Reversing Age To Inverse Our World

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What would you choose: living for centuries with the shadows of painful frailty and disease following every step, or a short life without hospitals, dementia or wheelchairs? You may not need to answer this question after all with modern evidence suggesting that "there's a clock in your body that can be reset" *David Sinclair, PhD.* What we should answer though, is what would we do if we never aged?

Most people do not consider ageing a disease. It seems too natural of a process, occurring to every human on our planet. However, several remarkable scientists have taken a new perspective on ageing. They are also the ones leading the search for a modern elixir for eternal youth, but in the process may unintentionally bring us to humanity's demise. This essay explores the three major intervention strategies that researchers have brought forth as anti-ageing therapies and discusses the implications of age reversal both on humanity and on the environment we live in.

Can ageing be technically reversed?

Reversing ageing is technically possible and has already been done in several experiments. A famous recent example is the study conducted by a student at David Sinclair's laboratory, where he seemingly irreversibly destroyed mouse retinal ganglion cells (RCGs), and after treating them with three Yamanaka factors (Oct4, Sox2 and Klf4 genes) (OSK) observed that they grew back into functioning RCGs after just 12-16 weeks (Eisenstein, 2022). This investigation brings us to one of the three main strategies for age-reversal: pharmaceutical intervention. The other two are a healthy lifestyle and supplemental intake. Before diving into these three anti-ageing techniques, however, let us speak about what ageing truly is. Several different theories have been proposed regarding this concept:

1. The 9 hallmarks of ageing
2. The cross-linkage theory of ageing
3. The free radical theory of ageing
4. The information theory of ageing

The first theory suggests that ten groups of biological changes observed in ageing organisms are what drives ageing itself. These hallmarks are: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication (Lopez-Otin *et al*, 2013).

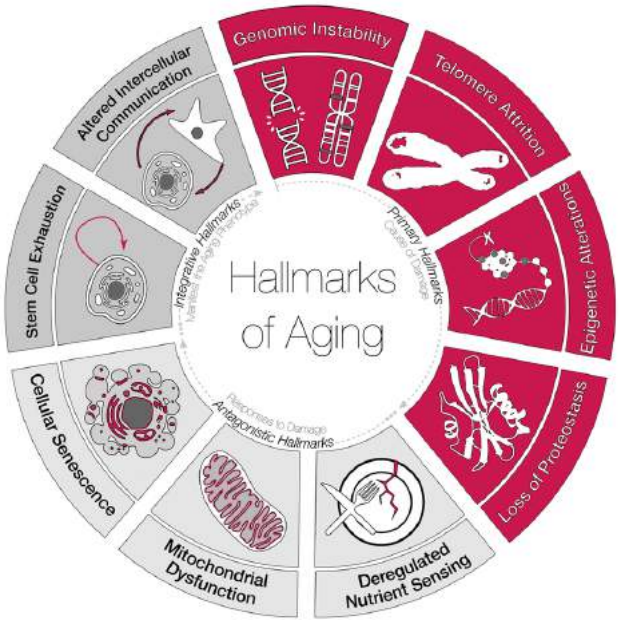

Figure 1: The 9 hallmarks of ageing

The second theory proposes that cross-linking, in other words the bonding of large molecules, is what drives loss of elasticity, reduced swelling capacity, increased resistance to hydrolases and probably enzymes generally, and thus an increase in molecular weight and a tendency toward embrittlement (Bjorksten, 1968).

The third theory, which is frequently considered outdated by modern longevity scientists, yet may still address an important topic for considerations, claims that it is the creation of free radicals within an organism that induces mutation, cancer and ageing (Harman, 1956).

The final and newest theory explains that a loss of epigenetic information through time, like a scratched vinyl disc, is the basis for age-associated cellular deterioration (Sinclair, 2019).

