Following Herodotus, the ancient Greek father of history, searching for the mythical "Water of Life" forever-lasting youth
Part 1: Chronological- versus biological age – a guide to longevity

The main risk factor for chronic diseases is age, but how old we are cannot be judged by our identity card

Throughout history, the dream of achieving everlasting youth while bathing in the "Water of Life" has inspired many artists to create famous paintings such as the "Fountain of Youth" by Lucas Cranach the Elder in 1546. The idea, of leaping into some pond and coming out as a shiny, beautiful, and handsome new self can be traced back to Herodotus (5th century BC). He described people living around the coast of Africa, of what we now call the Horn of Africa, who gained an extraordinarily long life thanks to a unique sort of water. It is not only a coincidence that Lucas Cranach composed his famous picture in the middle of the 16th century because, at that time, people were particularly fond of the idea of everlasting youth. So, for instance, a Spaniard explorer, the Governor of Puerto Rico, traveled to Florida in search of that mystical fountain.

Medicine, never short of practical solutions, moved from plastic surgery to cosmetic surgery. Science could not stand behind looking into an antiaging diet, recommending starving yourself healthy, and exploring the genetics of a long life (1-3). Nowadays, we continue dreaming about remaining young and shiny while watching, in front of the television, sophisticated produced advertisements for cosmetics or while passing by glittering cosmetic boots in shopping malls.

The main risk factor for non-communicable diseases is age

What is a sarcastic introduction to our wish to remain young forever has a substantial background. Aging is not a process we are fond of. It is related to adverse conditions which increase throughout our lifetime. Age is the leading risk factor for the primary diseases of interest for public health (4). Opting for a long healthy life of high quality should be the aim of every given health delivery system.

In the scientific context, the topic of longevity falls into "geroscience", formerly called biogerontology. Some time ago, geroscience was introduced to the faculty, students, and staff through a review of the "Khon Kaen Forum of Public Health (KKFPH)". KKFPH was the previous attempt of this blog to raise interest in new developments in the academic sector. The manuscript was based on a special issue in Science (6265), published in 2015, focusing on "healthy aging" and discussing the concept of the "biological age" in contrast to the "chronological age".

Life expectancy

In public health, we are not used to taking individuals into account in contrast to curative medicine. A more common statistical indicator, "life expectancy," is used in epidemiology. It offers an overall estimate of the life span throughout the whole population based on age-specific

death rates. It is “a hypothetical measure and indicator of current health and mortality conditions” (5). The indicator could be used to judge health delivery systems' quality while comparing two countries, regions, or developments over time. For instance, the tremendous increase in the world population, triggered, among other factors, by a spectacular rise in life expectancy, started around 1900 within only four generations, while it remained steady for 8.000 generations (6).

Eva wanted to know, succumb to temptation and paradise was lost

As individuals, “life expectancy” is of no interest to us. Everybody wants to live as long as possible and enjoy life, unless being suicidal. Unfortunately, according to the religious believers of Christianity, it was Eva, well knowing that God forbids eating apples from the tree of knowledge, and listening to the devilish serpent, not only did eat an apple but even gave it to Adam, as well. The result was an everlasting catastrophe, in that both were thrown out of paradise and were condemned to die ultimately. As some reinforcement, the Bible lets us know that God wants us to explore this world and make the best out of it. For this, we are provided by nature with a specific life span. So, it was Eva, the female, who inspired humanity to gain knowledge, explore the world, be curious about developments, and enjoy research and academic life. It seems that the Bible missed pointing this out. Anyhow, we are allowed to live on earth, but during our lifetime, we go through several periods, namely from adolescence to mid-life and old age.

Biomarkers for the biological age

Our age, from birth onwards, is measured as the “chronological age”. Everybody, however, goes through their lifespan differently. Some feel the burden of old age at a chronological age around 65 to 70 years old. Instead, others, with a chronological age of 80 years or even 90, are still very active and appear to be younger, contrary to the age on her or their identity card. “Healthy aging” means opting for a biological age trailing well behind the chronological age. The crucial point in the concept of “biological age” is how to measure it on the scale of the individual “chronological age”.

Telomeres

For quite some time now, the search was on to find one or more biomarkers that could distinguish the biological age (7). Based on the Nobel Prize for Physiology and Medicine in 2009, “telomeres” and the enzyme “telomerase”, even became known to the public (8). Two ladies and a male scientist got the Nobel Prize. Their research centered around the end of chromosomes named telomeres. For cell dividing, a certain length of the telomeres is required. Each time a cell divides, the telomere gets shorter. This process is linked to aging and diseases such as cancer. However, to circumvent disaster, the enzyme telomerase can repair and add to the length of the telomere. The initial excitement about the opportunity to look into the telomeres as biomarkers for aging and risk for cancer was also impaired by the fact that genetic factors and non-genetic-stimuli determine the telomere length and not only the age of an individual (9).

