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Dear Readers,



Improved environmental conditions mean that people are living longer and longer. As our genes also have a great influence on life expectancy, this issue of our Geneletter addresses the genetic basis of longevity.

- How do genes and lifestyle interact?
- Is there an upper limit to human life expectancy?
- Do women basically live longer than men? Is this because of genetic or other differences between the sexes?
- What possibilities to prolong the lifespan does gene research offer?
- And what does all this mean for the insurance industry?

Not only have we considered these questions in our Centre of Competence for Biosciences at Munich Re but we have also talked to Dr. James Vaupel, one of the world's most renowned researchers into longevity.

Even though the increase in life expectancy is in itself welcome, the costs of it still have to be financed. State social security systems have reached their limits, while longer periods of pension payment and rising costs of health and long term care are challenges for private insurance companies. Private insurers can adjust their calculations to allow for an increase in life expectancy, even if it turns out to be even more rapid in the future. It is essential, however, that premiums continue to be as risk-adequate as hitherto and that they are also calculated taking the sex of the applicant into account.

This Geneletter is intended to help you understand the complex relationships between genes and life expectancy and successfully face the challenges posed by longevity.

We hope you find it an interesting and informative read.

A stylized, handwritten signature in black ink, appearing to read 'Achim Regenauer'. The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Dr. Achim Regenauer
Munich Re Chief Medical Director

Genes and environmental conditions determine life expectancy

People are living ever longer. This is mainly due to improvements in living conditions since the 19th century; however, as our genes are also responsible for ageing, engineered modifications of them could possibly lead to a dramatic increase in life expectancy. Realistic opportunities or wishful thinking?

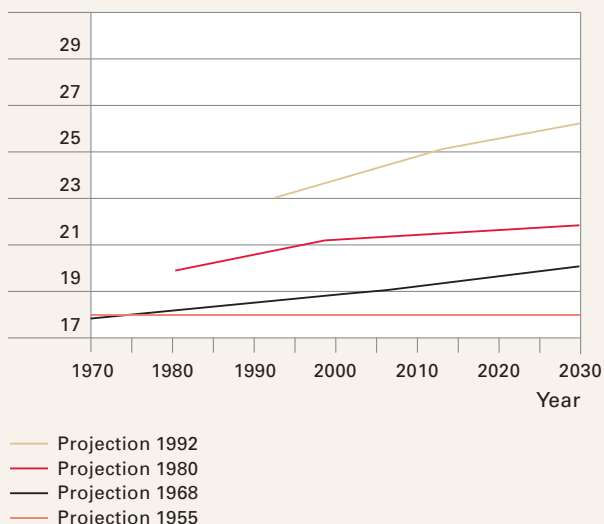
During each year of his time in office, the former federal president Johannes Rau congratulated about 3,830 German people on the occasion of their 100th birthday. Heinrich Lübke, who held this honourable position some 40 years before Rau, had to do this only 158 times a year. This clearly shows how dramatically life expectancy has risen within just a few decades.

Eternal life has always dominated mankind's dreams. In principle, medicine and the modern pharmaceutical industry always contribute to this indirectly by increasing the lifespan of sick people. Life expectancy has increased since the middle of the 19th century, thanks to better nutrition and the introduction of hygiene measures, as well as to increasingly successful diagnosis and treatment of medical conditions.

Increasing life expectancy

Calculation of the life expectancy of a 60-year-old male pensioner by the British Institute of Actuaries, CMI Bureau.¹ The projections were made in 1955, 1968, 1980 and 1992 and give the remaining life expectancy of a 60-year-old man in each calendar year. The graph clearly shows that projections have always had to be corrected upwards, because the actual development of life expectancy overtook the forecasts even in these short periods of time, and the reduction in mortality has been even more striking.

Life expectancy in years



Some experts concluded that the human genome (the genetic blueprint) allows a maximum life expectancy of about 120 years. However, animal experiments have shown that life expectancy can be increased dramatically by means of relatively simple gene modification – and why shouldn't this also be possible in humans? Genetics research has already produced a great many interesting findings on the retardation of ageing. Genes that directly or indirectly influence ageing have been identified and may serve as drug targets (points at which medicines intervene). Genetic modification to prolong the lifespan is not going to be feasible within the next ten years; whether it can be realised at a later date still remains to be seen – and will depend not only on medical advances but also on ethical, social and economic factors.

Is there a “longevity gene”?

It has been known for a long time that changes in many genes may shorten the natural lifespan. This is an indirect effect – for example, a mutation in the LDL-receptor gene raises the cholesterol levels in the blood and may give rise to coronary heart disease; this in turn may cause a potentially fatal heart attack. The LDL-receptor gene therefore has an influence on life expectancy but, even so, it cannot be referred to as a “longevity gene”. The same applies to the genes involved in breast cancer, BRCA1 and BRCA2, and the Huntington’s gene. These and many others have a pronounced effect in reducing life expectancy if they are defective. But the converse does not hold true for any one of these genes – none of them has a variant that predisposes to living longer.

A “longevity” gene can be considered one that has a direct effect on ageing processes. The Klotho gene and a particular region of chromosome 4 are being considered in this respect for humans. But in the end, it is difficult to distinguish “true” and “false” (i.e. direct and indirect) longevity genes. It is possible that just a few genes have a direct and pronounced effect on attaining a greater age, while a large number are indirectly responsible for shorter life expectancy.

