Is there a limit to human longevity?

Biostatistics Seminar, McGill University

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Lots of interest in the news!

Sister André, World's Oldest Known Person, Dies at 118 in France

The French nun had lived through two world wars and the 1918 flu pandemic. She survived Covid and was said to enjoy a daily dose of wine and chocolate.

3 MIN READ

Daniel Cole/Associated Press

SOCIÉTÉ

La longévité humaine a-t-elle une limite biologique? Le sujet divise toujours

Depuis 1950, le nombre de centenaires français a décuplé tous les dix ans pour atteindre 27 500 fin 2021.

Sœur André, la doyenne de l'humanité, est décédée à l'âge de 118 ans

Publié il y a 16 heures / Modifié il y a 13 heures

Née Lucile Randon le 11 février 1904 en France, sœur André avait été gouvernante à Paris avant de rentrer tardivement dans les ordres

Headlines following the death of Lucile Randon (Soeur André) on January 17th (New York Times, Radio-Canada, Le Temps)

Why study longevity?

Statistical analyses needed to assess biological theories about

mortality plateau

senescence

existence of finite lifespan

Exponential growth of mortality

> *It is believed that exponential growth of mortality with age (Gompertz law) is followed by a period of deceleration, with slower rates of mortality increase at older ages.*
>
> *Recent studies found that the exponential increase of the mortality risk with age (the famous Gompertz law) continues even at extreme old ages in humans, rats, and mice, thus challenging traditional views about old-age mortality deceleration, mortality leveling-off, and late-life mortality plateaus.*

