The future of human life expectancy

Do we know how little we know?

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A well-known picture to start with

The so-called record life expectancy (life expectancy in the "healthiest" country in the world) has been rising linearly for a long time. Speed: approx. 2.5 years per decade.

**Will this go on forever?**

Part 1: The Party is over!

There are numerous very good arguments to suggest that the increase in life expectancy will have to slow down significantly in the near future. Even a decline in life expectancy seems possible.
Arguments for a trend reversal

**Argument 1:** There has never been a "mechanism" that has uniformly increased life expectancy. Different things have influenced the “lx-curve” at different times in different ways. This has by pure chance led to a linear increase of LE (which is an aggregated parameter of this curve).

If the linear trend has emerged only by chance through a combination of a wide variety of independent effects, there is little to suggest that it will continue.
Arguments for a trend reversal

**Argument 2:** The relative reduction in mortality required to gain 1 year of additional LE is the larger, the larger the LE already is.

**Argument 3:** The slowdown of the increase has already started.

In some countries (e.g., the USA), life expectancy is already declining.

Source: Until 1999: figures from the chart by Oeppen und Vaupel (2002) (see above); own calculations for the years afterwards.
Arguments for a trend reversal

**Argument 4:** Numerous other risks that could potentially increase mortality.

- Climate change
- Environment (microplastics, fine particulate matter,...)
- Long Covid
- Increased probability of future pandemics
- Lifestyle
- etc.

Remark:

- Anything caused by "behavioral factors" would lead to an increase in the heterogeneity of mortality in the population.
- Annuitant mortality in insurers' portfolios likely to be less affected.
- Anything else could, in principle, affect the entire population.

Current paper on climate change

- It lists a wide range of possible effects
Arguments for a trend reversal

**Argument 5:** The higher the age, the less is to be gained from "typical medical progress". If you cure one disease in an 85-year-old, she will soon get (or already has) the next one (whack-a-mole effect).

**Conclusion:** As long as it is not possible to slow down ageing per se, the end of the "longevity party" seems inevitable!

Source: Collerton et al (2009) British Medical Journal Health and disease in 85 year olds: baseline findings from the Newcastle 85+ cohort study

Source: Nir Barzilai: How to die at a very old age. TEDx-Talk: https://www.youtube.com/watch?v=TsA4SHhUzt4

Source: S. Jay Olshansky (2016), presentation at the Longevity 12 Conference. The chart shows risk factors for cancer. The talk also includes images for heart disease and Alzheimer's disease.
Part 2: The Party hasn't even started!

There are numerous very good arguments to suggest that the increase in life expectancy will accelerate significantly in the near future.

Being able to slow down ageing seems to be within reach.

In what follows, I present a subjective (!) selection of advances in this field.*

*Note: There are numerous other developments that could have an impact on human LE by affecting individual diseases. Here also it is uncertain if and when progress will be made. However, because of the whack-a-mole effect, the potential impact is limited. Therefore, we do not address these aspects.

Disclaimer: This chapter deals largely with medical issues. The presenter is not an expert in this field. Therefore, no decisions should be made based on the following statements without independently verifying them.
The most important thing in advance: It is now understood what "ageing" actually is.

Ageing does not work like this..., but rather like this:

**Healthy** (and young)
- No Cardiovascular disease
- No Cancer
- No Alzheimer disease
- No Parkinson disease
- No Type II diabetes
- No Osteoporosis

**Sick** (and old)
- Get CVD
- Get Cancer
- Get Alzheimer’s
- Get Parkinson’s
- Get Diabetes
- Get Osteoporosis

**Diseases of ageing**
- Alzheimer’s
- Cancer
- Cardiovascular
- Parkinson’s
- Muscular degeneration
- Type II diabetes
- Osteoporosis

**Natural changes**
- Grey hair
- Wrinkles

**Others**
- Menopause
- Hearing loss
- Joint stiffness
- Immune diseases

**Sickness and death**

Source: Biology of Human Senescence, presentation of Richard Faragher, Professor of Biogerontology, at the 2023 „Living to 100 Symposium“.
What are the Ageing Mechanisms?

