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Pathways to longevity – but is it successful?

Longevity means living a long life, nowadays often considered a life span over 85 to 100 years. More and more people reach this limit in modern welfare societies, and citizens aged 90 years and over are said to be the fastest increasing group of people. This is a reality, but what are the background factors for this development? Many scholars think that it is mostly due to societal factors like improved hygiene, proper diet and safer environment. These are important but have mainly established the *sine qua non* for reaching old age through living past dangerous childhood and earlier adult life and becoming old. In modern societies, reaching longevity is jeopardized more by chronic non-communicable diseases which have replaced infectious diseases as primary causes of morbidity and mortality. By the way, according to the latest Global Health Estimates by the World Health Organization, during the first half of 2020, non-communicable diseases killed approximately 25 times more people than the ongoing COVID-19 pandemia (https://www.ecdc.europa.eu/en/covid-19-pandemic and https://www.who.int/healthinfo/global_burden_disease/estimates/en/).

The most common non-communicable diseases are cardiovascular diseases, chronic obstructive pulmonary diseases, cancer and degenerative diseases. Many risk factors for them have been identified. The important contribution of cholesterol, smoking and hypertension at the population level was demonstrated, for example, in Finland where in the late 1960s and early 1970s, cardiac mortality amongst men was the highest in the world. The 80% decline in coronary mortality during decades thereafter mainly reflects a great reduction of the cardiovascular disease risk factor levels – most importantly cholesterol, smoking and hypertension – due to health promotion interventions [1]. Numerous randomized drug trials have, on the other hand, shown that also drug treatment of cardiovascular risk factors, especially hypercholesterolaemia and hypertension, can decrease cardiovascular and total mortality and thereby postpone death.

But drug trials typically recruit 60- to 70-year-old participants, and trials routinely last only two to five years. The success story of decreasing risk factors amongst Finnish men has involved deaths before retirement age. Do these data prove that risk factor control can also increase longevity, *i.e.* living up to 90 years and over?

In this issue of the *Journal*, van Oort et al use a clever strategy, Mendelian randomization, to find out whether traditional as well as some newer risk factors are causally related to longevity [2]. They compared genetic traits which are related to longevity, defined as living at or above the 90th survival percentile, and traits which are related to various modifiable risk factors. These factors included those listed in the Life's Simple 7 initiative of the American Heart Association (glucose, blood pressure, cholesterol, body mass index, smoking, physical activity and diet) as well as education and sleep. Maybe not unexpectedly, but reassuringly, most of the Life's Simple 7 factors were causally related to longevity, too. The result is important and nicely completes existing evidence. The result also supports possibilities to realize James Fries' 40-year-old idea of 'compression of morbidity' [3] emphasizing prevention. Continuous efforts should be placed on 'dull' traditional risk factors like increased low-density lipoprotein (LDL) cholesterol level, high blood pressure, diabetes and preventing initiation of smoking. In contrast, the results of van Oort et al do not suggest, maybe surprisingly, that physical activity or fasting glucose level as such would be important for longevity. Also, the relationships between sleep duration and consumption of alcohol or coffee and longevity were not significant.

Because the cardiovascular risk factors were genetically driven in the analyses of van Oort et al, a next question arises: do the results apply to drug-induced control of risk factors? Totality of evidence, including vast number of randomized controlled trials with their post-trial follow-up studies, suggests that this is the case, but treatment should be started early enough [4] and adherence should be secured. Drugs do not work if you do not take them.

In Jonathan Swift's 1726 novel Gulliver's Travels, the novel's hero visits the nation of Luggnagg,

where individuals belonging to the Struldbrugg family live forever. Unfortunately, they did not enjoy eternal youth. Struldbruggs lived like mortals up to 80 years, where after they started to degenerate and the living was full of ailments related to ageing like loss of eyesight and hair, and loss of mortal friends around them. Living long is not nice if quality of life is bad. If control of cardiovascular risk factors extends life, does it also secure that extra years are worth living? Answering this question requires a life-course setting, because comparing quality of life to contemporary risk factor levels in old age does not necessarily reflect past risk factor status.

There is some research in this area relating midlife risk factors to health-related quality of life (HRQoL) in old age. In the Helsinki Businessmen Study cohort (men born 1919-1934) with follow-up through 2018, lower cholesterol, lower blood pressure, non-smoking status and less weight gain in midlife [5–8] were associated with lower follow-up mortality, but also with better HRQoL (assessed with RAND-36/SF-36 instrument) amongst old age survivors. [Correction added on 5th January 2021 after first online publication: higher has been changed to lower in the preceding sentence.] Those men who had generally low cardiovascular disease risk status at midlife – based on smoking, serum lipids, blood pressure, body mass index and glucose tolerance – had significantly higher probability of reaching 90 years of age than men with higher cardiovascular disease risk. Importantly, men in the Helsinki Businessmen Study with better risk factor status in midlife also had clearly better HRQoL when assessed at 82 years (unpublished observations).

According to the Bible, 'The days of our years are threescore years and ten (=70 years); and if by reason of strength they be fourscore years (=80 years), yet is their strength labour and sorrow; for it is soon cut off…'(Psalm 90:10). This well accords with the thoughts of biogerontologists: the warranty period of homo sapiens is 65 years, where after on the average 20 years can be attained, mainly depending on life-course factors. Whilst age 85 years is an upper limit to life expectancy at the population level, ca. 40% of the original birth cohort nevertheless can reach 90 years, 5-6% 100 years, few 100-115 years, and only a handful of individuals over that [9]. The study by van Oort suggests that control of traditional cardiovascular risk factors is important to reach the reasonable goal of 90 years and also supports the usual paradigm that ageing is 75% due to environmental and 25% to genetic factors – up to a certain point of age. Overall, it seems feasible that health span – healthy years of life – extension and successful ageing can be promoted with better and long-term cardiovascular risk factor control. However, for reaching 100 years and over the role of genetic factors affecting longevity strengthens. For most of the population, extending life span and especially health span over 90 years requires new methods to control the biological ageing processes, currently investigated in the realms of Geroscience, the Longevity Dividend, and the Global Roadmap for Healthy Longevity [9,10].

Conflicts of interest

I have had various cooperation (educational, research, consultative) with companies marketing cardiovascular medications.

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