A short lifespan – An interplay of many factors

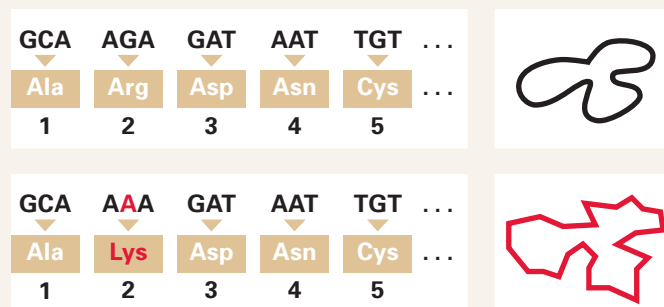
To a certain extent, ageing may be considered to resemble a complex disease: genetic factors and living conditions interact in ways that are not always transparent. Unfavourable environmental factors such as extreme temperatures, toxic substances, dietary deficiencies, natural enemies, and radioactivity can all accelerate ageing and lead to earlier death. Paradoxically, however, the same stress factors (i.e. nutritional deficiencies, heat or osmotic shock, etc.) in small, non-lethal doses can even prolong the life of some organisms, as has been demonstrated in yeasts, worms, fruit flies, mice, rats and dogs. Recently, ageing research has been able to explain some of these relationships in humans as well. For example, it is now possible to understand at a molecular level the life-prolonging effects of red wine drunk in moderation.

In general, a low-fat balanced diet is considered to be healthy and thus indirectly to prolong the lifespan. On the other hand, the “French paradox” has been recognised: a plentiful diet with a high-fat content from goose liver pâté, sausages, cheese, etc. is compatible in France with a relatively low mortality from cardiovascular disease. Investigation of this initially inexplicable observation showed that

other components of a typical French diet, especially red wine, compensate the risk of cardiovascular disease.² The healthy components of red wine, the polyphenols, are also found in certain fruits, e.g. grapes and apples.

Genetics: The effects of mutations

Even the smallest genetic differences cause large individual variation. Humans have approximately 30,000 genes; in its entirety, the genome consists of 3.2 billion letters. In the example shown below, a single letter has been exchanged in one gene. The mutation from G to A means a change in the genetic information: instead of the amino acid arginine, lysine is now incorporated into a particular human protein. This leads to a more angular structure instead of a smoothly rounded one. The person with this mutation suffers from a severe illness.



300 years old thanks to genetic anti-ageing?

Mutations in genes that regulate metabolic processes can triple or quadruple the life expectancy of worms. Perhaps it will also be possible in future to alter human genes in this way.

There have been exciting findings in molecular genetics in recent years; gene mutations have enabled worms (*Caenorhabditis elegans*) to live three or four times as long as normal members of this species. Prolongation of the same order of magnitude would result in a human lifespan of about 300 years. Interestingly enough, the genes whose mutations so remarkably increased the lifespan of worms are also to be found in humans. However, the results of this experiment have only limited application to humans, whose metabolism is much more complicated than that of a worm. And if only for this reason, is it highly unlikely that the genetic changes that prolong the life of worms would have the same effect in humans.

The genes that mutated in the extremely long-lived worms are involved in the insulin signalling pathways.³ These pathways are the body's communication systems, coordinating the energy supplies from glucose and lipids in tasks involving growth, energy storage and consumption. The insulin signalling pathway is activated if nutrients supplied stimulate the release of insulin-like substances in the brain. If no food is available, the insulin signalling pathway remains inactive; this was associated with a longer life in the worms studied. The same effects can be obtained if genes are modified directly with the appropriate technology, or if hypothetical medicines are used to attack the insulin signalling pathway. Such interventions in the insulin signalling pathway affect metabolic processes which are often disrupted in the typical diseases of civilisation: high blood glucose, raised blood lipids, high blood pressure, and obesity. This constellation, known as the metabolic syndrome, can often be found even years before a heart attack or a stroke, contributing to these conditions which are amongst the most common causes of death in industrialised nations. Sirtuins and other molecules in the signalling pathway now offer new drug targets for the treatment of metabolic syndrome.

Genetics: Laboratory animals – How worms improve the understanding of human ageing

Research is not carried out on animals just for the sake of it, but in order to answer fundamental questions in biology – most of which relate to humans too. The number of animal and other species that can be usefully studied therefore tends to be small – which has the advantage of a certain degree of standardisation. Species classically used for biological research include yeasts (*Saccharomyces cerevisiae*), worms (*C. elegans*), fruit flies (*Drosophila melanogaster*) and mice (*Mus musculus*).

Many cell functions were already perfected at a very early stage of evolution and the genes have hardly altered since then. For this reason, many genes in humans, mice, flies, worms, yeasts and, of course, all other species of animal are identical or similar. Of the approximately 30,000 genes found in humans, only about 1% is exclusive to *Homo sapiens*. So it is worthwhile investigating some genetic processes in lower orders first and only afterwards in humans.