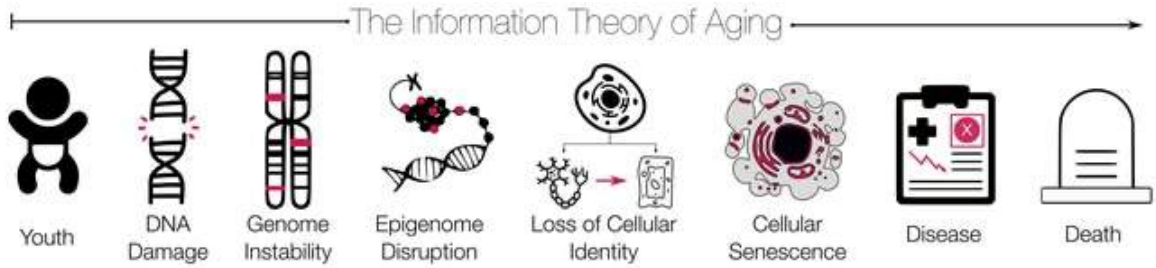

Figure 2: The information theory of ageing (Sinclair, 2019; Vujin, 2020)

Clearly, there are varying theories on ageing, and each one is being investigated by experts in the field. These scientists are rapidly unearthing not just the genetic or epigenetic processes involved in ageing, but even larger concepts, such as the effect of a mother's lifestyle and age at gestation on the ageing of her child (Duncan *et al.*, 2019). Despite the variety of theories on what characterises ageing, a general consensus about the aim to slow or even reverse ageing has been found. So how is ageing currently being targeted?

Pharmaceutical intervention

As mentioned, studies in mice have already been conducted to showcase the effects of genetic and epigenetic alterations on ageing. However, humans have also undergone studies with a variety of different pharmaceuticals. For example, rapamycin - initially used as an immunosuppressant for organ transplants - has been tested in humans and has shown to slow down ageing and all age-related diseases in humans (Blagosklonny, 2019). Metformin - originally prescribed to patients with type 2 diabetes - induces anti-ageing transcriptional changes in humans, yet deeper analysis questions whether this compound has any beneficial effect on lifespan in non-diabetics. Spermidine is a drug that suppresses age-related cardiovascular decline in mice, yeast and nematodes and flies, and new evidence suggests that it also reduces overall, cardiovascular and cancer-related mortality in humans (Maedo *et al.* 2018). Gemfibrozil - a lipid lowering drug - has shown to lower neuronal ceroid lipofuscinosis in children, which is a diseases resulting in progressive motor and cognitive decline (Kim *et al*, 2017). Resveratrol - initially used as an anti-inflammatory and anti-platelet agent - possess life-extending and health-benefiting properties in model organisms, potentially having advantageous effects on humans as well.