Gavrilova & Gavrilov (2015), *Journals of Gerontology: Biological Sciences*

Theory of senescence

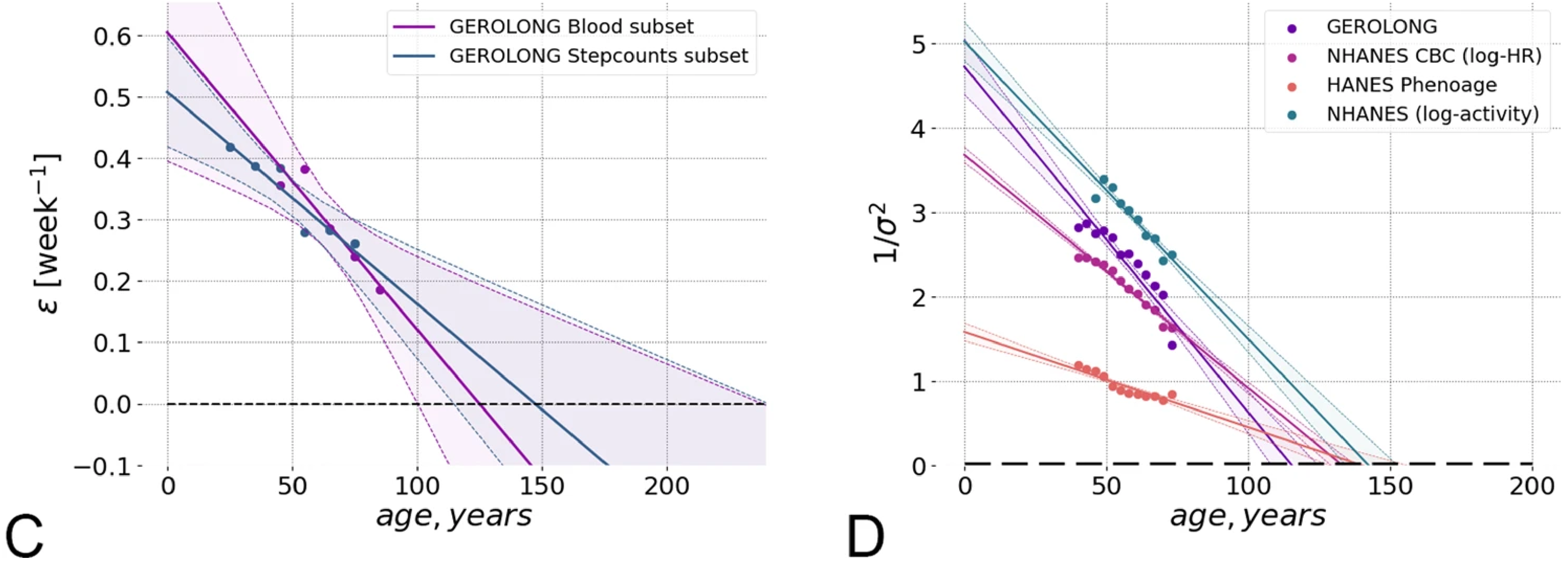


Figure 3 of Pyrkov et al. (2021), Nature Communications, doi:10.1038/s41467-021-23014-1.

Decreasing max reported age at death?

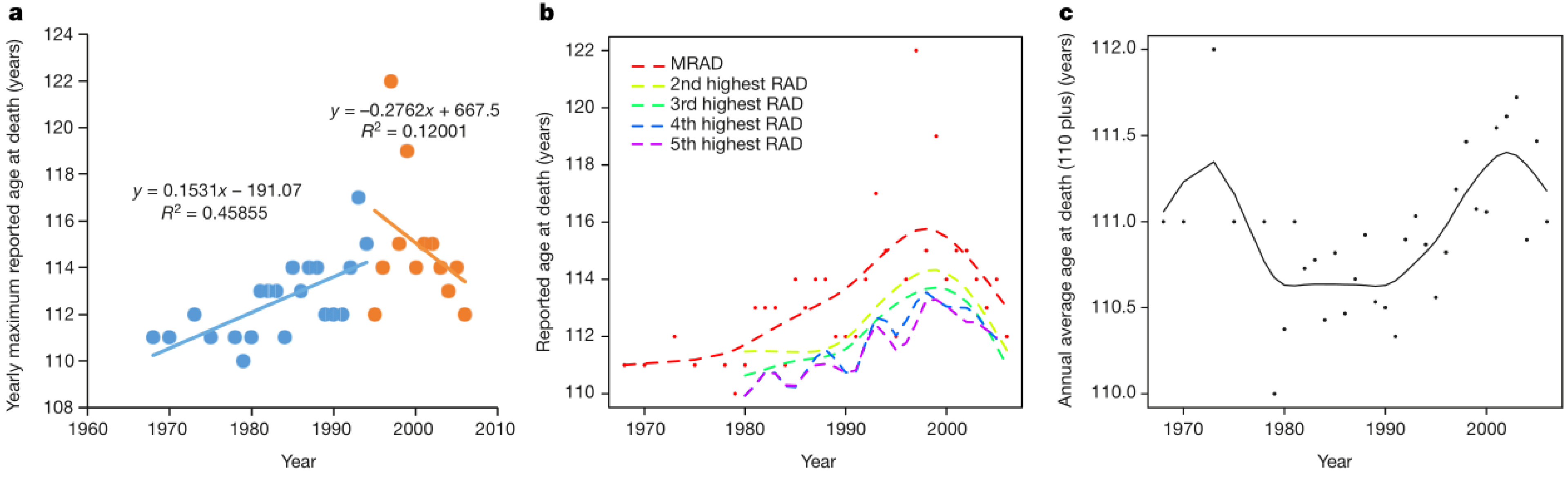


Figure 2 | Reported age at death of supercentenarians. All data were collected from the IDL database (France, Japan, UK and US, 1968–2006). **a**, The yearly maximum reported age at death (MRAD). The lines represent the functions of linear regressions. **b**, The annual 1st to 5th highest reported ages at death (RAD). The dashed lines are estimates of the RAD using cubic smoothing splines. The red dots represent the MRAD. **c**, Annual average age at death of supercentenarians (110 years plus, $n = 534$). The solid line is the estimate of the annual average age at death of supercentenarians, using a cubic smoothing spline.

Evidence for a limit to human lifespan by X. Dong, B. Milholland and J. Vijg (2016), Nature, doi:10.1038/nature19793.

Estimating human lifespan

The study of human longevity is full of pitfalls for the unwary...

