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## 50 Shades of "de Grey" International Drivers of Longevity Outliers

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## Today's Topic

# Survival & Mortality



Source: By Ciaurlec - Own work, CC BY-SA 3.0, <https://commons.wikimedia.org/w/index.php?curid=16214368>



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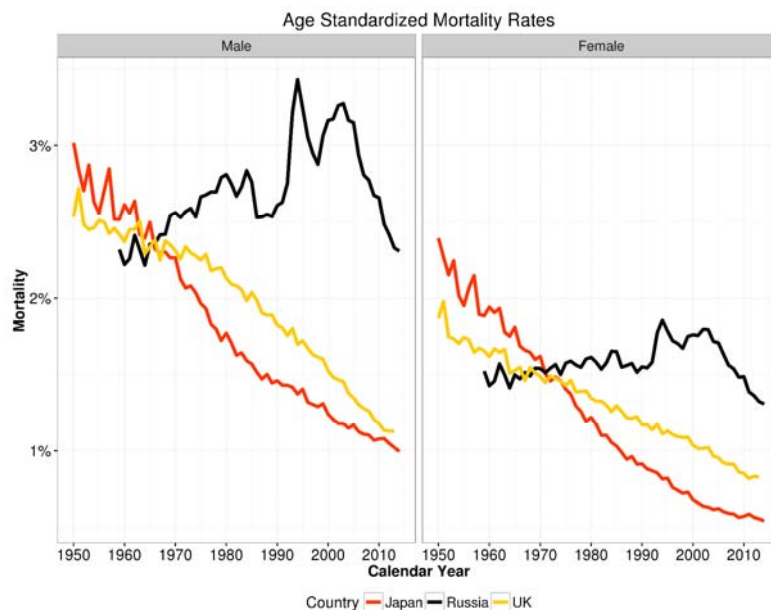
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## Living Forever : The Oldest Old

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## What we know

- Mortality gains – in most countries
- Historical gains in life expectancy have been attributed to a reduction in early-life mortality
- More recent data, however, show evidence for a decline in late-life mortality



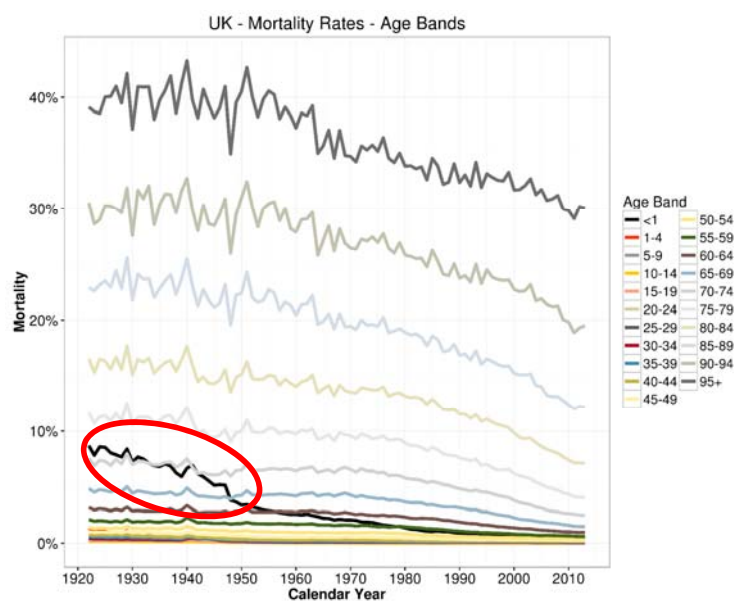
Source: mortality.org

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## What we know

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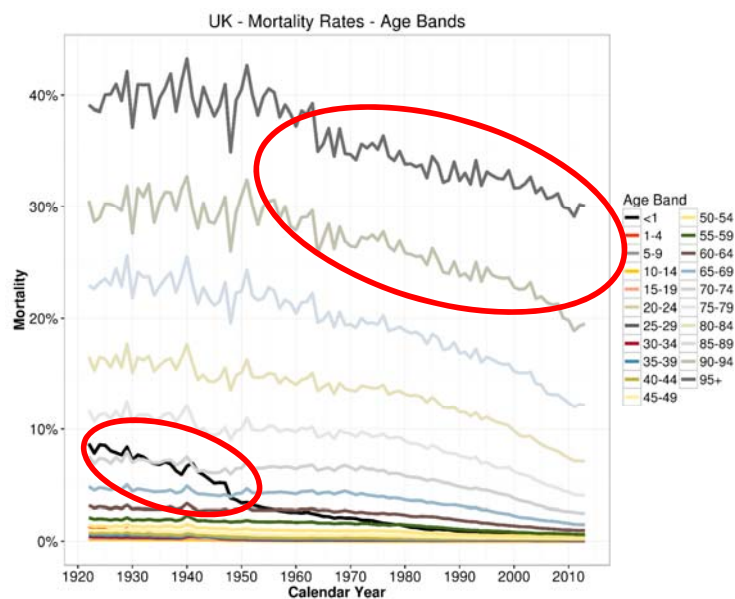
Source: mortality.org

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## What we know

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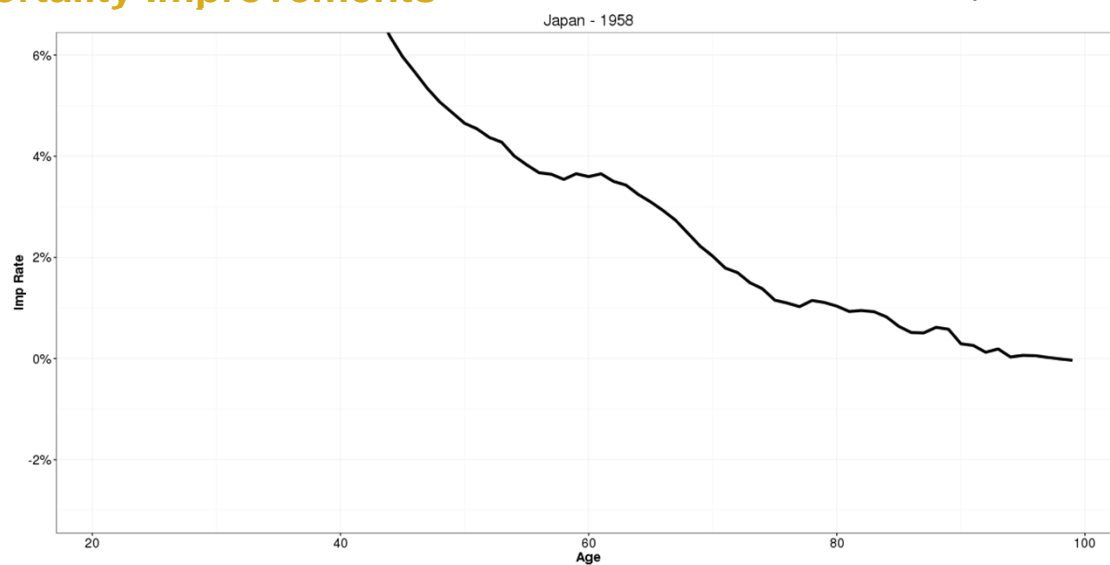
Source: mortality.org