The most popular representation: Hallmarks of Ageing

An alternative approach - based on damage processes and “maintenance”

Consensus among experts seems to be: "Mechanisms that cause ageing are known and druggable!"*

Geroscience is the science that targets the Hallmarks of Ageing.

* Quote is from the already cited talk “Biology of Human Senescence” by Richard Faragher.

Currently discussed approaches to influence the ageing process

**Caloric Restriction (CR):**
- Put simply: eat only enough to barely survive.
- This extends life expectancy in many species - in some significantly.
  - presumably also has a positive effect in humans
  - but who wants to do that permanently?
    - Therefore, hardly any long-term studies with people
    - And can we trust self reported calory intake?
  - Results in other organisms look impressive, e.g., mice (see chart)

Currently discussed approaches to influence the ageing process

**Rapamycin:**

- Inhibitor of the protein mTOR; numerous effects in the body, including improving **autophagy** ("cleaning up" damaged cells/cell components).
- Already approved for various purposes.
- Strongly (!) simplified: Rapamycin tricks the body into thinking it is under CR.
  - Hope: slowing ageing like CR but without its drawbacks.
  - Increase LE in mice (to lesser extent than actual CR but almost as high in some studies).

**Effect on human ageing is currently being researched.**

Already approved drug → "Safety" basically already tested. But: Permanent intake comes with side effects. Current studies: Short-term use every now and then has a similar effect in mice as long-term use.


Currently discussed approaches to influence the ageing process

**Telomerase (enzyme that lengthens telomeres):**
- Telomeres shorten with each cell division
  - If they are too short, the cells can no longer divide (they die or become "senescent cells", see below).
- Telomerase counteracts this
  - significant successes in terms of lifespan in mice
  - in humans, it comes with an increased likelihood of cancer.

My impression: After initial optimism, this topic became much quieter recently.

Source: Presentation: Novel Approach to Extending Human Healthspan - Insights from a Natural Experiment - Dr Douglas Vaughan at 2022 Fasano Longevity Conference; https://www.youtube.com/watch?v=ghOuNSHiOVU
Currently discussed approaches to influence the ageing process

Senolytics (drugs for the elimination of senescent cells):
- In the course of life, senescent cells become more and more. The immune system becomes worse and worse and no longer manages to "clean them up".
- Accumulation of these cells contributes substantially to ageing.
- Challenges:
  - How can drugs be made to attack only senescent cells (and not normal cells as well)?
  - Senescent cells can also have a benefit
- Currently great progress, just two examples
  - In senescent cells, "senescence-associated beta-galactosidase" is present. This "eats" a special type of sugar. If the senolytics are "packaged" in these sugars, they only reach the senescent cells.
  - Approaches to convert senescent cells back into "normal" cells (resveralogues).
Currently discussed approaches to influence the ageing process

**Heterochronic parabiosis and variations thereof (bloody science):**

- The old mouse is rapidly getting better, the young one worse
- Apparently both: “harmful” stuff in the old blood, and “useful” stuff in the young blood
- Not yet fully understood what exactly would need to be "filtered out" of the old blood
- It already seems to be beneficial to feed young blood plasma to old mice or to filter out old blood plasma and replace it with saline.
- Very recent research: administration of bone marrow cells from young mice to old mice.


For more details, see, e.g., interview "Longevity update with Dr. Aubrey de Grey" [https://www.youtube.com/watch?v=KEdRTzl2DgY](https://www.youtube.com/watch?v=KEdRTzl2DgY) starting at about minute 46 and publications of the researchers mentioned there.
Currently discussed approaches to influence the ageing process

Metformin:
- Standard diabetes drug. Diabetics who receive this, "age more slowly" (higher LE than non-diabetics!).

- Metformin currently probably most promising candidate for first medically based therapy against "ageing", cf. TAME study. Metformin was not chosen because it promised the greatest benefit, but because it has the lowest risk (safety already tested).