The problem raises several statistical problems revolving around

data quality **models**

sampling **extrapolation**

Data quality

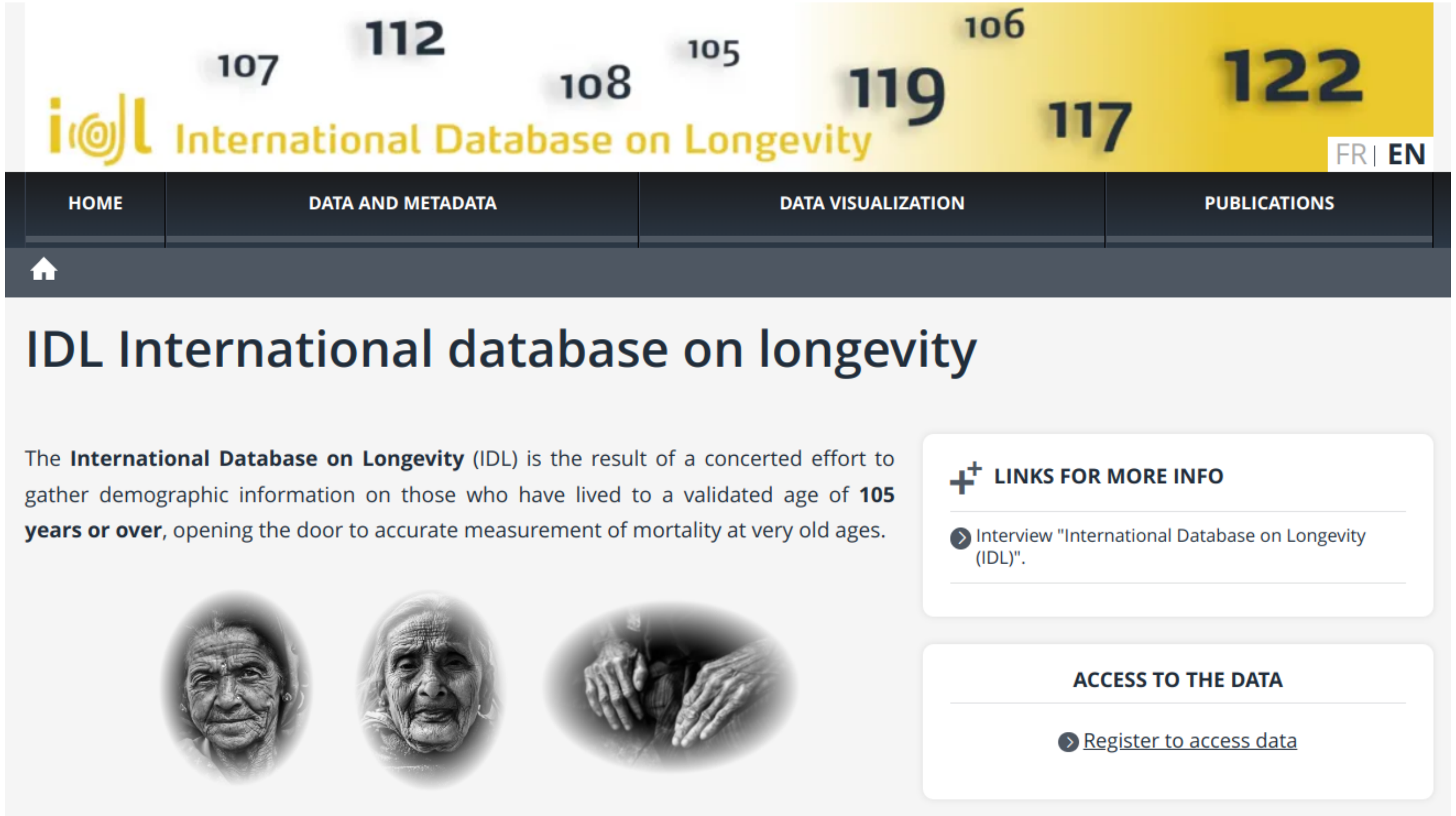
Samples

Information limited due to availability of historical records.