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## Mortality Improvements

Japan - Females



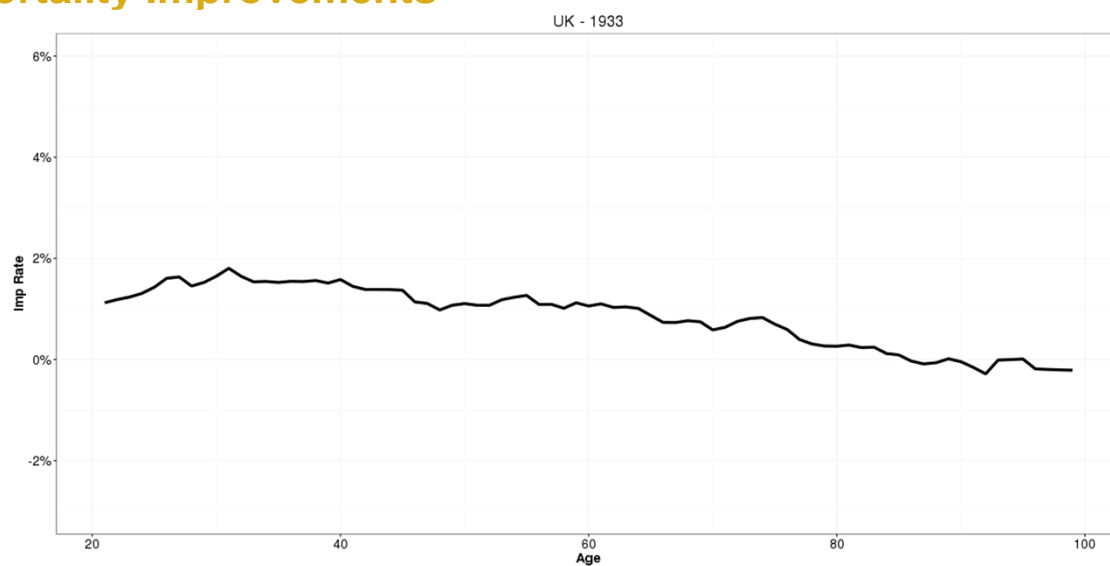
Source: mortality.org

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## Mortality Improvements

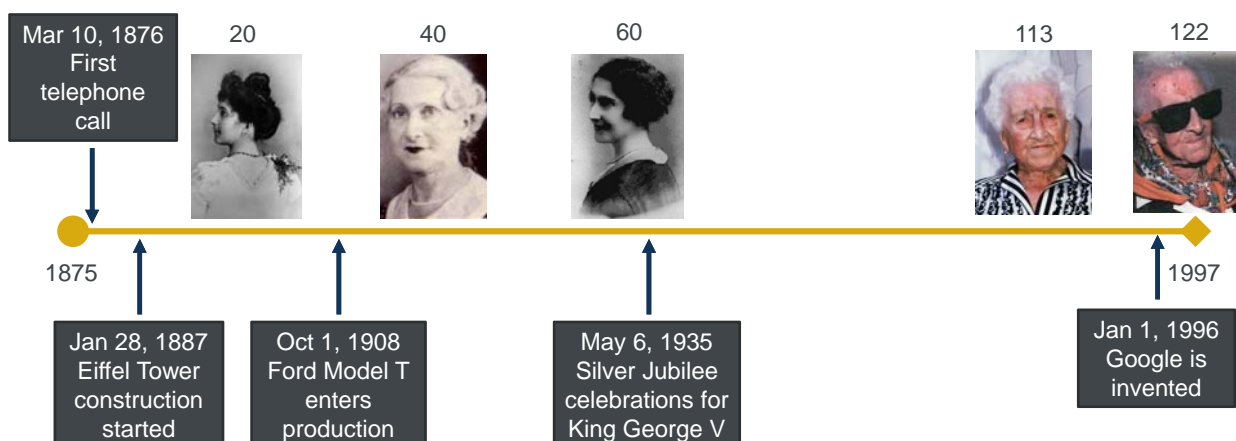
UK - Females



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## Madame Jeanne-Louise Calment



Source: <http://www.grg.org/jcalmentgallery.htm>



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## Madame Jeanne-Louise Calment



- **Good genes** - mother lived until 86, father lived until 93
- **Wealth** - married a wealthy man
- **Exercise** - Spent much time playing tennis, swimming and cycling. Cycled until she was 100 years old.
- **Relaxing** - Learned to play the piano and enjoyed the opera
- **Smoking** – smoked from 21 until 116
- **Diet** – Ate ~1kg of chocolate per week. Drank port wine as part of her daily diet.

Source: <http://www.grg.org/icalmentgallery.htm>



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## Even Older?



- “The world’s oldest man has been named as Indonesian Mbah Gotho, who is 145 years old, with documentation that says he was born in 1870.”
- Has official documentation which shows his age
- If documents can be independently verified will go down in the record books

Source: <http://www.telegraph.co.uk/news/2016/08/27/longest-lived-human-says-he-is-ready-for-death-at-145/>



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## Competing Camps

| No Limits   | Limits  |
|---|---|
| <ul style="list-style-type: none"> <li>Human life expectancy steadily increased since the 19th century</li> </ul>               | <ul style="list-style-type: none"> <li>Past is not necessarily a guide to the future</li> </ul>                                 |
| <ul style="list-style-type: none"> <li>Increasing reports of supercentenarians</li> </ul>                                       | <ul style="list-style-type: none"> <li>Limited scope for future improvements</li> </ul>   |
| <ul style="list-style-type: none"> <li>Lifespans of animals can be extended through genetic or dietary modifications</li> </ul> | <ul style="list-style-type: none"> <li>Increase in life expectancy &amp; maximum human lifespan will eventually stop</li> </ul> |



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## Limits on Life Expectancy?

Oeppen and Vaupel:

1. Experts have repeatedly asserted that life expectancy is approaching a ceiling – these experts have repeatedly been proven wrong
2. The apparent levelling off of life expectancy in various countries is an artefact of laggards catching up and leaders falling behind
3. If life expectancy were close to a maximum, then the increase in the record expectation of life should be slowing – it is not.



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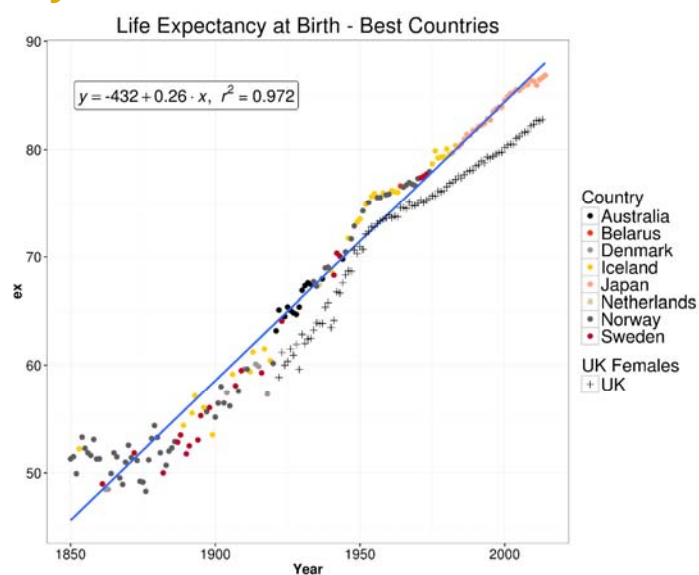
Source: Oeppen and Vaupel, Broken Limits to Life Expectancy, Science – Vol 296 – 10 May 2002

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## Life Expectancy at Birth

HMD Covers  
38 countries



Source: mortality.org



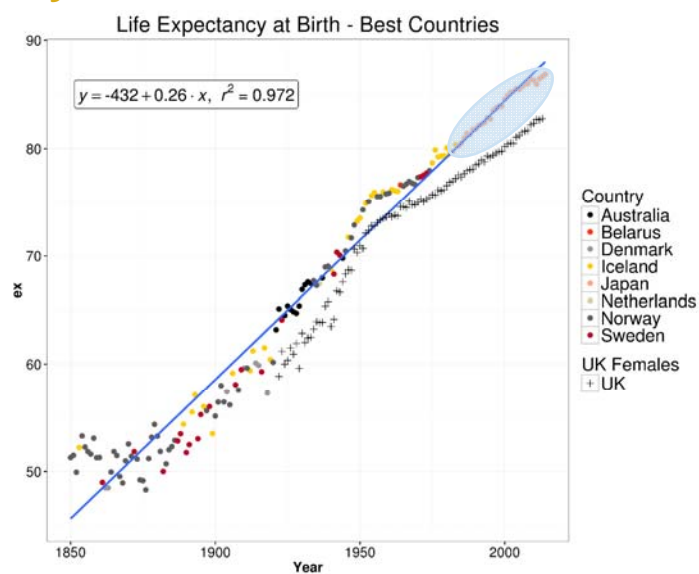
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Source: mortality.org