Currently discussed approaches to influence the ageing process

**PAI-1** = protein that delays the dissolution of blood clots (plasminogen activator inhibitor-1; aka SERPINE1).

- Insights from an Indiana Amish community
  - Woman with strange disease: not a bleeder, but: After injury bleeding stops normally, after 1-2 days it starts again. Reason: anomaly in a gene that controls PAI-1 level - she has too little PAI-1.
  - Douglas Vaughan became curious because he had done research on related proteins and knew that reduced PAI-1 levels in animals increased life expectancy.
  - because the Amish live relatively isolated: little genetic variation
  - A member who entered the community at the end of the 19th century brought this gene anomaly with him.
  - He had 17 children and 142 grandchildren. Today, about 15% of the 20,000 members have this gene anomaly and the reduced PAI-1 level (only very few in connection with the above-mentioned disease).

- Findings from comparison of community members with and without gene anomaly:
  - Those with gene anomaly (i.e., with the lower PAI-1 levels)
    - Have longer telomeres
    - Not a single person one of them has diabetes (in the comparison group, analogous to the total population)
    - Have higher Ix; (but: small sample size!)
  - There are already phase 3 trials on pills that lower PAI-1 level. (TM5614)

Source: Presentation: Novel Approach to Extending Human Healthspan - Insights from a Natural Experiment - Dr Douglas Vaughan at the 2022 Fasano Longevity Conference. https://www.youtube.com/watch?v=qhQuNShiOVU
Currently discussed approaches to influence the ageing process

**Dancing molecules** (supramolecules activate processes in the body by sending a variety of signals → possible therapies in regenerative medicine).

Application examples:

- BMP-2 ("bone morphogenetic protein") is used for regeneration of bones and cartilage; massive side effects possible in the necessary doses. In combination with signals from supramolecules, the dose can be greatly reduced.

- Special supramolecules (dancing molecules); "dancing movements" increase likelihood of signal reaching receptor. Can "repair" injured spinal cord.

Source: Presentation "Use of Dancing Molecules to Reverse Paralysis After Spinal Cord Injuries," Dr Samuel Stupp at 2022 Fasano Longevity Conference
https://youtu.be/mG7M2VzZaX0
Part 3: Stuff that seems important to me but doesn't fit into any other chapter.
Future developments could happen much faster than before.

Epigenetic Clock

- DNA methylation measures the "true age of the body".
- Epigenetic Clock
- Pioneer of this research: Steve Horvath
- Requires DNA methylation at (only) about 1,000 genes
- Calculates from this with a regression model the so-called Grim Age
  - "Works" to predict individual LE in humans and 120 other mammals.

Hope (greatly simplified): In the future, clinical trials will no longer have to wait for many years to see how a treatment changes mortality. Rather, we will be able to measure how the grim age (or another epigenetic clock) changes after a rather short period of time.

But also: Asymmetric information and resulting adverse selection in annuity markets?
The most optimistic player in this game

He proposed the above-mentioned 7 „deadly things“.

probably overoptimistic in the presentation of his theses

- e.g. Longevity escape velocity
- e.g. LE 1000
- e.g. "First person to live to 200 is already alive".

But: serious research

- SENSE
- LEV Foundation
- Currently investigating different combinations of rapamycin, senolytics, telomerase and variants of heterochronic parabiosis
Why everyone is talking about healthspan

Narrative:
- Past: Survival pushed into the "red zone"
- Future: pushing the "red zone" out to higher ages

Claim (not correct in my opinion):
- This will result in an increase of (almost) only healthspan and hardly any lifespan.

Source: Keynote presentation by S. Jay Olshansky on the panel discussion "Futurism - Medical Knowledge of ageing" at the 2023 "living to 100" Symposium.
Part 4: Consequences of this uncertainty for measuring, modelling and managing (long term) longevity risk.
Natural cascade for dealing with risks

- Understand
- Model
- Measure
- Manage

It is often assumed, that the structure of a risk is understood. However, this is not so clear, with respect to longevity risk.