The shorter generation time has a particular advantage in ageing research: just months in the life of a mouse or weeks in the life of a worm are equivalent to human years. Results obtained from experiments on worms can be tested out in mice, for example, before they are finally analysed in humans. Despite genetic similarities, results can never be directly extrapolated from a model organism to humans. Experience has shown that some processes observed in mice, for example, are completely different in humans.



A favourite “pet” of geneticists:
The lowly worm (*Caenorhabditis elegans*).

Eat less – Live longer

It works in laboratory mice and some people follow this principle. A strict diet seems to delay ageing. Anyone who does not want to spend a lifetime feeling hungry but still hungers after a long life can put their faith in the effects of resveratrol in red wine and fruit.

Experiments with standard model organisms of yeasts, worms and mice show that a low-energy food intake can markedly prolong life.⁴ Limiting the amount of food to just enough to maintain a minimal body weight is known as calorie restriction. This strict diet delays the appearance of signs of ageing, as it triggers mechanisms that protect the cells.

The findings in animal models have awakened new hope in humans. From the high degree of congruence between the species studied – at least from the biologist's point of view – it can be concluded that a general mechanism applies, which has been preserved throughout evolution. A few people in the USA have already formed the "Calorie Restriction Society": they promise themselves a particularly long lifespan through constant fasting. But the results are controversial; there is no hard evidence that a drastically reduced calorie intake can prolong human life, although there are many indications that this might be the case. However, it is difficult to prove its effectiveness in humans, as hardly anybody is prepared or able to follow this extreme diet for an entire lifetime. For most people, it is far more important to know whether there is any possibility of drug therapy to intervene in this signalling pathway in such a way as to prolong life without the need for a radical diet.

Sirtuins: Enzymes for a longer life?

The key role of sirtuins was discovered in the search for the molecular mechanisms which prolong life by calorie restriction. These enzymes are being thoroughly investigated at present. Even though many questions on their effects and multiple interactions within the cells remain open, it is clear that the sirtuin system is important in the ageing of both the individual cell and the whole organism. As their key role in processes that influence ageing has now been convincingly demonstrated, the next thing to be considered is how the sirtuins could be activated without having to resort to calorie restriction.

Red wine stimulates the production of sirtuins

Certain small molecules can inhibit or stimulate the activity of sirtuins. Many researchers are working with plant polyphenols and addressing the question of whether these compounds could be used therapeutically. Polyphenols are often produced by plants in reaction to various assaults and environmental stresses – in the case of wine, for example, by stress due to drought. It has been shown that resveratrol, a polyphenol found in red wine and other food-stuffs, prolongs the life of worms and flies. Yeasts survive up to 70% longer. For resveratrol to develop its life-prolonging effect, however, it requires functional sirtuins. In humans this polyphenol confers protection against age-related diseases such as cancer, Parkinson's disease, Alzheimer's disease and atherosclerosis. Since it interacts with many structures in the body, however, there could be problems in administering it as a medication.



Red wine in moderation could protect against age-related diseases.

Genetics: Sirtuins – enzymes that can prolong life

Sirtuins are enzymes that support biochemical reactions in bacterial, plant, animal and human cells. They form part of a feedback system that improves the survival of the cell under stress. Various studies have shown that a low-energy diet increases sirtuin activity. More intense stimulation of this activity in turn correlates with prolonged lifespan. The complex of “calorie restriction” and sirtuins is particularly interesting for several reasons.

– There is a connection with the insulin signalling pathway, a system that is disrupted by many diseases of civilisation and is therefore responsible for a great deal of the morbidity of older people.

– There is an association with the polyphenols found in many “healthy” foods, especially in red wine, green tea, fruit and vegetables.

– Sirtuins and other molecules that play a role in these signalling pathways are potential drug targets (points of intervention for medicines) in the treatment of diseases such as diabetes and the metabolic syndrome. This increases life expectancy indirectly. It is also conceivable that intervention in this signalling pathway directly increases the lifespan of people who are not ill to start with.

The stopwatch in the chromosomes

Nobody can stop time. But every gene that longevity researchers reveal as a participant in the processes of ageing is a potential target for intervention to delay ageing.

Our living conditions leave traces. The climate in which we live, our diet, stress, etc. are also responsible for how quickly we age. In addition, our individual genetic makeup probably affects the rate of the ageing process. Our genes may be permanently damaged by sunlight and environmental toxins or wrongly copied in cell processes. That is completely normal: most of the damage is continuously repaired in healthy people. Even so, damage to the DNA accumulates with time and may occur at a faster or slower rate depending on individual predisposition. This is why some sixty-year-olds look much younger, while others look older and some look exactly their age: the genetic material of those who look older could well be more severely damaged.

DNA damage causes cells to age

The different levels of DNA damage can be seen particularly in mitochondrial DNA. In contrast to nuclear DNA, it is not repaired, which inevitably leads to the build-up of defects in mitochondrial genes. This happens ten to twenty times faster than in nuclear DNA. The accumulation of errors in mitochondrial genes mainly affects cell energy production and this in turn can accelerate ageing of the cell. The genetic basis of mitochondrial ageing has not yet been studied in detail. Nevertheless, it has been possible to stimulate energy-depleted cells of infertile women to new activity by transplanting mitochondria, resulting in successful fertilisation and pregnancy. The oldest of these children are now a few years old.⁵ It may also be possible to transplant “young” mitochondria into “old” cells of living people, in order to make them younger. Whether that could be done and quite how is still completely unclear at the present time.