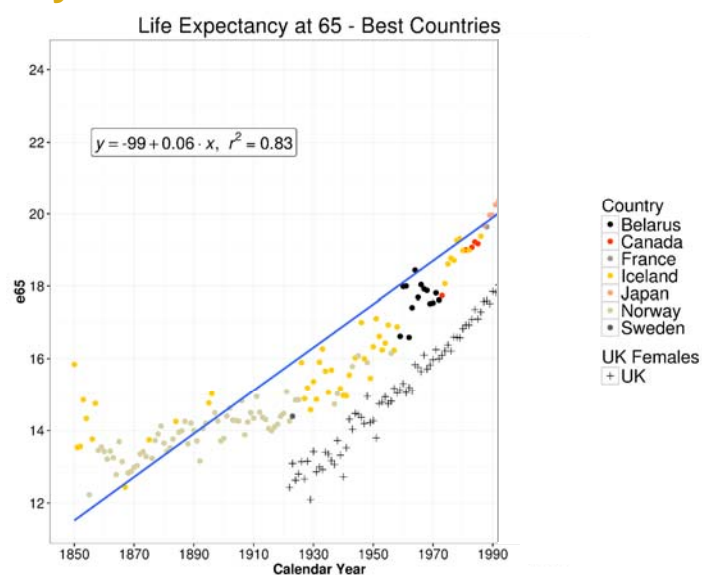
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## Life Expectancy at 65



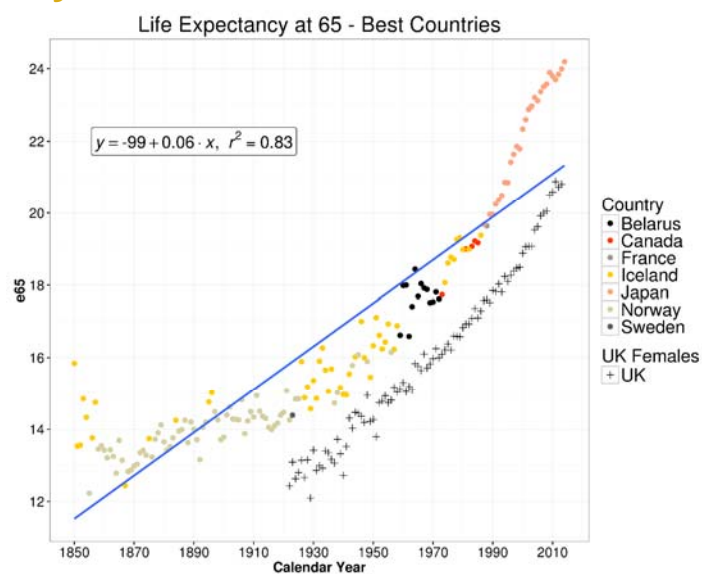
Source: mortality.org

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## Life Expectancy at 65



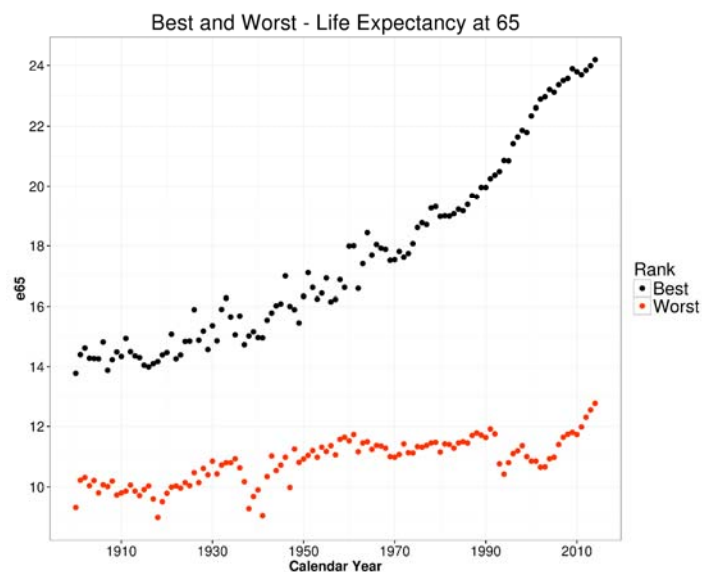
Source: mortality.org

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## Gap Between Best and Worst

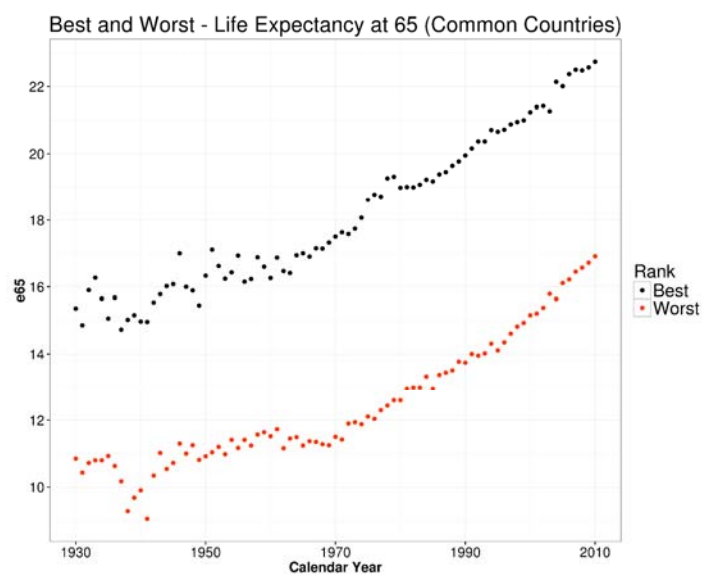


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## Gap Between Best and Worst

