# Conceptualisations of successful ageing and leads for lifestyle modification

# Valorisation

## Successful ageing

If the twentieth century was the century of population growth, then the twenty-first century will become the century of ageing.[1] The number of old and very old adults (aged 65 and over, and 80 and over respectively) is rapidly rising in all European countries, and represents a progressively growing percentage of the general population.[2] At the same time, the proportion of working aged individuals is declining.[3] These changes in the population pyramid, as well as increasing life expectancy, is challenging the stability of health and social care systems.[4] Furthermore, age-related diseases are mounting as a result of healthy life expectancy lagging behind increased life expectancy.[1]

Biological ageing varies markedly between individuals,[5] and this disparity between individuals only grows with age.[6] Although partially genetically determined, 75 percent of human longevity is believed to be determined by modifiable factors including diet, lifestyle and socioeconomic status.[5] In order to understand whether any intervention aimed at promoting healthy ageing is effective, a benchmark for the assessment of healthy ageing is needed. Due to the multidimensional nature of ageing, and age-related pathologies, assessing healthy ageing by combining information across many different measurements would seem to be the solution.

In the past and maybe the present, health has been over simplified into single units of measure. Given this over simplification there is substantial room for the development of personalised health. This is particularly true in an era when we have the ability to measure everything that

matters, from activity trackers, sleep, vital signs, blood pressure, heart rate and stress and develop algorithms in combination with genetic and physiologic information for the purposes of making personalised recommendations.[7] We need to consider the synergisms and interactions between different aspects of human life in a broader sense. By understanding the dynamic ways in which we age, the ability to differentiate between exceptional disease-free ageing from one associated with increased frailty and decreased quality of life, will not only aid us in the comprehending disease and ageing processes but also grants us the opportunity to develop targeted therapies. However significant progress in this field has been hampered by a lack of consensus on the definition of successful and or healthy ageing.[8]

## Societal and economic relevance

Ageing and disease are intertwined but they do not have to be. But studying ageing gives us an insight into disease, and disease insight into ageing. Recent developments in scientific literature suggest it may be possible and realistic to slow the ageing process.[9] Delaying ageing could increase life expectancy by 2.2 years most of which could be spent in relatively good health, while saving 7.1 trillion dollars over the next fifty years according to an American simulation study.[9] The same efforts put into heart disease and cancer treatment would result in declining returns as improvements in health and longevity would diminish by 2060 according the same model.[9] Moreover, if chronic metabolic diseases were dealt with using appropriate dietary strategies, statistical models estimate the death insurance claims would drop by 13 percent, meaning a reduction in premature loss of life from preventable conditions.[10] Therefore, efforts to establish a definition, metric and benchmark of optimal or healthy ageing could potentially save trillions of dollars through the use of early targeted preventative health interventions.

## Relevance of new research methodology

Our research shows that complex measurements can be combined into meaningful metrics using data driven methods, and that these metrics are predictive of the risk of developing frailty. Specifically, we show that walking speed and dependency risk can be predicted over a nine-year period using a combined measurement. Moreover, we emphasise the usefulness of using data driven methods in this field from our failure to validate the Healthy Ageing Phenotype model that was based on systematic review of available literature. Not only does this method allow us to make use of a wide array of data, it demonstrates the potential value of future research using machine learning techniques.

The sequencing of the human genome opened the door to characterising traits of health and disease and linking it to genetic information.[11] However the function of many genes remains unknown, and what is known, is limited to a few cell types, tissues or physiological contexts.[11] Difficulties in information collection, differences in disease manifestations, descriptive phenotypes or disease subclasses requires extensive examination of the discrete components of disease phenotypes, information which is not typically recorded in medical charts and further complicates elucidation.[11] Delving into this information may help to link seemingly unrelated conditions which share common biological pathways and/or disease mechanisms[11] or help us better understand the process of cellular and organismal senescence.

By carefully examining the genes most likely to be involved in disease processes, such as with meta-analyses it helps to weed out some of the statistical noise; the genes shown to be statistically associated with the development of a particular gene, but in reality, only show statistical significance due to the large number of genes tested. When this shortened list of genes then further examined within a biological context, where we can see how gene and gene products potentially interact in a system, we can make better hypotheses about which genes are most and least likely to be involved in the disease process. Furthermore, by studying how individual suspect genes, i.e. the ones with strong risk associations and plausible biological relationships, have changed from their 'natural' form, we can examine what the downstream implications may be. From these, focused traditional laboratory studies can be designed, the results of which can help in the development of new treatments and therapies.

Combining measurements, predictive models, trackers to genetics, understanding how these interactions work, and what the consequences are, helps us to develop targeted preventative treatments and therapies. Moreover, it will help us to understand how, when and in whom disease will develop. Assuming a positive ethical environment, one where such information will not be abused, and only used for preventive care, potentially saving thousands of dollars in healthcare costs in addition to improving quality of life. However, even if all treatments in the end are optimised, key is in prevention, and once a disease has developed, prevention of progression is also of the utmost importance. Until structural changes of disease can be reversed, such as alveolar wall destruction in emphysema, most therapies in chronic obstructive pulmonary disease are merely symptom control. Therefore, available and new strategies to maintain or improve lifestyle remain relevant particularly given the difficulty in

adhering to healthy lifestyles. In patients with COPD for example, even after pulmonary rehabilitation (PR), where emphasis is put on exercise training and physical activity, the uptake of a more active lifestyle upon the completion of PR is inconsistent.[12-14] However, it is unlikely that these drivers are unique to chronic diseases such as COPD. Impediments to healthier lifestyles are likely almost universal in nature and may include low levels of self-control. Any research improving adherence will greatly improve health status by reducing the risks of inactivity, namely progression of exercise intolerance[15] and increased risk of mortality.[16] We present a trial to improve self-control through working memory training. Should this trial be successful in improving working memory in COPD patients, and if this translates into improved self-control, physicians may be able to add another tool to regular PR therapy. Moreover, it represents a cost effect treatment option for other lifestyle related chronic diseases.

## Translation into practice

Combining new definitions, metrics and interventions will bring us further into the future. By defining health, we can measure it. By measuring it we can predict who, what, and where a disease or risk of disease will develop. With predictions we can intervene to mitigate further risks and hopefully improve quality of life while reducing health costs, and by improving interventions, we can help people adhere to healthier lifestyles. Taken together this research can be further explored in different diseases and therapeutic areas to improve prediction models and potentially disease therapies, should our trial prove to be effective. Which can act together to improve quality of life but also aid in reducing health care costs, lost productive time, and curb the affects population ageing.