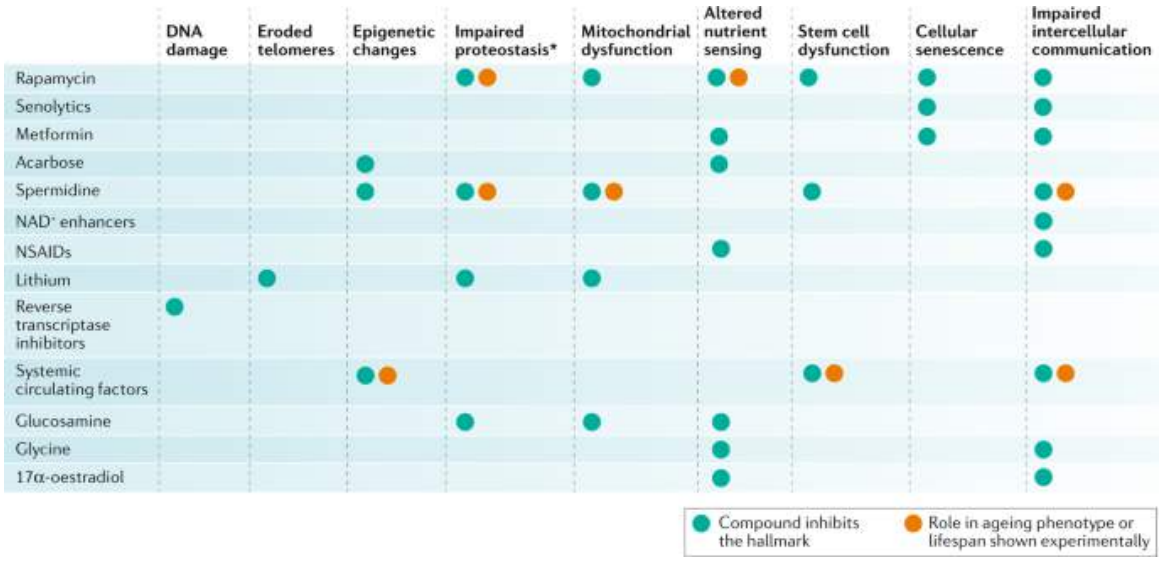

Figure 3: The individual effects of potential anti-ageing drugs on the 9 hallmarks of ageing. (Partridge, Fuentealba, Kennedy, 2020)

These are just some of the well-known drugs currently investigated for anti-ageing properties, and many more are hypothesised to follow their lead as the longevity field grows. An important consideration is that many pharmaceutical compounds carry different effects based on an individuals' genomes. Resveratrol, for example, famously increases lifespan only when a class of genes, called Sirtuins, are present (Sinclair, 2019). It is therefore important to consider the genetic basis before administering any drugs with claimed longevity advantages. Nevertheless, the presence of existing FDA-approved anti-ageing compounds, for instance rapamycin (Blagosklonny, 2019), already points to the fact that age reversal is being actively realised.

Supplemental intervention

Another large area of age-related research is regular supplemental intake. NAD+ boosting molecules, such as nicotinamide mononucleotide, trigger shifts that enhance energy production, increase insulin sensitivity, suppress age-related adipose tissue inflammation, improve mitochondrial and neuronal function and upregulate cellular repair pathways across all studied species (Shade, 2020). Alpha-ketoglutarate is another longevity-promoting supplement, which decreased biological age in humans by almost 8 years in several months, according to a study conducted by Juan Ponce de Leon (Mazin, 2021). Surprisingly, vitamin A, vitamin C, vitamin E, beta-carotene and selenium supplementation found no benefit to longevity, according to a meta-analysis of randomised trials involving over 230 000 participants. In fact, increased intake of these supplements may increase mortality (Minor *et al.,* 2010). Several other studies investigating these common compounds in relation to their antioxidant effects found no data to support any benefit from them. However, it must be stated that avoiding deficiencies of these supplements is vital for normal physiological functioning.

Behavioural intervention

Perhaps one the most rapidly growing anti-ageing strategies is changing people's lifestyles through sport, diet, sleep and body temperature. It has been shown that moderate aerobic training at a level when it is somewhat difficult to speak throughout the exercise is effective in reducing frailty in the long-term (Sinclair, 2019) (Vina *et al.,* 2016). In fact, all-cause mortality is decreased by about 30% to 35% in physically active as compared to inactive subjects (Reimers, Knapp, Reimers, 2012). However, the duration, intensity and frequency of exercise should be taken into consideration, as extreme exercise has shown to negatively affect the cardiovascular system (Eijsvogels *et al.*, 2018). Calorie restriction and intermittent fasting are two dietary interventions that benefit neuronal activity, the microbiome, oxygen radical metabolism, and cellular stress response systems (Martin *et al.,* 2009). In fact, these two strategies are considered the most effective ones out of all the behavioural interventions currently known (Sinclair, 2019).