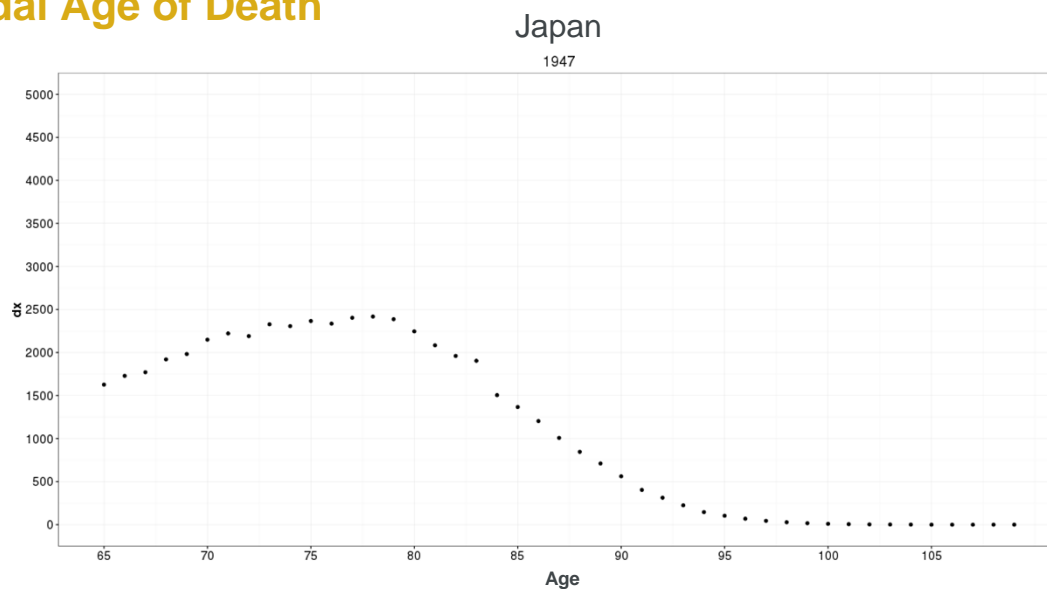


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## Modal Age of Death

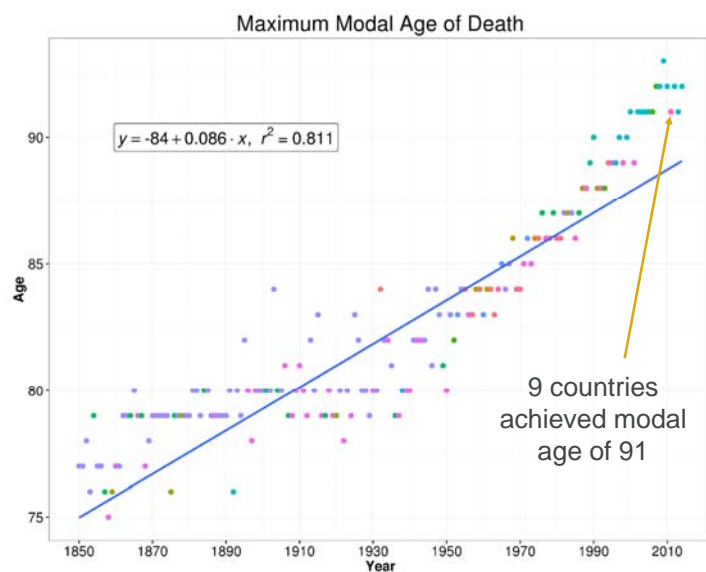


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## Modal Age of Death

- Calculate modal age of death for each country and year
- For each year take the **maximum** modal age across all countries



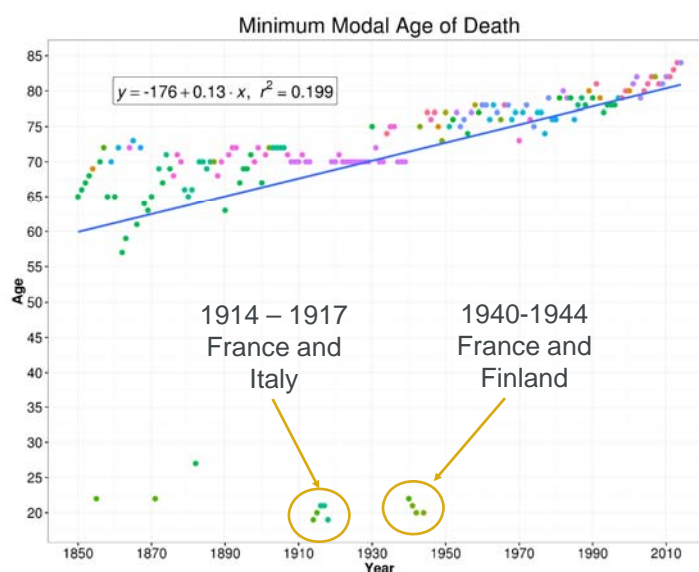
Source: mortality.org

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## Modal Age of Death

- Calculate modal age of death for each country and year
- For each year take the **minimum** modal age across all countries



Source: mortality.org

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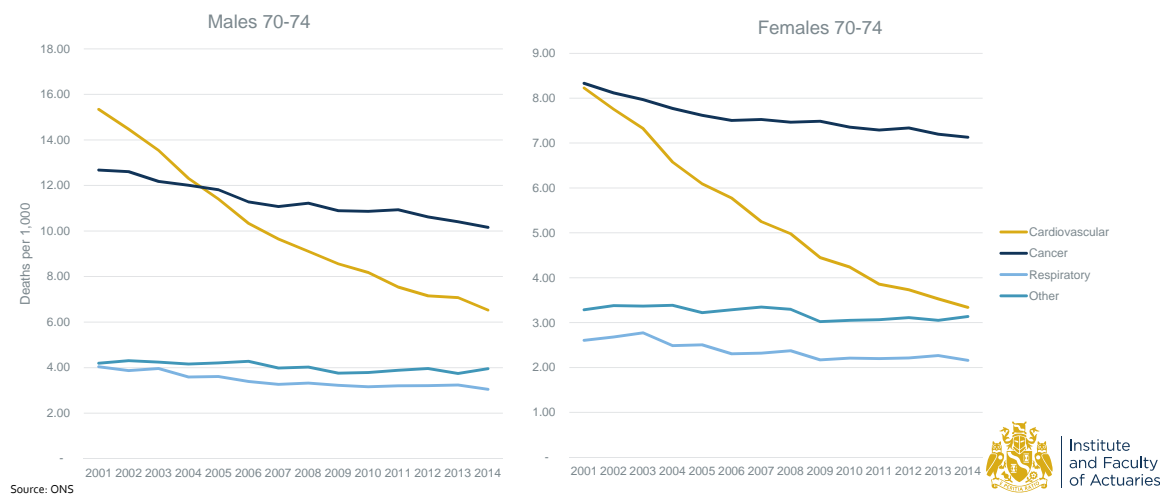


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## Mortality by Cause

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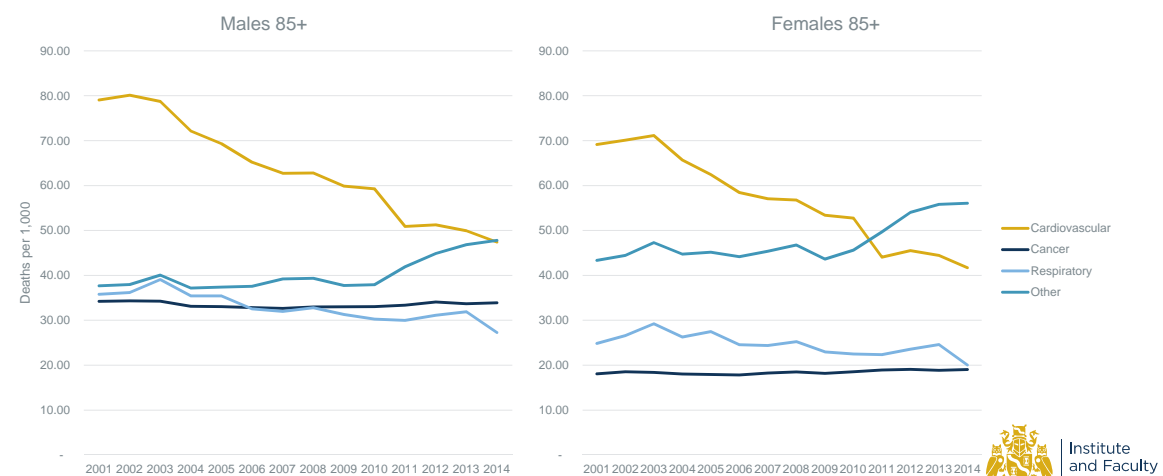
## Mortality rates by cause – England & Wales