Genetics: Mitochondrial DNA – genes that were “outsourced” from the cell nucleus to the power house

In humans, as in all other life forms, only a very small quantity of genetic material is found in the mitochondria – only a few dozen genes, in fact. In comparison, our nuclear DNA consists of about 30,000 genes. The term “nuclear” refers to the fact that they are found in the cell nucleus. It is actually quite amazing that we have mitochondrial genes at all. The mitochondria basically act as the “power house” of the cell: from nutrient energy and oxygen they produce cell energy, which can then be used for functions such as muscle contraction. According to the laws of biology: if a principle has been universally distributed and sustained, then it is the best available solution under the prevailing conditions.

Defective DNA repair leads to premature senescence

Functional DNA repair is necessary so that continual damage to the genetic material by ultraviolet radiation, toxins and copy errors does not become harmful to health. If, however, the DNA repair mechanism itself is defective, less and less damage can be corrected. The accumulation of mutations finally leads to the disrupted cell functions becoming clinically apparent. In two rare diseases – Werner’s syndrome and Hutchison-Gilford progeria syndrome – DNA repair is disrupted; the WRN or the LMNA gene, both of which are involved in repairing the genetic material, has mutated. These conditions cause the appearances of old age in childhood. Before they are even adults, these children have grey hair or are bald, with the wrinkled skin and liver spots of old age. And what is even worse, they also have type 2 diabetes, cardiovascular disease and cancer. Their life expectancy is 20 years at the outside.

Short telomeres, short life?

Telomeres are a kind of protective cap at the end of the chromosome. They become a little bit shorter with each cell division, as they are never copied in their entirety. Once the telomeres have been “used up”, the cell can no longer divide and it dies. Telomeres are therefore a factor that influences the life of the cell. Genetic variants that alter the length of the telomeres also affect the cell lifespan. There has already been speculation whether ageing could not be stopped by preventing the shortening of the telomeres. This hope has proved to be somewhat problematic, however, as malignant cells in particular are characterised by their immortality. For this reason, research is no longer being carried out to maintain the length of the telomeres, but – on the contrary – efforts are being made to block their extension in cancer cells. This may provide an opportunity to stop these cells living forever. Together with other treatment, this could help patients with cancer to become free of malignant cells.

The length of the telomeres in any individual depends up to 80% on the genes, especially on a specific region of chromosome 12, which alone is responsible for 50% of the variation in telomere length.⁶ There may indeed be a gene in that region which markedly influences ageing – ongoing research still has to determine whether this is really the case.

The Klotho gene: Bringing hope but with adverse effects

Not long ago a gene was discovered that seemed to prolong life. Researchers gave it the name of the “Klotho” gene, after Klotho (or Clotho) the Greek Fate who spins the thread of life.

Studies have shown that increased expression of the Klotho gene extends the average lifespan of mice – by 19% in the females and as much as 31% in the males.⁷ The gene acts on the insulin signalling pathway, and really does seem to suppress ageing, even though this is not devoid of adverse effects in mice. Mice with pronounced Klotho overexpression have half the number of offspring of normal mice. Conversely, mice with deactivated Klotho genes age more rapidly and develop atherosclerosis.

Klotho plays a role in humans as well. A particular variant, VS, has already been associated with a shortened life expectancy. The marked atherosclerosis seen in mice with deactivated Klotho genes led to this relationship being investigated in humans. And in fact, the incidence of narrowed coronary blood vessels was found to depend on the Klotho status.⁸ This means that heart attacks could be the reason for the noticeably shorter life expectancy of Klotho VS carriers. Klotho VS is quite common: about one quarter of the population has a mutation in the Klotho gene that leads to atherosclerosis and reduces life expectancy.



Still blowing strong.

Determinants of lifespan

For the Geneletter, Dr. Joachim Bürger of Munich Re's Centre of Competence for Biosciences (CoCB) talked with Dr. James Vaupel, one of the most respected experts on genetics and life expectancy.

Bürger: Mr. Vaupel, how much does our life expectancy depend on our genes and how much on the rest?

Vaupel: By comparing how long identical twin pairs live and how long fraternal twin pairs live, we can get an estimate of the importance of genetics. It turns out that the conclusion of the twin studies in Denmark (which has been replicated in Sweden and Finland and other places) is that about 25% of the variation in how long people live is due to genetic variation among people and 75% is due to non-genetic variation, that is, behavioural and environmental variation.

Bürger: Are there any important components identified already or is it mostly due to stochastic effects?

Vaupel: A lot of it has to do with good luck or bad luck. You know, stepping in front of the truck is very bad luck. People have tried to break the 75% down into how much of this is due to things that happen to you when you are young, for example your education or diseases which you have. And how much is due to the things that are happening to you when you're older. Only about 10% of the variation in how long people live is due to things that happened to people when they were young. So the education level, the diseases that they suffer, how wealthy their parents were, all those things put together, account for maybe 10% of variation. The remaining 65% of the variation is mainly due to things that have happened recently. People sometimes say: You die from your whole life, but the truth of the matter is that you mainly die from yesterday. The things that are happening right now are the main effect.

Bürger: If you look at the ages your parents or grandparents died, can you draw conclusions about your own life expectancy?