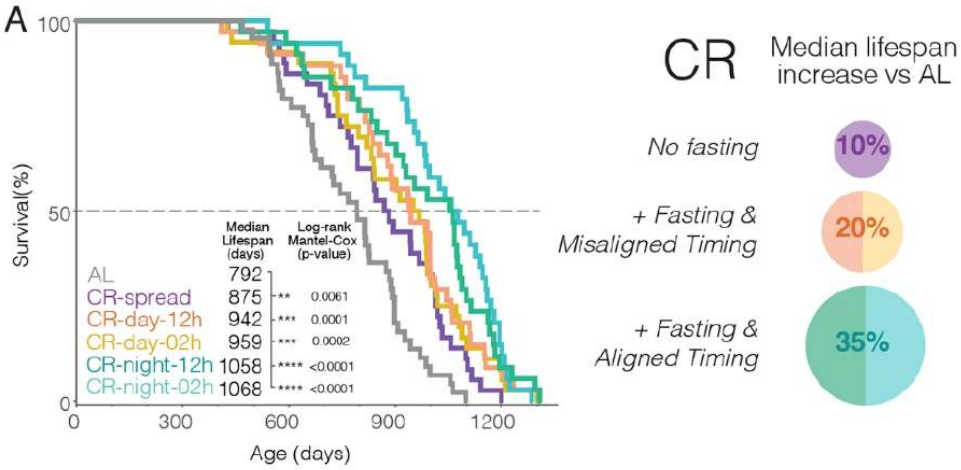

Figure 4: A Kaplan-Meier graph demonstrating the effect of fasting on mouse lifespan (Mazin, 2022)

Sleep has a variety of effects, however is best known to alter genetic expression and epigenetic biomarkers. A study showed that mice with sleep deprivation for 5 and 10 days were older by all measures than mice with normal sleeping patterns (Gaine *et al.,* 2018; ARDD 2022). Finally, there is some evidence for a correlation between a lower body temperature and increased longevity for a range of different species, such as the famous 30-year living naked mole rat (Keil *et al.,* 2015). However, there is also counter evidence for this, such as the fact that females, who on average have slightly higher body temperatures than males, still live longer despite this. Their longer lifespan, however, may also be a result of hormonal regulation differences from men and other lifestyle intervention.

Collaboration for longevity

Longevity, being an entirely new area of science, has fewer organisations and researchers in comparison to prominent biological fields, such as biochemistry, neuroscience and molecular biology. One could say that all subdivisions of natural sciences are studied when addressing ageing, however, it is clear that few consciously work towards age-reversal, and instead address specific and official diseases. Nevertheless, longevity has been rapidly growing, and international conferences, such as the Aging Research and Drug Discovery conference, where I spoke about my findings for the cancer/age trade-off hypothesis through a multi-omics analysis of glioblastoma multiforme this year, have substantially increased the number of collaborations on age-research.

Figure 5: Me (Andrea Olsen) speaking at the 2022 Aging Research and Drug Discovery conference in Copenhagen about a glioblastoma multiforme study I conducted at Insilico Medicine, during which I found evidence for the cancer/age trade-off hypothesis.

Companies such as Lifespan.io and VitaDAO are improving not just the funding and technological possibilities for longevity work, but are also recruiting scientists internationally to promote collaboration and progress in this field. Such advancement is key to standing a chance at age-reversal, as it means experts with a varied skill set can combine their forces, which may lead to new insights and faster development. Furthermore, bringing young people into longevity can, and already has, promoted meaningful improvements in age-research. Take the example of Laura Deming - a famous longevity science prodigy, who has inspired countless students around the world to enter this fascinating field.

Thinking twice before reversing ageing

Ageing is the primary cause of prevalent diseases in developed countries: cancer, cardiovascular disease and neurodegeneration (Niccoli, Partridge, 2012).