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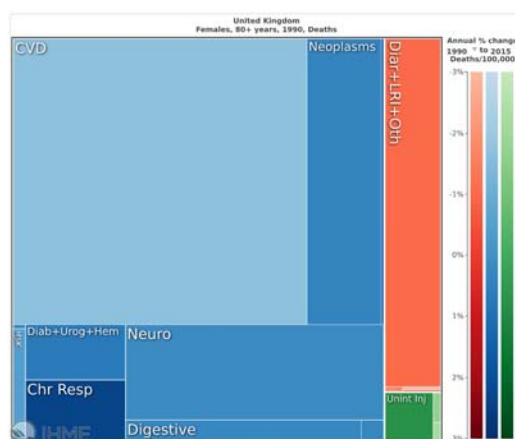
## Mortality rates by cause – England & Wales



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## Mortality rates by cause – England & Wales



Source: Institute for Health Metrics and Evaluation (IHME). *GBD Compare Data Visualization*. Seattle, WA: IHME, University of Washington, 2016. Available from <http://vizhub.healthdata.org/gbd-compare>. Accessed October 2016

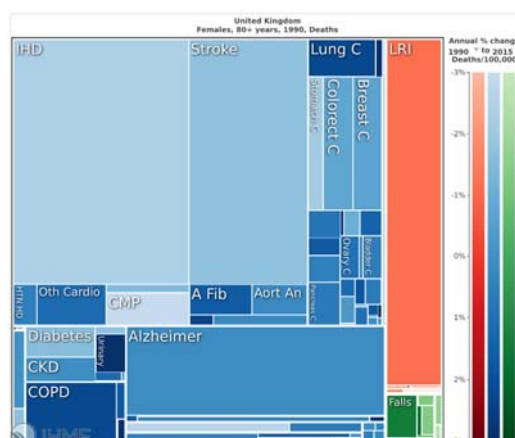


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## Mortality rates by cause – England & Wales



Source: Institute for Health Metrics and Evaluation (IHME). *GBD Compare Data Visualization*. Seattle, WA: IHME, University of Washington, 2016. Available from <http://vizhub.healthdata.org/gbd-compare>. Accessed October 2016



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## Mortality rates by cause – England & Wales



- Increasing share of deaths from Cancer
- Reducing share due to CVD
- CVD reduction due to IHD and stroke, while other CVD conditions have increased
- Increasing share of other conditions associated with old age Alzheimers & other chronic diseases

Source: Institute for Health Metrics and Evaluation (IHME). *GBD Compare Data Visualization*. Seattle, WA: IHME, University of Washington, 2016. Available from <http://vizhub.healthdata.org/gbd-compare>. Accessed October 2016



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## Mortality rates by cause – France



- Larger proportion due to injuries
- Smaller proportion due to Lower Respiratory Infections
- Non-communicable diseases – similar proportion to UK
- CVD improvements more than UK

Source: Institute for Health Metrics and Evaluation (IHME). *GBD Compare Data Visualization*. Seattle, WA: IHME, University of Washington, 2016. Available from <http://vizhub.healthdata.org/gbd-compare>. Accessed October 2016

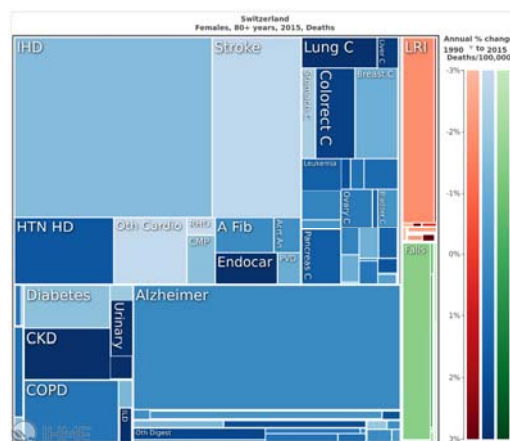


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## Mortality rates by cause – Switzerland



- Similar to France...
- ...but with several causes experiencing increasing rates of death:
  - Hypertensive Heart Disease
  - COPD
  - Chronic Kidney Disease
  - Colorectal cancer

Source: Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2016. Available from <http://vizhub.healthdata.org/gbd-compare>. Accessed October 2016



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## Mortality rates by cause – Japan



- Looks much more like UK
- COPD much lower (and improving)

Source: Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2016. Available from <http://vizhub.healthdata.org/gbd-compare>. Accessed October 2016



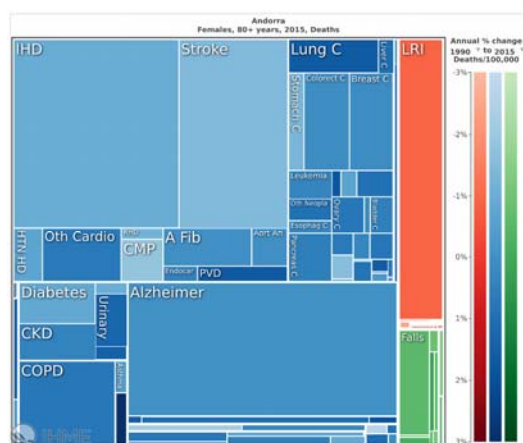
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## Mortality rates by cause – Andorra



- Similar to UK, with less Lower Respiratory Infections (LRI)

Source: Institute for Health Metrics and Evaluation (IHME). *GBD Compare Data Visualization*. Seattle, WA: IHME, University of Washington, 2016. Available from <http://vizhub.healthdata.org/gbd-compare>. Accessed October 2016

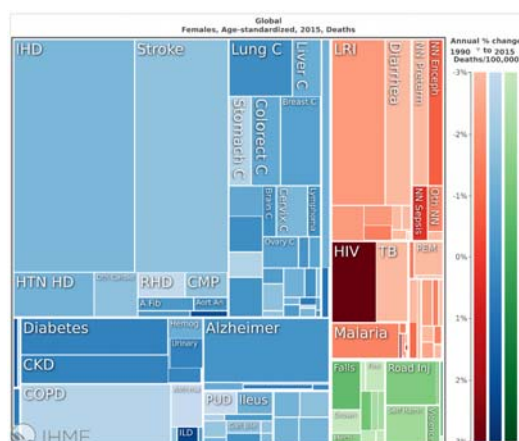


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## Mortality rates by cause – Global, age standardised



- N.B. Age standardised vs 80+
- Infectious diseases & Injuries far higher
- Cancer also has a higher share

Source: Institute for Health Metrics and Evaluation (IHME). *GBD Compare Data Visualization*. Seattle, WA: IHME, University of Washington, 2016. Available from <http://vizhub.healthdata.org/gbd-compare>. Accessed October 2016

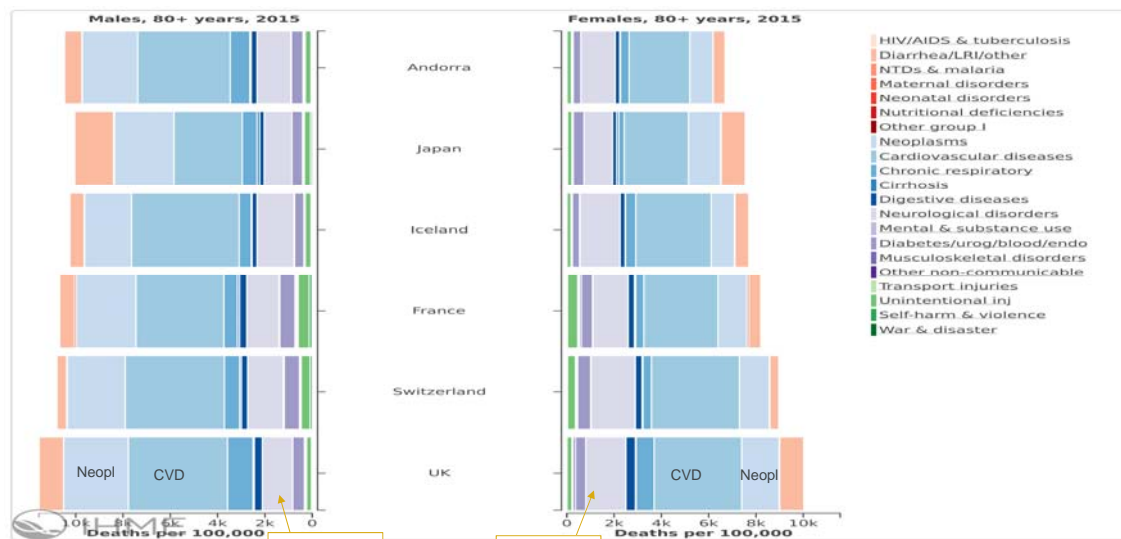


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## Mortality by cause – top 5 – deaths per 100,000 – 80+