- If there are aspects that increase future uncertainty but are not observable from past data, calibrating the "dispersion parameters" of a model to historical data may not be appropriate, see below.

- If the facts clearly indicate that uncertainty is (much) higher over long periods than over short periods, one should (at least for modeling long-term risks) only use models that exhibit this property (see chart on the right).

Example: A mortality model calibrated to historical data. Then the parameters of the model are projected stochastically into the future with different processes. Graph: possible range for future “e60”.

(Only) processes that allow for future trend changes meet the requirement that risk is higher for long periods of time.

- Estimate required for probability and intensity of trend changes.

Possible approaches to dealing with these findings include

1) Observe and evaluate current developments

A suitable institution within the insurance and pension industry should

- ... systematically monitor developments
- ... assign a (qualitative) estimate to the developments (short-term vs. long-term; high vs. low probability; high vs. low impact if successful, etc.).
- ... present the results to market participants in a comprehensible form.

The question of whether these findings give rise to a need for action on the part of each company (pension fund / annuity provider) must of course be answered individually for each company.

2) Derive scenarios (understanding and modeling risks)

In my opinion, it would be desirable to derive scenarios that could be used for scenario analyses and also as "calibration supports" for stochastic models.

- E.g., optimistic scenario: drug A comes to market in 10 years, drug B in 15 years
  - What would the life expectancy be in this path?
- Analogously: pessimistic scenario: no breakthrough in slowing ageing, but climate change and microplastic
  - What would the life expectancy be in this path?
- Possible benefit
  - Use of these scenarios in scenario analysis
  - If statements of the following type can be made:
    - "The probability that things will be even better (worse) than in the optimistic (pessimistic) scenario is x% (y%)"
  - Then stochastic models can be calibrated accordingly.

Interdisciplinary cooperation required!
Possible approaches to dealing with these findings include

3) Risk analyses (measure risks)

With the scenarios and models derived in 2), the risks of a company (e.g., pension fund) can be analyzed.

In particular, this allows an assessment whether previous risk management measures are sufficient.

4) Derive options for action (manage risks)

Options for, e.g., an annuity provider could be:

- No change required.
- No longer offer lifelong annuities
- Product design with lower “systematic longevity risk” for the insurer
  - weaker guarantees
  - tontines
  - etc.
- Hedging of longevity risks (see chart on the right)

There are numerous different hedging instruments (mortality derivatives), which differ greatly in their effect.

When dealing with this issue, it is essential to analyze the following questions simultaneously:

- What’s the impact? (Risk reduction)
- What does it cost (price of the hedging instrument, for insurers also savings on the cost of capital)
  - If you believe that "the market" also underestimates uncertainty: "Price<Value".

A brief conclusion and a thesis
A brief conclusion and a thesis

Conclusion: With regard to the future development of life expectancy, changes are possible in both directions.

- The aspects that argue for a slowdown in the increase in life expectancy are already present. A dampening seems very likely in the near future (and can already be observed in some countries).
- The slowing of the human ageing process could (in a more distant future) lead to a rather large increase in human life expectancy.
- No one can seriously predict today if and when "something will happen" and how big the impact will be.
- However, the sheer number of possible therapies, some of which are already very advanced, suggests that something will happen in the next few decades with a probability that is clearly > 0 (but not 100%!!!).
- That’s uncertainty!
- In particular: This can become relevant before a typical insured person buying a deferred annuity today will have died.

Thesis: The insurance industry must pay more attention to this topic in the future than in the past.

- **Individual view**: Uncertainty of individual life span (which is usually even more uncertain than life expectancy) is much larger than most people think.
  - Managing this uncertainty through lifelong income (buying an annuity) is becoming increasingly important.
- **Collective view**: The so-called systematic longevity risk on insurers’ books may be greater than assumed. Typical stochastic models might underestimate this risk.
  - More innovative risk management measures could gain importance (reinsurance, "longevity derivatives", alternative product design (e.g. tontines),...).

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Degree of individuality by company