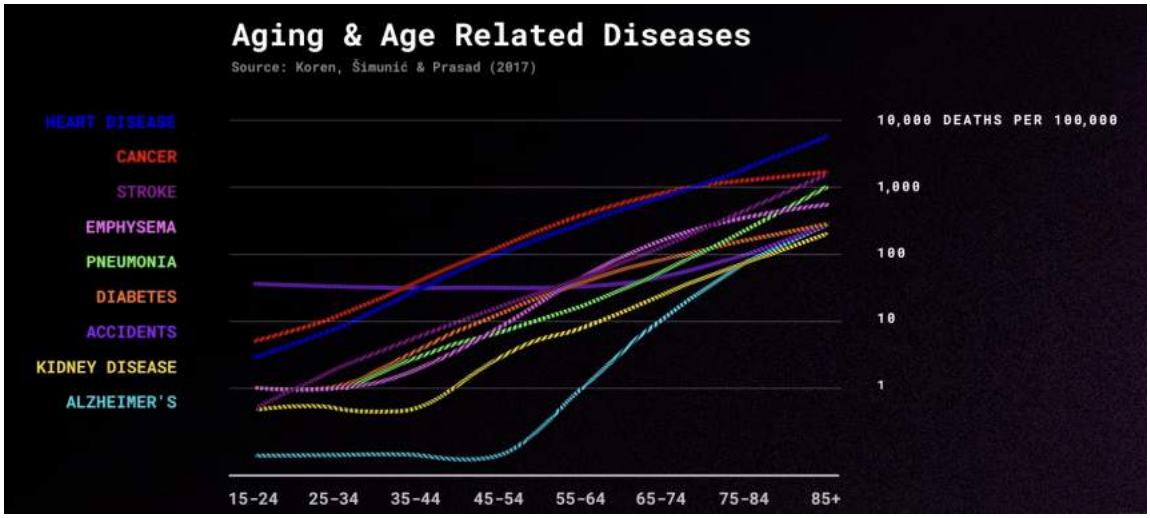

Figure 6: Ageing and age related diseases (Bloomberg, 2021)

This reason on its own seems large enough to deploy all resources into conquering ageing. Yet the long-term effects of such a scientific revolution could cause more damage than what most expect.

Before delving into the implications of age-reversal, I would like to thank Dr Julien Reboud (University of Glasgow) for our discussion regarding the ethical aspects in this text. The opportunity to speak with him about this extraordinary subject was a fantastic experience that made me think much deeper about longevity research than ever before.

Familial burden

An important ethical question to consider when working towards age-reversal is what burden families would experience from having access to anti-ageing medicine. Caring for the elderly is becoming ever more important, as the number of those over 65 has almost reached 10% of the global population (The World Bank, 2019). This may notably strain younger family members, especially if they are unable to support themselves financially, let alone help their children, parents and grandparents. Furthermore, if anti-ageing drugs turn out to be

expensive, as some propose, this will not only make elderly-care more challenging, but could also bring a wave of inequality that would further widen the poverty gap. Those born into wealthy families would be destined to live longer, and those from poorer ones would be at an unnatural disadvantage from their very birth. On the other hand, it is argued that because current anti-ageing pharmaceuticals have been derived from existing treatments (for example metformin, which is meant for diabetics), future longevity-promoting drugs may be rather cheap and accessible to people. In this case, would it be unethical for parents not to supply their children or elderly family members with such medicine even when these parents can afford it? The recent Sars-CoV-2 epidemic was a good example of the effects of parents neglecting to vaccinate their children for various reasons. Strict regulations were set up to the point where people could not enter public spaces unless they had proof of full vaccination. Could the same occur for anti-ageing remedies?

Who to prioritise in our world of 7.8 billion?

The question of who receives anti-ageing medicine first is also an important one. Most agree that the elderly should be prioritised, but who is next in line? In addition, funding the distribution of such medicine would be difficult as well. Many rely on the WHO to take care of this, but even this organisation has a budget, and it may consider ageing less important than other diseases.

Let us consider a world with existing, cheap and accessible anti-ageing medicine. Would rejecting such treatment strain national health security? Since ageing is the root cause of most diseases, reversing age would significantly decrease international healthcare spending. This would be incredible financial health to the world, considering that England's healthcare expenditure alone is estimated at £277 billion per year (Cooper, 2022). However, if people choose not to take anti-ageing medicine, they would be doing so at the expense of the health care sector.

Will the world want it?

Many longevity researchers fear that society might outlaw ageing medicine before its true potential is reached. Some argue that because a large portion of the current intervention involves lifestyle changes, such as diet and sport ameliorations, this point may not be a major issue. Yet others claim that the FDA approval of rapamycin and the discovery of this drug's side effects (Blagosklonny, 2019) has pushed many away from considering pharmaceutical intervention for ageing. Moreover, the use of such medicine would have to be coupled with genome sequencing of patients, which would lay additional costs on the use of longevity prescriptions.

Are we too many?