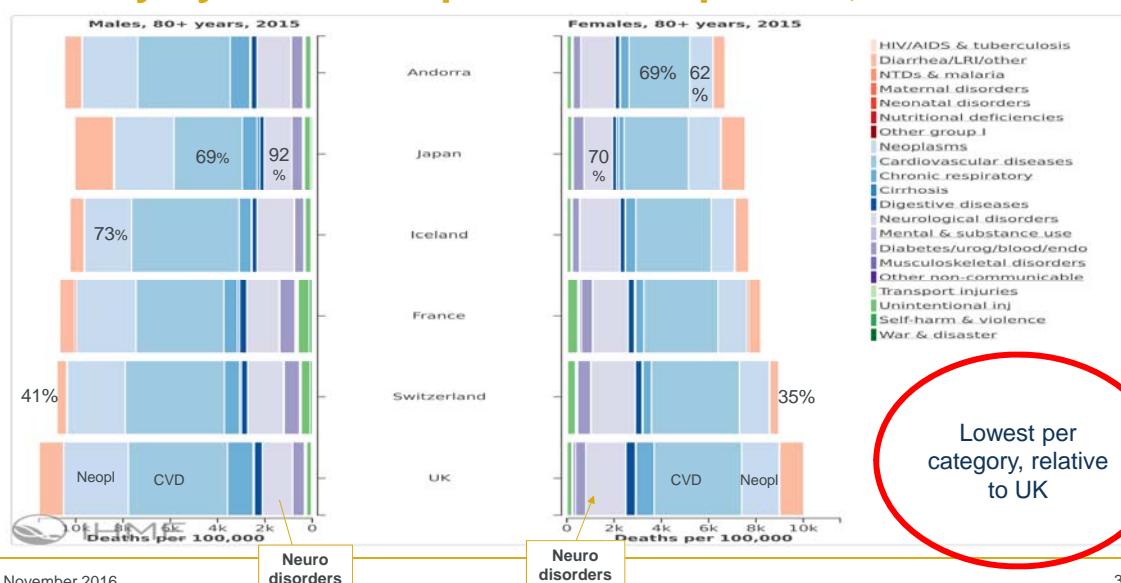


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Source: Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2016. Available from <http://vizhub.healthdata.org/gbd-compare>. Accessed October 2016

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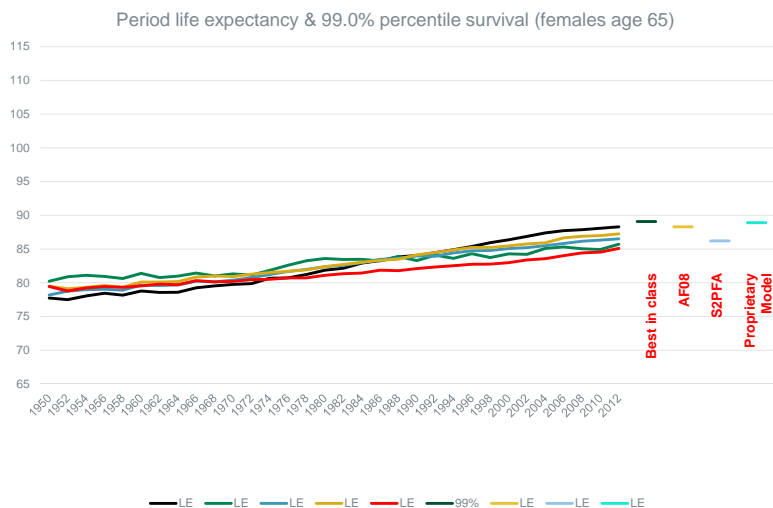


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Source: Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2016. Available from <http://vizhub.healthdata.org/gbd-compare>. Accessed October 2016

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## Life Expectancy & “best in class” by cause



Take best in class for each group and apply to UK mortality for “Top 4” causes

- Total impact is 30% reduction in mortality
- Potential for life expectancy at 65 to increase to 88.5 – based on current best in class
- Life expectancy consistent with current life expectancy for subsets of UK



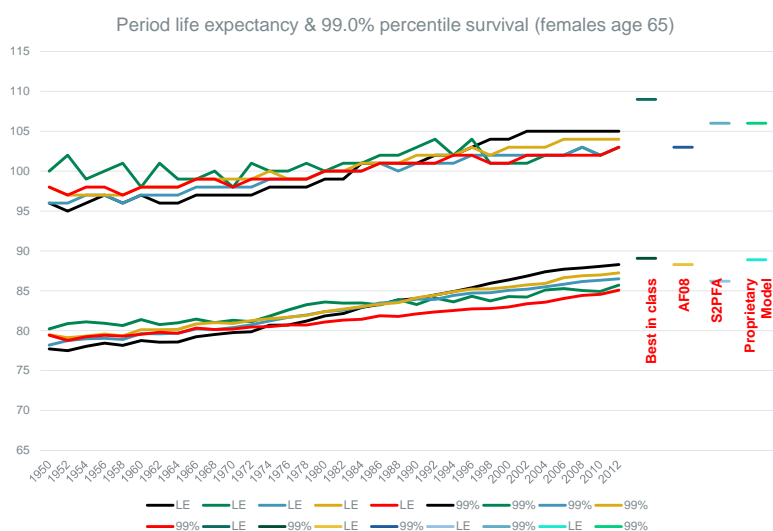
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Source: HMD / CMI & Own calculations

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## Life Expectancy & top percentile survival



Take best in class for each group and apply to UK mortality for “Top 4” causes

- Total impact is 30% reduction in mortality
- Potential for life expectancy at 65 to increase to 88.5 – based on current best in class
- Life expectancy consistent with current life expectancy for subsets of UK
- Potential for large gain in top percentile survival?



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Source: HMD / CMI & Own calculations

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## Limits of Human Lifespan

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### The Answer's 115



- "For the first time in history we've been able to see this, it looks like the maximum life span - this ceiling, this barrier - is about 115."

