

# Conceptualisations of successful ageing and leads for lifestyle modification

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## Summary

The relevance of ageing successfully is becoming increasingly important as life expectancy increases and birth rates fall. Successful ageing means maintaining health and wellbeing into old age. Meaning, by aiding individuals to age well, we can prevent millions of premature deaths, chronic disease, disease related disability and years with reduced quality of life. Therefore, the ability to measure such factors influencing the life course is an important public health concern. Risk factors for disease and dependency can be considered non-controllable, distal, and intermediate. By developing an effective metric considering these factors, we could not only predict who is likely to age successfully, but also measure the effectiveness of interventions, and improve and personalise interventions in order to maximise the therapeutic effects.

## Measures of successful ageing

There is great interest in developing tools to measure healthy ageing as well as in identifying the early stages of health impairment. However, there is lack of consensus as to how to exactly define healthy ageing. Unsurprisingly, due to the lack of clear definition, there is also significant diversity in so called healthy ageing assessment tools. Despite controversy, progress is being made in describing and devising tools to capture the healthy ageing phenotype. Attempts to measure healthy ageing have relied primarily on cross-sectional data collected in older people. More recent studies assessed the healthy ageing phenotype by using markers of multiple functional domains and used longitudinal data to model the dynamics and trajectories of healthy ageing. These attempts, however, relied on markers and data from earlier cohort studies and are limited by the tools used to collect data in those studies. Such data are often

unsuitable to detect early subtle declines in function and/or are inappropriate for use in younger old adult populations.

### Measuring successful ageing

The development of tools to measure ageing has been limited by the lack of appropriate outcome measures, and operational definitions of successful ageing. In this thesis, however, we proposed to measure successful ageing, or at least a proxy of it by designing a tool that includes representative variables of physical function, cognitive status, social interactions, psychological status, blood biomarkers, disease history, and socioeconomic status. For this, we used data driven methods and found a four-domain health model, including; neuro-sensory function, muscle function, cardio-metabolic function and adiposity. This model could predict walking speed and dependency at baseline and longitudinally over a nine-year period. Unfortunately, the same model was not able to predict self-rated health or emotional vitality, thereby, suggesting a multi-domain health model can be used to predict objective but not subjective measures of successful ageing.

### Other models of healthy ageing

There are many models of healthy ageing which have been proposed, but few have been tested. We tested whether a multidimensional model based on systematic review of literature and expert opinion, the Healthy ageing phenotype (HAP), was an appropriate operationalization of healthy ageing in a Dutch population. We used cross-sectional data from the Maastricht Study (TMS) and selected variables based on the HAP five domain model (i.e. cognitive function, social wellbeing, physical capability, psychological wellbeing, and physiological and metabolic health). Among individuals from the south of the Netherlands,

aged between 40 and 70, we discovered that, although this model makes sense theoretically, data could not be combined in this way using statistical analysis, indicating that this model does not fit the data. Subsequent exploratory analysis suggested a two-domain model, including physiological, cognitive, social, physical capability domain, as well as a psychological domain may have been more appropriate in this population.

### COPD and Accelerated ageing

COPD is considered a model of accelerated ageing as it exemplifies the key features of ageing including telomere shortening, cellular senescence, activation of PI3 kinase-mTOR signalling, impaired autophagy, mitochondrial dysfunction, stem cell exhaustion, epigenetic changes, abnormal microRNA profiles, immune senescence, and low-grade systemic inflammation. Moreover, the risk factors for COPD are similar to many other chronic diseases. Smoking is the most important risk factor for COPD. Not all smokers, however, develop COPD, suggesting that other lifestyle-, environmental- and genetic factors may play a role in the development of COPD. In this thesis, we reviewed all available meta-analyses reporting on genetic variants, lifestyle or environmental factors associated with development of COPD. For genetic variants, we found 42 relevant publications, including data on 281 genetic variants. Of these 281, 74% (n=208) showed to be significantly associated with COPD, with COPD with odds ratio's ranging from 0.17 to 3.33. For lifestyle/environmental factors, 11 relevant publications were identified and reported on exposures to various types of pollution such as exposure to vapours, cigarette smoke etc. as well as poor diet. Of the 281 genetic variants we identified, 74 percent (n=208), and 87 percent (seven) of the lifestyle or environmental factors showed a significant association with COPD with odds ratio's ranging from 0.17 to 3.33 and 0.45 to 9.50 respectively.

## Network analysis

The list of gene mutations associated with disease risk has little value outside of prediction models unless they are considered within biological systems. By examining genetic factors in a biological context, individual genetic risks or single nucleotide polymorphisms (SNP's), as well as possible therapeutic targets, can be better predicted. In this thesis, we were able to look at the SNP's associated with COPD more closely, by making use of network analysis and variant effect prediction analysis. As a first step, we classified genes into 11 different functional classes such as detoxification and cellular metabolism based on their (hypothesised) function. This allowed us to more easily examine the SNP's and their associated genes, and study which genes were most likely to have significant environmental interactions. Of the 315 identified biological pathways, derived from 181 statistically significant genetic risk factors for COPD, we found that only seven had a potentially influential mutation, namely in *AK9*, *SERPINA1*, *IL27*, *CYP1A1*, *EPHX1*, *SLC22A11* and *TESMIN*. Functional analysis of genes highlighted that of all the identified mutations, only mutations in the genes involved in inflammatory and detoxification pathways are likely to be relevant with respect to COPD risk. Furthermore, these analysis show that more emphasis needs to be placed on gene-environment, gene-behaviour and gene-lifestyle interactions, instead of looking only at predispositions.

## Interventions in unsuccessful agers

Although a great deal of work needs to be done, with respect to better disease prediction models, effective interventions are still highly needed for those who have already aged unsuccessfully and developed chronic disease. For COPD, key parts of these interventions involve lifestyle changes, improving diet, exercise and smoking cessation. However, historically changes adapted in therapeutic settings are poorly adhered to once the active intervention

has ended. Exercise and healthy diet are key for prevention and maintenance of good health; this is relevant for COPD patients, but is also important for maintaining health and preventing other chronic illnesses. However, when inactivity and poor diet behaviours are deeply ingrained, change is difficult to achieve and or maintain. Recent evidence suggests that working memory training may aid in self-regulation and the adherence to healthy lifestyle goals, thereby reducing sedentary activity and improving dietary habits. This is supported by recent evidence in other problem populations in which working memory training was shown to reduce alcohol intake in problem drinkers. We hypothesise that this type of cognitive training will also be beneficial in COPD patients, and that it may also help them to reduce sedentary activity and improve dietary intake.