Epigenetic clock and other predictors

Besides the telomere, molecular biology worked on additional biomarkers linked to the biological age, such as the "epigenetic clock" (7). The "clock", as the name expresses, is based on one feature of epigenetics, namely DNA methylation. The DNAmAge "clock" is independent of major classical risk factors and very promising in predicting all-cause mortality (10-12). Additional attempts related DNAmAge with phenotypes such as certain blood cell types and fitness, as well as with diseases such as cancer. "Transcriptomic predictors" based on gene expressions, "proteomic predictors" investigated protein glycosylation, "metabolic-based predictors" was tested with lipids and amino acids, and "composite biomarker predictors" made use of extended extensive population surveys in combining several variables assessed such as serum creatinine and glycated hemoglobin (7).

Bodily function, the biological age, and death because of old age

The biological age predictors mentioned so far are based on population surveys. As a person, our interest in overall mortality, as manifested by DNA methylation, is limited. Being young and healthy, we simply hope it will remain so with any thought of one or the other age category. Those, who are not healthy, especially patients suffering from one or more diseases, might think differently because the disease indicates something went wrong in their bodily function. The concept of biological age is based on physiological and pathophysiological processes.

The reasons for a deficit in function, and consequently for death, are manifold. Seldomly death can be simply accounted only for a very advantaged age. The cause for the death of Queen Elizabeth II., at the age of 96, was announced as "old age". It could be that a person without a disease finally dies at a point when the body can no longer function. But from the medical view, even for the demise of the Queen, it is questioned that there is no specific cause for her death.

Biomarkers are also thought to estimate either the risk or the advantage of lowering or increasing the biological age in relation to the chronological age of a given individual. Not only a patient suffering from a "chronic" disease but also clinicians are interested in biological age predictors. For the clinicians, "biomarkers of this kind could also help to tease out which elderly people are healthy enough to benefit from hip replacement or new medication, who needs extra support, training, or nutrition before such an intervention, or who shouldn't be treated at all" (13). Whether such an attitude goes along well with an "aging friendly society" might be questioned and hopefully won't be the main reason for the curative sector to be interested in the biological age. For the clinician less concerned with public health, measuring biological age could be relevant while studying widespread illnesses.

Biomarkers proposed for clinical use

Considering the leading causes of death worldwide, cardiovascular and cerebrovascular effects, numerous biomarkers for the biological age are proposed (14). The pathophysiology of the two main conditions for death is the deadly damage of the heart, the brain, and the kidney caused by arterial degeneration and hardening. Biomarkers of biological vascular aging could be categorized into two groups, i.e., molecular and cellular markers, and functional and structural indicators. For instance, telomere length, inflammation markers, and low-density lipoprotein are

listed among the first group. At the same time, blood pressure, signs of atherosclerosis, and arterial stiffness, measured by carotid-to-femoral pulse wave velocity, belong to the second group. Also, composite biomarker predictors, i.e., a combination of molecular and functional predictors, were assembled using machine learning artificial intelligence. The Vascular Aging Index for predicting cardiovascular diseases combined “carotid-to-femoral pulse wave velocity” and “aortic pulse wave velocity” (15). The Frailty Index 34 is based on 34 methods assessing the health and functions of various organ systems (16), and the Klemera-Doubal Method Biological Age includes 10 biomarkers (16, 17). However, the complexity of the composite biomarkers limits the application for investigation and research.

Public health and deceleration of the biological age

Essential is a healthy dietary pattern. All in all, not only the “biological vascular age” is obstructed by chronic diseases, lifestyle, and environmental factors, being male or female, as well as heredity (14). Public health has several well-known suggestions to positively influence biological age on the individual level, such as refraining from smoking, not drinking alcohol in excess, lowering sodium intake, and being physically active.

Recently antiaging diets, such as caloric restrictions and fasting, were recommended, so to say, as a substitute for the “Fountain of Youth”, by “decelerating” the biological age. Part 2 of this entry will review how effective antiaging diets are, whether it pays to torture ourselves through fasting and whether our genetic setting could be influenced so that we can be younger and active also in an advanced chronological age.

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Frank P. Schelp is responsible for the content of the manuscript, and points of view expressed might not reflect the stance and policy of the Faculty of Public Health, Khon Kaen University, Thailand

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