Along with increased life and health span comes the problem of overpopulation. The results of this: resource shortage, lack of space, wars, increased waste, rapid anthropogenic climate change, and species extinction. Many question, however, the expected growth in numbers on our planet, suggesting instead that people will choose to not have children, which is becoming more popular in Europe with every decade (Hunt, 2019). Perhaps the spread of

such a choice could naturally regulate the human population, similarly to Adam Smith's invisible hand in the economic market.

Centenarian presidents and death of political reform

What does a world with centenarian presidents and government officials look like? The older population tends to conserve views they formed many years before, and naturally become less open to change as they age (Tilley, 2015). If individuals of this kind hold positions of high power, few reforms and little advancements can be made to the political state of the world, leading to an anti-globalist wave. It would take longer for new ideas to be implemented into society, which could eventually bring a halt to technological, scientific and social development in the world.

Moreover, retirement age would increase dramatically with the growth of ageing-intervention, but not necessarily for all jobs. It may not be fair to expect those working in physically demanding jobs to retire as late as those holding office positions - an important point to consider for balancing the future economical and health situation of the world.

Golden opportunities

Despite the potentially negative effects of reversing ageing, there are countless positive aspects to it as well. First of all, people will be healthier and happier. More time can be spent with family, friends and engaging in a favourite activity. The quality of life will increase dramatically as people will have more time for pursuing education, sports and other interests. Secondly, we should also consider that older people have great experience, which they may teach to the younger population to combine creativity and knowledge into a colourful mixture of success.

To conclude, reversing ageing is possible, and has already been demonstrated through a variety of organisms. With pharmaceutical, supplement and behavioural interventions, different theories of ageing have been addressed in an attempt to prolong both health and life span in humans with the goal of increasing overall quality of life. After all, a long and happy life is what most want to experience, and that is exactly what longevity research is geared towards. The question is though, should we reverse ageing, considering the ethical implications of overpopulation, familial burden, and slowed political reform? I believe each one of us should answer this individually for ourselves, because we all experience this world differently with our unique perspectives. Each of us has our own life's adventures to embark on, and it is up to us to decide how long these exciting journeys will last.

Bibliography:

Eisenstein M., (Jan 2022), *Rejuvenation by controlled reprogramming is the latest gambit in anti-aging*, Nature, https://www.nature.com/articles/d41587-022-00002-4?proof=tr (Accessed: 03.07.22)

López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G (Jun 2013) *The hallmarks of aging,* Cell Press, https://pubmed.ncbi.nlm.nih.gov/23746838/, (Accessed: 03.07.22)

Bjorksten J. (1968), *The crosslinkage theory of aging,* Oxford: Blackwell; https://agsjournals.onlinelibrary.wiley.com/doi/abs/10.1111/j.1532-5415.1968.tb02821.x (Accessed: 05.07.22)

Harman D., (1956) *Aging: a theory based on free radical and radiation chemistry.* J Gerontol. https://pubmed.ncbi.nlm.nih.gov/13332224/ (Accessed: 13.08.22)

Sinclair D, LaPlante MD, Delphia C (2019) *Lifespan : why we age– and why we don't have to*. ISBN 1-5011-9197-7

Vujin A., (2020), *The information theory of aging: Hacking Immortality?* Health Science Inquiry, https://healthscienceinquiry.com/index.php/hsi/article/view/304 (Accessed: 20.08.22)

Duncan G., Lee K., Rosales-Rueda M., Kalil A, (Dec 2019), *Maternal Age and Child Development*, Demography, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6392079/ , (Accessed: 20.08.22)

Blagosklonny M., (Oct 2019), *Rapamycin for longevity: opinion article*, Aging (Albany, NY) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6814615/, (Accessed: 05.09.22)

Madeo F., Carmona-Gutierrez D., Kepp O., Kroemer G., (Aug 2018), *Spermidine delays aging in humans*, Aging (Albany NY), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6128428/, (Accessed: 05.09.22)

Kim K., Kleinman H., Lee H., Pahan K., (Jun 2017), *Safety and potential efficacy of gemfibrozil as a supportive treatment for children with late infantile neuronal ceroid lipofuscinosis and other lipid storage disorders*, Orphanet J. Rare Disease, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5474050/ (Accessed: 20.08.22)