Vaupel: No! There is very little information, about how long you are going to live that can be drawn from how long your relatives lived including your parents and grandparents. If you know how long your father lived, that will explain only about 2 or 3% of the variation in how long you're going to live. The same thing goes for your mother.

Bürger: That's not very much, so we can forget how long our parents lived?

Vaupel: Almost entirely. The main thing about how long you're going to live is that if life expectancy continues to go up 2.5 years per decade and you were born when your parents were something like 30 years old, then you can expect to live something like 7.5 years longer than the generation of your parents and something like 15 years longer than the generation of your grandparents.

Bürger: In worms and in other animals we can see dramatic extensions of the lifespan – doubling or tripling – by some approaches, which change or alter only a few genes. Do you think it is possible in humans, that we can have such dramatic effects as well?

Vaupel: It's certainly possible in the future some time, but it's not all clear. A lot of research has been done over the past 10 to 20 years on the genetics of human longevity. No gene has been found up until now that has a major effect. A number of genes have been found that have fairly minor effects, but nothing major.

Bürger: Which multiplication factor for human life expectancy is possible?

Vaupel: Well, it is completely unknown right now. Human life expectancy has been going up for the last couple of hundred years, but it has been going up because of non-genetic improvements in behaviour and environment. There has not been any increasing human longevity because of the use of genetic information. And there is no genetic knowledge right now that would enable medical doctors to intervene in a way that would substantially increase human life expectancy. The most important gene so far that's been found is called APO-E. It comes in three varieties and one variant, the APO-E4, raises older peoples' chance of death by roughly 10% per year. The APO-E2 variant tends to lower the chance of death by about 10% a year. But that is only 10%, it's not a really major effect.

Bürger: Some ageing experts have proposed a kind of an upper limit of human lifespan in the range of approximately 130 years. Do you think they are right?

Vaupel: There is no empirical evidence for a limit to human life expectancy at age 130 and there is no theoretical reason that there should be such a limit. So this is just speculation and I would not put any weight on it. In 1840



Dr. James Vaupel is, among other things, Founding Director of the Max Planck Institute for Demographic Research in Rostock, a professor at Duke University, Durham, NC, USA and a member of the National Academy of Sciences in the USA.



Dr. Joachim Bürger is a consultant for genetics, gene technology and molecular medicine in Munich Re's Centre of Competence for Biosciences.

There is no empirical evidence for a limit to human life expectancy at age 130 and there is no theoretical reason that there should be such a limit.

Swedish women had the world's longest life expectancy and it was 45 years on average at birth. Last year Japanese women had the world's longest life expectancy, and it was 86 years at birth. So between 1840 and last year life expectancy went up by little over 40 years. Life expectancy in the countries that are doing well has been going up about two and a half years pro decade for the last 160 years. If you look at this record of two and a half years increase of life expectancy every decade, there is no sign of any deceleration. There is no sign of reaching any kind of limit. The two and a half years per decade has been constant for the last 160 years.

Bürger: Is there possibly a sign of acceleration?

Vaupel: There is acceleration in bringing down the mortality of older people. Before 1950 there was very little improvement over time in death rates among people above 60. But since 1950 and especially since 1970 there has been a dramatic improvement in bringing mortality down among older people. And this acceleration is continuing, so at older and older ages – now among people in their 90s – there is a substantial decline of mortality.

Bürger: Would you expect this to continue in the future? Do you see a possibility that we can further increase life-span with medical interventions, maybe by new methods like gene therapy or stem-cell therapies?

Vaupel: There is no reason to think it will not continue. Bio-medical scientists are beginning to understand the basis of the really important diseases that affect older people. And then, as you mentioned, there are some new possibilities that have started to be developed. One promising approach would be to try to base medical interventions on

an understanding of genetics, to give people medicine that depends on the genes that they have. A person with certain genes will get one kind of medicine and a person with other genes gets a different kind of medicine. Perhaps 20 years from now, it might be possible to replace a bad gene with a better gene. In addition to that, there has been a major increase in knowledge of regenerative medicine, so that scientists are beginning to understand how to regenerate the heart, the liver, the kidneys and so on.

Bürger: So you think we as insurers really need to prepare ourselves for a further increase in life expectancy caused by new medical or biological therapies?

Vaupel: That's right. I would suggest that, as a rough estimate, you should plan for an increase in human life expectancy of about two and a half years per decade for the next few decades.

Bürger: Coming to something different, looking at the genetics of lifespan, we face the problem that the Y chromosome, i.e. being male, appears to shorten life.

Vaupel: This is complicated, actually. For humans today in Europe, the United States, Japan and so on, it is absolutely true that women live longer than men. But it is only since 1900 that there has been a big divergence between male and female longevity and life expectancy. This has been caused in considerable part by modern civilisation that has given men opportunities to kill themselves.

Bürger: Because of testosterone-based behaviour?

