintenance of health and preventing frailty over the lifecourse, and thus, there is a need for a much better understanding of the relationship between the nature and duration of physical activity and health outcomes.

(iv) There is evidence to show that even short periods of sleep debt and poor sleep quality have detrimental effects on physiological functioning, including a loss of metabolic flexibility and insulin resistance. With age, quantity and quality of sleep deteriorates and given that there has been a reduction in the population’s total average sleep time over the past 100 years the relative impact of these changes could increase. The role of sleep in maintaining the healthy phenotype throughout the lifecourse has been under-explored and this needs to be addressed.

(v) The integrated study of the biology and psychology of optimal functioning and its relation to health is a relatively new area of research that could provide promising insights into healthy ageing. For example, high levels of wellbeing have been associated with improved cardio-metabolic health, neuro-endocrine regulation, as well as, resistance to infection. However, both the underlying mechanisms and effective strategies for enhancing wellbeing across the lifecourse remain unclear. This should be an area of research to focus on in the future.

(vi) Both pharmacological and lifestyle interventions contribute to the prevention of major chronic conditions such as hypertension, insulin resistance, dyslipidemia and diabetes. Given the historical under-resourcing of research on prevention, there is a significant opportunity to invest in research on effective strategies for behaviour modification to optimise lifestyle at different stages of the lifecourse and to explore the potential of combined lifestyle and pharmacological interventions to achieve superior health and functionality outcomes.

(vii) Understanding the lifecourse trajectories followed by those living to old age while maintaining a satisfactory level of health and functionality could constitute a helpful route to identify and design optimal preventive strategies.

(viii) The future development of interventions and preventive strategies should also acknowledge the holistic nature of
human health. Research has shown that many age-related conditions share common underlying pathways, and thus to maximise the benefits of intervention and prevention strategies, it may be appropriate to target common pathways. The scope of lifestyle interventions towards the prevention of morbidity and mortality should incorporate positive modifications of diet, exercise, sleep and behavioural patterns as well as the preservation of emotional wellbeing.

(ix) A final recommendation relates to capability building: the ageing of the population could be regarded either as an important opportunity for society or a big societal threat. To keep positive and fruitful engagement of the older population we need to shift the population to a healthier phenotype. Ageing research will need integrated programmes comprising of multi-disciplinary teams, including basic and clinical scientists, clinicians, psychologists and behavioural scientists. Additionally ageing research should engage strongly with stakeholders groups notably the NHS (and equivalent organisations), government, charities and industry to ensure effective communication, translation and implementation of scientific findings.

Conflicts of interest

The authors report no conflicts of interest to declare.

Acknowledgements

The authors would like to thank Min-Min Teh, Lucy Boniface and Diana Parry for their collaboration in organising the Spark workshop and Dr. Jonathan Powell, Dr. Joe McNamara, Dr. Mark Pitman and Prof. Stephen Holgate for their valuable comments. The Spark meeting was jointly funded (50/50) by the MRC UK and Unilever Corporate Research.

List of Participants

Dr. Avan Aihie Sayer

Professor Michael Catt

Professor Eve van Cauter

Professor Tim Church

Professor David Crossman

Professor Luigi Ferrucci

Dr. Jane Fisher

Dr. Oscar Franco

Professor Linda Fried

Professor Tim Hardingham

Dr. Hilde Hendrix

Dr. Natalie Hiscock

Professor Albert Hofman

Professor Stephen Holgate

Dr. Kavita Karnik

Professor Tom Kirkwood

Professor Art Kramer

Professor Diana Kuh

Professor Lewis Lipsitz

Professor Janet Lord

Professor William Marsden-Wilson

Professor John Mathers

Dr. Joe McNamara

Professor John Morrison

Professor Linda Partridge

Dr. Mark Pitman

Professor Jose Ordovas

Dr. Frans van der Ouderaa

Professor Neil Poulter

Dr. Jonathan Powell

Medical Research Council Southampton, UK

Unilever Corporate Research, UK

University of Chicago, USA

Pennington Biomedical Research Center, USA

University of Sheffield, UK

Imperial College, UK

National Institute on Ageing (NIA), National Institutes of Health, USA

Medical Research Council, UK

Unilever Corporate Research, UK

University of Warwick, UK

John Hopkins Bloomberg School of Public Health, USA

University of Manchester, UK

Unilever Corporate Research, UK

Erasmus MC Rotterdam, The Netherlands

University of Southampton, UK

Unilever Corporate Research, UK

University of Newcastle upon Tyne, UK

University of Illinois at Urbana, USA

University College London, UK

Harvard University, Boston, USA

University of Birmingham, UK

Medical Research Council, Cambridge, UK

University of Newcastle upon Tyne, UK

Medical Research Council, UK

Mount Sinai Medical School, USA

University College London, UK

Medical Research Council, UK

Tufts University, USA

Unilever Corporate Research, UK

Imperial College, UK

Unilever Corporate Research, UK

References


[30] Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. JAMA 2007;297(May (19)):2081–91.


[50] Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ 2003;326(June (7404)):1419.