Partridge L., Feuentealba M., Kennedy B., (May 2020) *The quest to slow down ageing through drug discovery*, Nature, https://www.nature.com/articles/s41573-020-0067-7 (Accessed: 20.08.22)

Shade C., (Feb 2020) *The Science Behind NMN–A Stable, Reliable NAD+Activator and Anti-Aging Molecule*, Integr Med, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7238909/ (Accessed: 20.08.22)

Mazin A., (Dec 2021) *Alpha-Ketoglutarate Decreases Biological Age in Human Study*, Lifespan.io, https://www.lifespan.io/news/alpha-ketoglutarate-decreases-biological-age-in-human-study/ (Accessed: 20.08.22)

Minor R., Allard J., Younts C., Ward T., Cabo R., (Jul 2010) *Dietary Interventions to Extend Life Span and Health Span Based on Calorie Restriction*, J Gerontol A Biol Sci Med Sci https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2884086/ (Accessed: 13.08.22)

Vina J., Rodriguez-Manas L., Salvador-Pascual A., Tarazona-Santabalbina F., Gomez-Cabrera M., *Exercise: the lifelong supplement for healthy ageing and slowing down the onset of frailty*, J Physiol, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4933124/ (Accessed: 13.07.22)

Reimers C., Knapp G., Reimers A., (Jul 2012), *Does Physical Activity Increase Life Expectancy? A Review of the Literature*, J Aging Res, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3395188/ (Accessed: 21.07.22)

Eijsvogels T., Thompson P., Franklin B., (Aug 2018), *The "Extreme Exercise Hypotesis": Recent Findings and Cardiovascular Heahtlh Implications,* Curr Treat Options Cardiocasv Med, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6132728/ (Accessed: 21.07.22)

Martin B., Mattson M., Maudsley S., (Jan 2009), *Caloric restriction and intermittent fasting: Two potential diets for successful brain aging*, Ageing Res Rev, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2622429/ (Accessed: 19.07.22)

Mazin A., (May 2022) Caloric Restriction, Feeding Times Lengthen Mouse Lifespan, Lifespan.io https://www.lifespan.io/news/caloric-restriction-feeding-times-lengthen-mouse-lifespan/ (Accessed: 19.06.22)

Gaine M., Chatterjee S., Abel T, (Feb 2018) *Sleep Deprivation and Epigenome*, Front Neural Circuits, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5835037/ (Accessed: 03.06.22)

Keil G., Cummings E., Magalhaes J., (Apr 2015), *Being cool: how body temperature influences ageing and longevity*, Biogerontology, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4486781/, (Accessed: 03.06.22)

Niccoli T., Partridge L., (Sep 2012), *Ageing as a risk factor of disease*, Curr Biol, https://pubmed.ncbi.nlm.nih.gov/22975005/ (Accessed: 09.06.22)

(Feb 2021), *Meet the Scientists Trying to Reverse Aging*, Bloomberg Quicktake, https://www.youtube.com/watch?v=a5_JgBRl6UU, (Accessed: 20.06.22)

(2019), *Population ages 65 and above (% of total population)*, The World Bank https://data.worldbank.org/indicator/SP.POP.65UP.TO.ZS (Accessed: 15.09.22)

Cooper J., (May 2022), Healthcare expenditure, UK Health Accounts provisional estimates: 2021, Office for National Statistic, https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthcaresystem/bulletins/healthcareexpenditureukhealthaccountsprovisionalestimates/2021 (Accessed: 15.09.22)

Hunt E., (Mar 2019), *BirthStrikers: meet the women who refuse to have children until climate change ends*, The Guardian, https://www.theguardian.com/lifeandstyle/2019/mar/12/birthstrikers-meet-the-women-who-refuse-to-have-children-until-climate-change-ends (Accessed: 14.09.22)

Tilley J., (Nov 2015), *Do we really become more conservative with age?*, The Guardian https://www.theguardian.com/commentisfree/2015/nov/03/do-we-become-more-conservative-with-age-young-old-politics (Accessed: 14.09.22)