Vaupel: That's right. Testosterone, interacting with cigarettes, alcohol, automobiles and so on. Males are more aggressive than females in many species. Another aspect of this is that males are healthier than females at most ages including old age, but they die younger. It is a paradox. If you do objective tests of an older man and an older woman, the older man has greater hand-grip strength, can walk across a room faster, has greater lung capacity, has stronger leg muscles, can get out of a chair more easily, suffers less from arthritis and other debilitating diseases. According to objective measures, older men are healthier than older women of the same age. Furthermore, if you ask older men how healthy they are and ask older women how healthy they are, the men say that they are healthier. But they die younger. The reason probably is that men do not go to the doctor in time and do not take proper care of their health, while women take better care of their health. Although this may have some kind of biological basis – men may be stupid because they are males – nonetheless it is not biological in the sense that men die earlier because they are unhealthier.

If you do have good health behaviour, you may live five or ten years longer than the average life expectancy of your cohort.

Bürger: The Bavarian “cloister study” supports the claim that men and women actually have the same lifespan if they only live under identical conditions. But is a cloister population really one you can draw conclusions from for the general population?

Vaupel: No, there are limits to generalising about cloister populations. But in addition to the cloister data, there are the other data that I briefly told you about. It is certainly true that male behaviour accounts for a big part of excess male mortality.

Bürger: We face political action against our concept of sex-specific insurance premiums, e.g. in pension or life insurances. These are adjusted to the real life expectancy of men and women, usually in developed countries, where women live longer than men.

Vaupel: As I mentioned before, in the year 1900 life expectancy for men and women was quite close in most countries. Over the course of the 20th century the gap emerged. In most countries recently, the gap is not getting any wider – the gap is staying about the same. A lot of it has to do with behaviour.

Bürger: But behaviour is a trait that is also to some degree genetic!

Vaupel: Oh yes, you're right. There is an interaction between the genes that men have and the way they behave, but there is also a cultural and social component to behaviour.

Bürger: Finally, as a longevity expert, what do you do to grow as old as possible?

Vaupel: This is a very good question, because one of the reasons that people doubt that life expectancy can continue to go up is that they don't know how themselves to live longer. If I wanted to live to 100, I would not be able to figure out some strategy that would guarantee that I would celebrate my 100th birthday. There are actually relatively few things that an individual person can do to live longer. Most of the reasons that people are living longer have to do with public health, cleaner water, cleaner air, better nutrition, safer highways, less cigarette smoking because of public health interventions, and so on. Also biomedical knowledge is leading to better medical practice. But nonetheless, a particular person can do a few things: So, I try to get some exercise every day. I try to watch my weight. I try to eat a nutritionally balanced diet, not too much fat. I don't smoke. I don't drink excessively. I don't drive an automobile when I've drunk alcohol. When it's cold, I put on a hat. When it is raining, I have an umbrella or raincoat. The bottom line is that if you want to live as long as possible, you should do what your mother told you to do.

Bürger: This is not very spectacular. You are not telling me to take some kind of anti-ageing medicine?

Vaupel: No, I do not think there is some magic solution. But nonetheless, doing what your mother told you to do is quite important. If you do have good health behaviour, if you go to the doctor when you are sick, you put on a coat when it is cold and so on, you may live five or ten years longer than the average life expectancy of your cohort. Because a lot of people do stupid things. They get sick because they do not take proper care for their health. They are overweight, they smoke, they drink too much, they do not wear proper clothing in the winter.

Bürger: Mr. Vaupel, thank you very much for this interesting conversation.

Sex-based differences in life expectancy

Women live longer than men. Men face more risks than women. Scientists cannot agree on why this should be so. However, there is some evidence suggesting that the different genetic predispositions of the sexes have a direct effect on life expectancy.

Women in Germany have an average life expectancy of 82 years, men of 76 years. In the USA, girls who were born in 2000 can reckon to live to be 80 while men can only count on 75 years of life. In Canada, women born between 1990 and 1992 will reach an average age of 81 years, while it is predicted that men born during the same period will die on average six years earlier.

The greater life expectancy of women can be seen in all highly developed countries for which data are available. The reasons for this are the subject of scientific controversy. It is not disputed that there are whole series of biological and non-biological differences between the male and female organism, and this applies not only to the genetic and hormonal makeup but also to gender-specific behaviour that originates from genetic as well as societal and cultural factors. What is difficult to assess is whether there is a causal relationship between particular sex-specific differences and life expectancy.

XX or XY decides more than just the sex

A person's sex is determined at the moment of conception – two X chromosomes mean that the baby will be a girl; one X and one Y chromosome are responsible for the development of a male child. Following fusion of the egg and sperm cells, an undifferentiated mass of cells forms. The SRY (sex-determining region Y) gene on the Y chromosome in male embryos promotes the development of male gonads. In female embryos, one of the two X chromosomes is deactivated in each cell. Which chromosome is deactivated is pure chance.

A chromosome is a large piece of DNA with a complicated structure, which carries the genetic information. As one X chromosome is deactivated in every cell, women actually have both of their X chromosomes active – although in each case in only half of the cells. The advantage of this over the male sex is that a possible defective X chromosome is active in only about 50% of the cells, whereas in a man it would be active in all cells. Women can therefore compensate for some defects with their second X chromosome. This is not possible for men, and they become ill. This can be seen with rare X-linked diseases such as Duchenne's muscular dystrophy or certain diseases of the blood which occur almost exclusively in men. For this

Average life expectancy

Abridged mortality table		1996/98	1998/00	2002/04
At age 0	Men	74.04	74.78	75.89
	Women	80.27	80.82	81.55
At age 40	Men	35.84	36.46	37.37
	Women	41.35	41.84	42.46
At age 80	Men	6.75	7.01	7.24
	Women	8.23	8.47	8.64

Women live longer: The mortality table of the Federal Statistics Office shows the different life expectancies of the sexes in Germany.