Nice headline ... *but what did the paper show?*

Source: <http://www.bbc.com/news/health-37552116> (5th October 2016)

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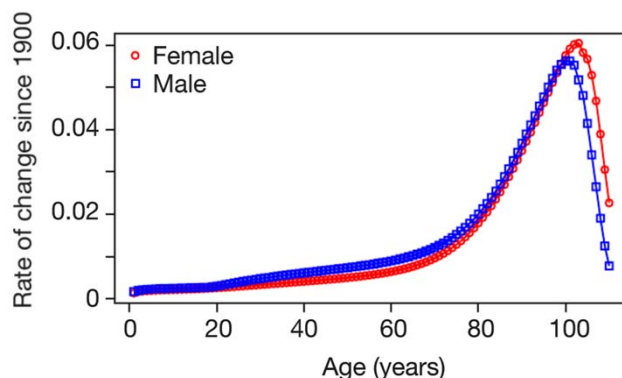
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## Dong et al – Evidence for a Limit to Human Lifespan

### Drop Off

Rate of improvement in survival peaks and then declines for very old ages



- Used data from the Human Mortality Database
- Regression of the fraction of people surviving to old age since 1900

$$\log(l(x, t)) = a_x + b_x t$$

- Chart is essentially  $y(x) = b_x$

Source: Evidence for a limit to human lifespan, Dong, Milholland & Vijg - Nature doi:10.1038/nature.2016.20750



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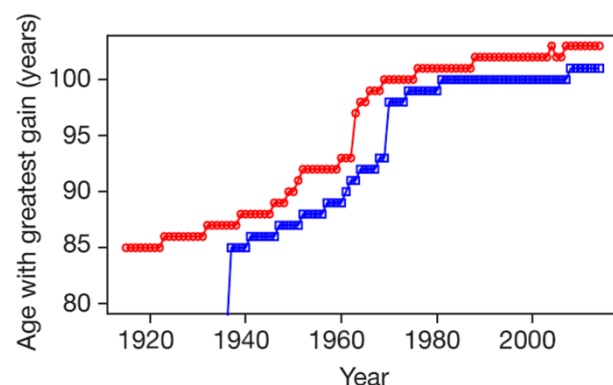
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## Dong et al – Evidence for a Limit to Human Lifespan

### Survival Plateau

The age that experienced the greatest annual increase in survival stopped significant increasing after 1980



- If no upper limit on lifespan  $\Rightarrow$  biggest increase in survival should be experienced by ever-older age groups.
- Found that age with greatest improvement in survival got steadily higher since the early 20th century then started to plateau at about 99 in 1980.

Source: Evidence for a limit to human lifespan, Dong, Milholland & Vijg - Nature doi:10.1038/nature.2016.20750

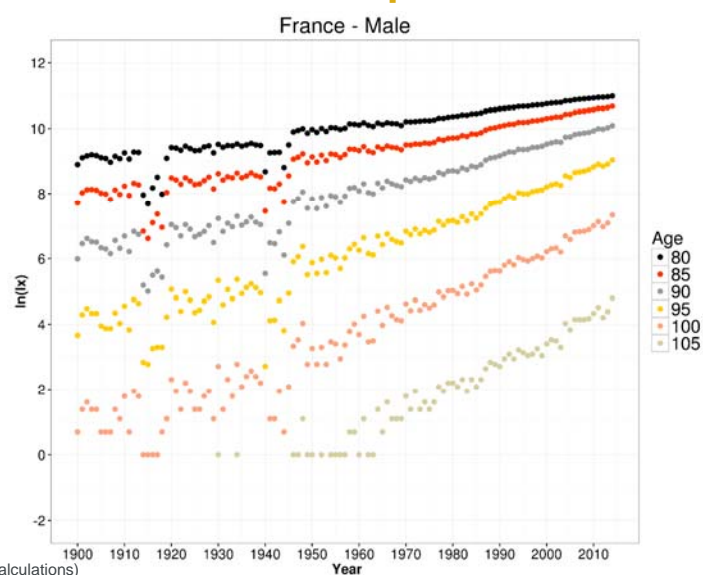


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## Survival Improvement Rate Drop-off?



Source: mortality.org (own calculations)

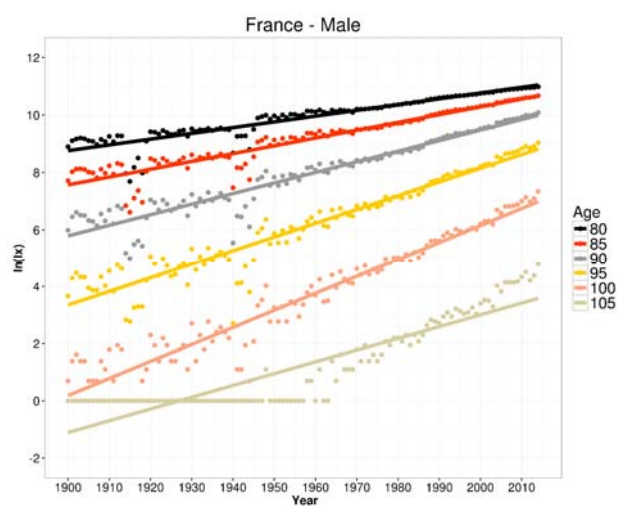


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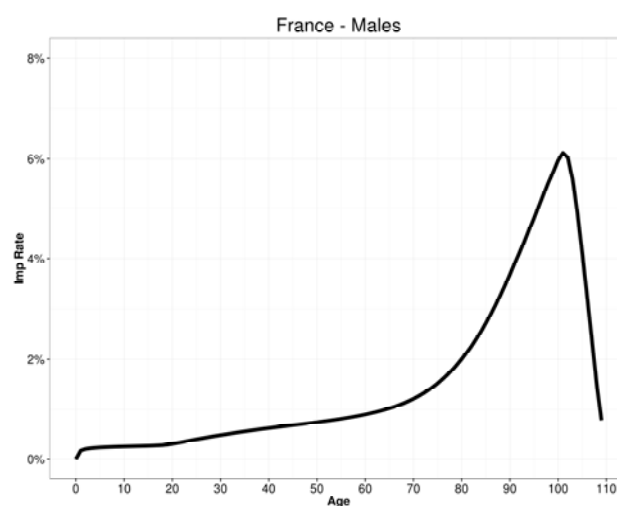
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## Survival Improvement Rate Drop-off?



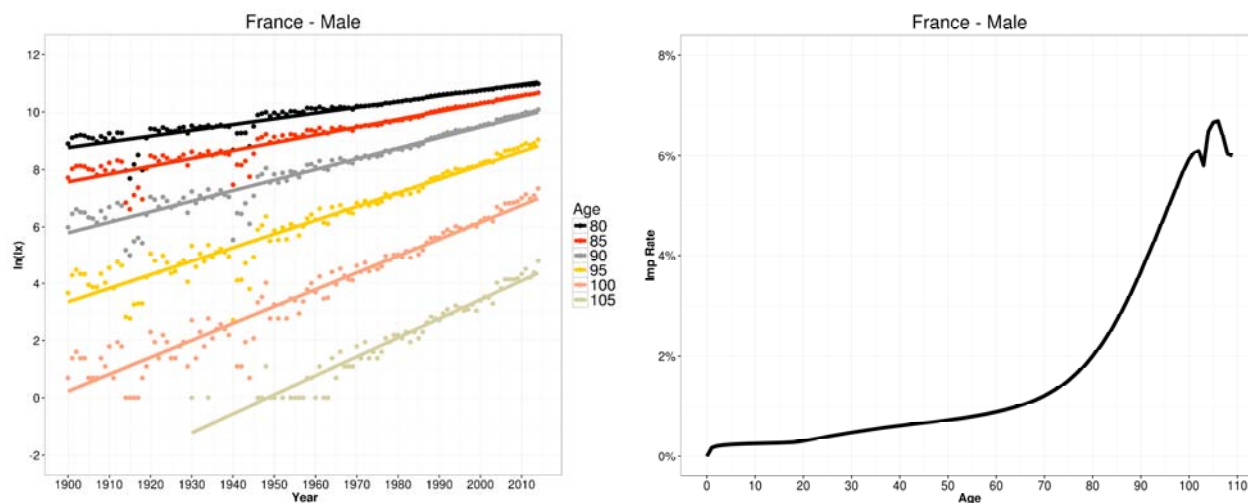
Source: mortality.org (own calculations)

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## Survival Improvement Rate Drop-off?