“Everyone in medicine and related fields understands that there are marked sex-based differences in the epidemiology, clinical manifestations, course, and therapy of disease. Although very few of these differences are understood in molecular or cellular terms, the explanations must derive from the fundamental biologic differences between the sexes.”

Daniel D. Federman, Harvard Medical School⁹

reason, serious learning disabilities are also far more common in men. The different X chromosome status may possibly also play a role in complex diseases such as heart attacks, cancer or Alzheimer’s disease.

There are great differences between men and women in the clinical picture of “autoimmune diseases” where the immune system attacks the body’s own tissues. The incidence of thyroiditis (inflammation of the thyroid gland) is seven times higher in women than in men. Myocarditis (inflammation of the heart muscle) affects the sexes in equal numbers but tends to be more serious in men. The course of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) changes during pregnancy because of higher oestrogen levels: SLE (humoral autoimmunity) becomes worse, RA (cellular autoimmunity) gets better.

Men and women also react differently to certain medicines and vaccines. Women produce more antibodies¹⁰ after many vaccines and break down many medicines such as theophylline, erythromycin, prednisolone and phenytoin more quickly. In contrast, men metabolise certain antidepressants more rapidly.¹¹ These effects have not been adequately investigated. However, it is conceivable that antidepressants have a stronger effect on women – and also worse adverse effects – while achieving only relatively low therapeutic levels in men, who thus suffer more from the underlying disease. This cannot be ruled out as a reason for the higher risk of suicide in men.

The hormonal status is a further indirect sex-based difference. Oestrogens and progestogens dominate in women while testosterone is the major male hormone. This has consequences for survival if, for example, cancer occurs in the breast, uterus, ovary, prostate or testes, as these tumours are often hormone-dependent.

Of course not only is there a biological basis, but behaviour also impacts to a great extent on human life expectancy. Men behave differently from women in many ways, especially when it comes to making provision for the future or consulting a doctor when they are ill. The probability that they seek medical help is only 25% in comparison with women. The consequences can be seen with skin cancer, for example: it affects similar numbers of men and women but the men die of it four times as often.¹²



Sex-based differences in life expectancy: Relevance to the insurer

For the insurance industry, the different life expectancies of men and women are important, as premiums for personal insurance are calculated on the basis of mortality. The European Union has issued antidiscrimination directives which, among other things, forbid discrimination in social security, healthcare and the provision of services. Some parties with a vested interest argue that insurers should be forbidden to include the personal characteristic “sex” in the calculation of premiums, because this is discriminatory. In fact, sex-based premium calculations reflect the respective risks both correctly and fairly. Men

pay lower premiums for private pension and health insurance because their life expectancy is lower on average. Women pay lower premiums for life insurance because they live longer on average.

Not only the insurance industry but also the clients have an interest in maintaining premiums commensurate with risk, so that the applicant’s sex should still be taken into account when calculating the premiums.



High testosterone levels are linked to aggressive behaviour.

Men die earlier, but why?

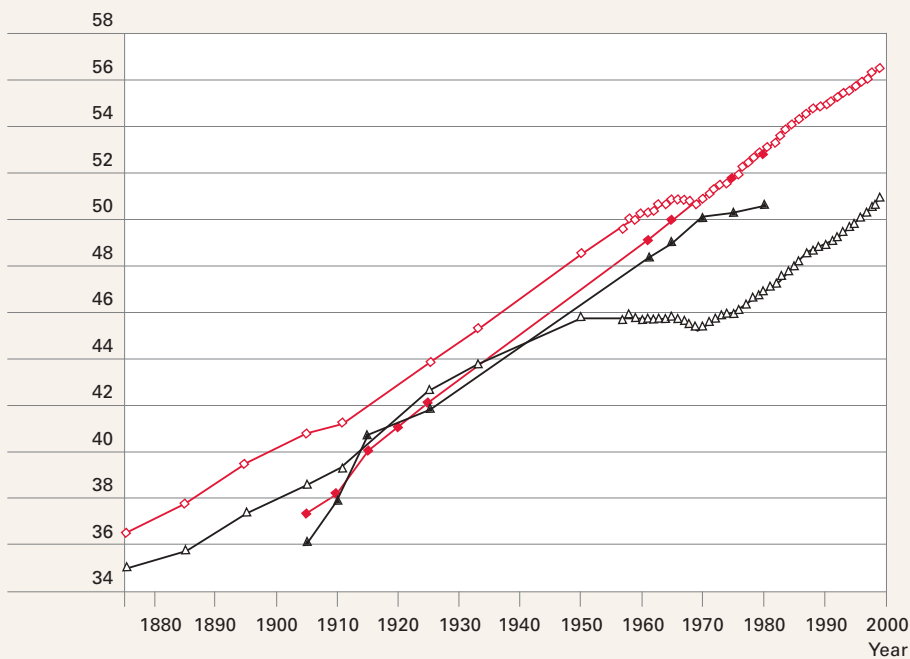
Whenever the topic touches on the reasons for sex-based differences in life expectancy, the media like to cite the “cloister study”. Not least in the discussion of premium differentiation in private insurance – in connection with “unisex rates” – this study has often been presented as evidence that the higher mortality of men is not biological but is related to behavioural risk factors. According to this, men and women would have approximately the same life expectancy if their lifestyles were more or less the same, as is the case in a monastery/convent.

The author of the study, Dr. Marc Luy, assistant professor of demography at the University of Rostock, distinguishes between biological, behavioural, and environmental factors. He takes biological factors to be those that are not influenced by humans, i.e. the genetic and hormonal predisposition; behavioural and environmental factors are those of lifestyle and occupational risks that also affect people directly or indirectly.¹³

Nevertheless, most human behaviour patterns depend to a considerable extent on the genes. Sex-specific behaviour is nothing other than genetically determined behaviour. That men are more likely to commit violent crimes or to perform extreme sports and thus considerably reduce their life expectancy can be attributed to the male hormone testosterone.¹⁴ Even within one of the sexes, certain behaviour can be partly explained by simple biological parameters such as hormone levels. Marc Luy’s separation into biological and behavioural factors is therefore fairly arbitrary and scientifically questionable.

The Bavarian "cloister study"

Life expectancy at the age of 25 years



The Bavarian "cloister study" shows that the mortality of nuns and monks is nearly the same because monks live longer than men outside the monastery.

—◇— Women
—◆— Nuns
—▲— Monks
—△— Men

Not representative: Life expectancy in a monastery/convent

Nobody takes the step of entering a monastery/convent by chance. Monks and nuns are therefore not representative cross-sections of the population; the decision to embrace a spiritual life in itself has a selection effect. The choice of this lifestyle may well be attributed to particular psychological factors and personality features. The person must be able to abstain from certain things; this is probably reflected in any tendency not to smoke or drink alcohol, both of which habits clearly contribute to an earlier death, especially in men. Men without these burdens would also have an above-average life expectancy outside the monastery walls. Tranquillity and seclusion, which are inherent in monastic life, contrast sharply with typical male patterns of aggression and risk-taking behaviour.

Luy explained his observations in part by attributing the same mortality of the sexes within the monastery/convent to similar patterns of behaviour, but there could be other explanations for the reported difference in mortality between monks and other men. It is thoroughly plausible to conclude that the life expectancy of the men in the monastery is not increased, but rather that there is simply segregation of the male population. Men living in a monastery tend to be those who anyway do not exhibit typical aggressive male behaviour, because they have lower testosterone levels and as a result of this they live longer. In epidemiology, such concealed variables that might upset the results of a study are called "confounders", and when these confounders are not taken into account it is difficult to assess the results scientifically. To conclude from observations in the monastery/convent that the life expectancy of the sexes is generally identical is not justified unless the study population has been checked for possible selection effects such as testosterone levels. This was not done in the Bavarian "cloister study".



High life expectancy in a monastery or convent due to tranquillity and seclusion?

As a result, it has methodological weaknesses which mean that it is not possible to draw well-founded conclusions that can be extrapolated to the population as a whole. But even if we can accept the conclusion that the mortality of men and women would be the same, the fact remains that there is a large difference in life expectancy between the sexes in the general population. Furthermore, besides the Bavarian "cloister study", other studies have been conducted on life expectancy of monks and nuns, e.g. one in Poland in the 1980s, where both cloistered sexes were found to have a slightly increased life expectancy of 2–3 years.¹⁵ The two studies thus contradict each other in their most basic conclusions.

Females also live longer in other animal species

The fact that sex-based differences in life expectancy are seen not only in humans but also in other animals argues strongly for a direct biological sex-based influence on lifespan. The following table gives the maximum life expectancy for the two sexes of certain animal species.

	Male	Female
Sheep ¹⁶	20.0	24.0
Pilot whale ¹⁷	46.0	63.0
Opossum ¹⁸	12.0	17.0
Seal ¹⁹	52.0	56.0
Capuchin monkeys ²⁰	25.0	40.5
Macaque ²⁰	38.0	40.0
Chimpanzee ²⁰	56.0	59.4

Many female animals have a higher life expectancy than their male counterparts. As humans are genetically closely related to other animals, it can be concluded that there is a common biological basis for the difference in life expectancies between men and women.

The golden rules for a long life

First and foremost: non-smokers live longer.

Drugs? Never.

Alcohol? Better not ... perhaps just a little.

Sufficient, regular but not excessive exercise:
Use 2,500 to 3,000 kilocalories per week in endurance and strength training.

Low-fat diet, eat lots of fruit and vegetables.

Don't sunbathe too often – your skin will never forget.

Cardiovascular risk factors that can be monitored should be kept at favourable levels (this can be achieved through lifestyle changes, possibly also with medication):

- Weight and body mass index (BMI)
- Blood lipids (cholesterol and triglycerides)
- Blood glucose
- Blood pressure.

Drink plenty – mainly non-alcoholic beverages.

Seek out mental challenges.

Have vaccinations appropriate to the infection risks.

Avoid unnecessary risks and violence.

And, as Prof. Vaupel said earlier, there is no patented formula.
You should simply do what your mother told you to do as a child.

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