Source: mortality.org (own calculations)

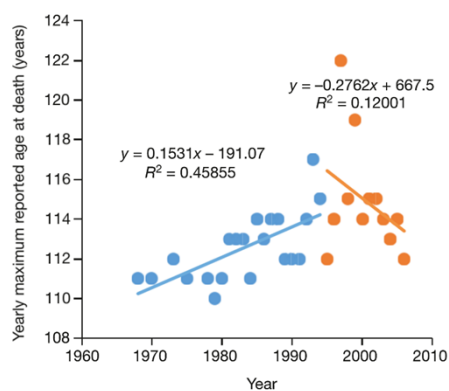
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## Dong et al – Evidence for a Limit to Human Lifespan

### Longevity Limit

The ages of the oldest people to die in a given year suggest a limit on human longevity of about 115.



- Plotted yearly max reported age at death (MRAD)
- Age at death increased rapidly between 1970s and early 1990s – plateaus around 1995
- Results indicate a trend break between 2 groups:
  - Before 1995 increased by 0.15 years per year
  - After 1995 decreased by 0.28 years per year
- Modelled MRAD as a Poisson distribution  
 $\Rightarrow P(\text{MRAD} > 125) < 1 \text{ in } 10,000$

Source: Evidence for a limit to human lifespan, Dong, Milholland & Vijg - Nature doi:10.1038/nature.2016.20750

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## What does Aubrey say?

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## What is Ageing?

- Ageing is a consequence of physics, not biology
- It is the life-long accumulation of “damage” to the body that occurs as an intrinsic side-effect of the body’s normal operation
- The body can tolerate some damage, but too much of it causes disease and disability

Source: sens research foundation

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## Diseases vs Ageing

| Diseases                              |  |   | Ageing   |
|---------------------------------------|--|---|--|
| Communicable                          | Congenital                               | Chronic   |  |
| Tuberculosis<br>Malaria<br>HIV<br>... | Tay-Sachs<br>MELAS<br>Li-Fraumeni<br>... | Alzheimer's<br>Cancer<br>Atherosclerosis<br>... | Frailty<br>Sarcopenia<br>Immunosenescence<br>... |

Source: sens research foundation



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## Diseases vs Ageing

| Diseases                              |  | Ageing  |  |
|---------------------------------------|--|---|--|
| Communicable                          | Congenital                               | Specific  | General  |
| Tuberculosis<br>Malaria<br>HIV<br>... | Tay-Sachs<br>MELAS<br>Li-Fraumeni<br>... | Alzheimer's<br>Cancer<br>Atherosclerosis<br>... | Frailty<br>Sarcopenia<br>Immunosenescence<br>... |

Source: sens research foundation

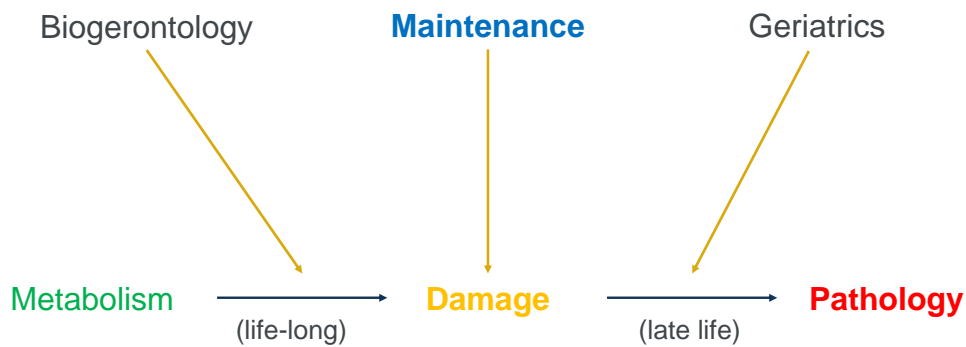


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## What is Ageing?



Source: sens research foundation



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## Seven Deadly Things

| Ageing Damage                   | Rejuvenation Biotechnology       |
|---------------------------------|----------------------------------|
| Cell loss, cells atrophy        | Replace, using stem cells        |
| Division-obsessed cells         | Resist, using telomere control   |
| Death-resistant cells           | Remove, using suicide genes etc. |
| Mitochondrial mutations         | Resist, using backup copies      |
| Intracellular waste products    | Remove, using foreign enzymes    |
| Extracellular waste products    | Remove, using immune system      |
| Extracellular matrix stiffening | Repair, using crosslink-breakers |

Source: sens research foundation

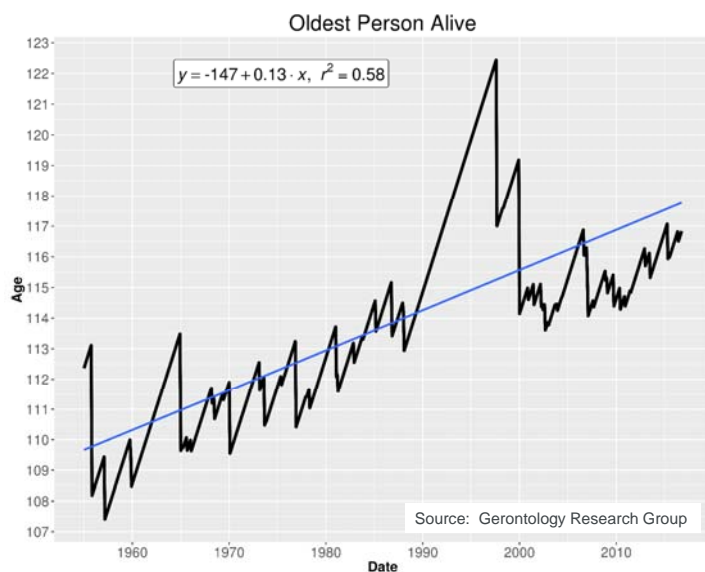


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## Oldest living person?



Increasing at  
0.13 years per  
calendar year

Will reach 1000  
in year 6000 ?

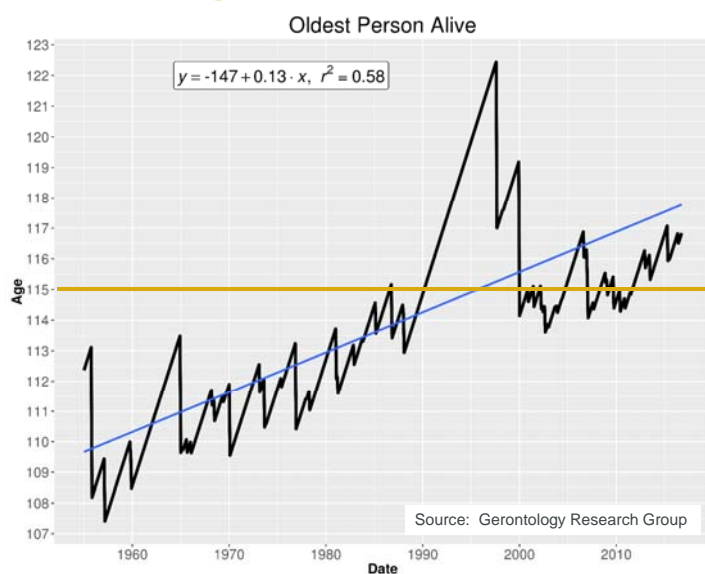


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## Oldest living person?



A  
realistic  
limit?



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## Conclusion

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### Acciaroli – Early Findings

- Diet – Rosemary & Anchovies
- Environment – Unpolluted
- Stress – a stress-free life
- Active – spending time outdoors
  - Swimming
  - Gardening



Source: By Ciaurlec - Own work, CC BY-SA 3.0, <https://commons.wikimedia.org/w/index.php?curid=16214368>

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## Acciaroli – Early Findings

- Diet – Rosemary & Anchovies
- Environment – Unpolluted
- Stress – a stress-free life
- Active – spending time outdoors
  - Swimming
  - Gardening
  - Sex



Source: By Ciaurlec - Own work, CC BY-SA 3.0, <https://commons.wikimedia.org/w/index.php?curid=16214368>

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## Questions

## Comments

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