- Validation is key
  - necronyms
  - record falsification
  - mistakes in data registers
- Most databases (e.g., *Gerontology Research Group*) include self-reported records.

Opportunity samples

Show me your (meta)data



[International Database on Longevity](https://www.supercentenarians.org/en/)

To draw reliable conclusions, we need **representative samples**.

International Database on Longevity

The IDL (supercentenarians.org) includes

- **validated supercentenarian (110+)** from 13 countries
- plus (partly validated) **semi-supercentenarian (105-109)** for 9 countries
- Age-ascertainement bias-free

17 798 records, of which 1161 validated supercentenarians

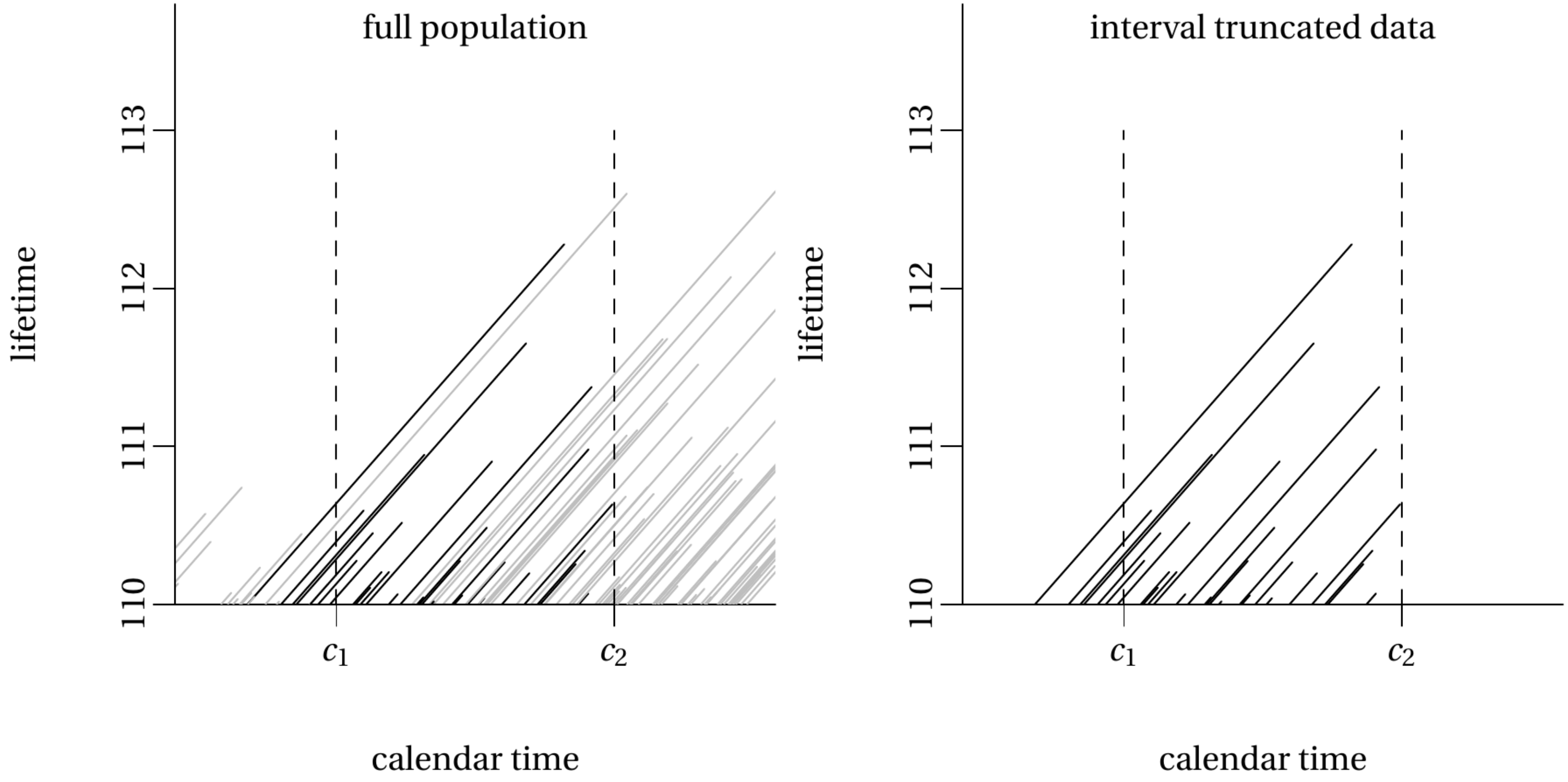
Sampling

Sampling mechanisms

Data are obtained by **casting a net** on the population of potential (semi)-supercentenarians.

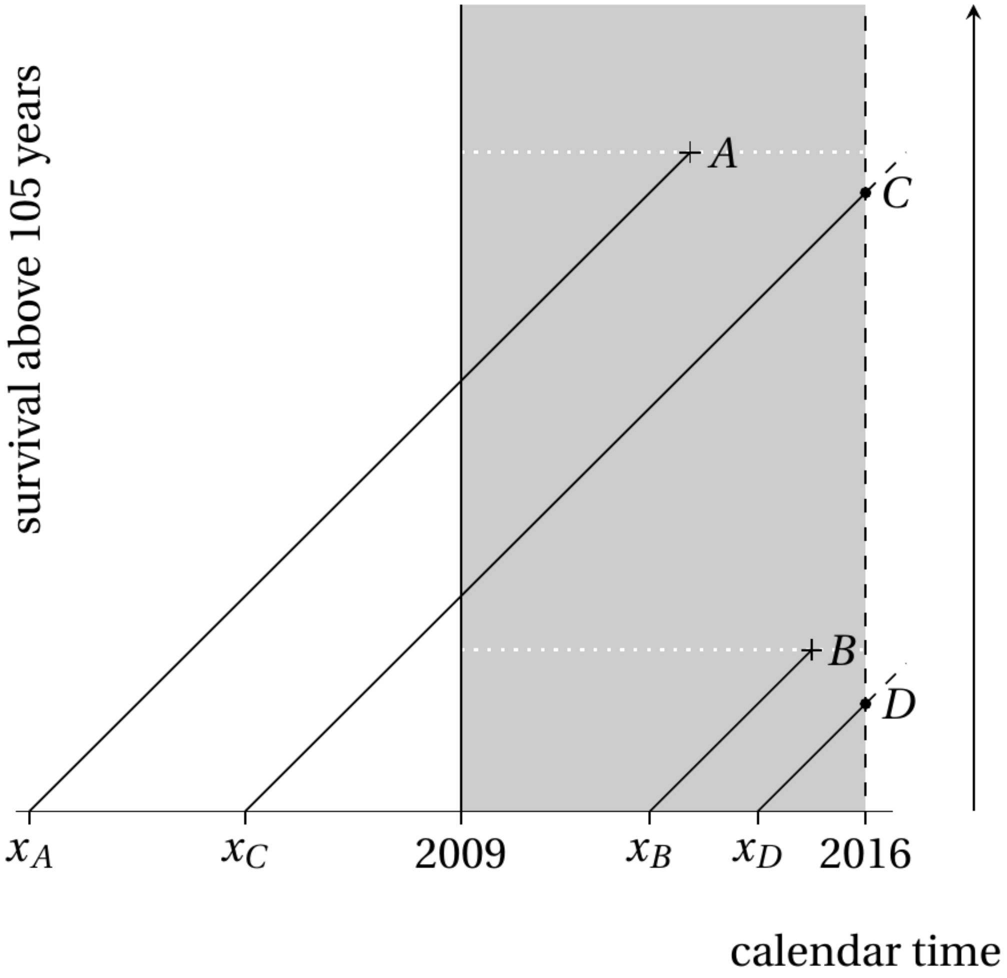
- for IDL, (only) supercentenarians in a country **who died** between dates c_1 and c_2.
- records for the candidates are then individually validated.

Lexis diagram for interval truncation



Lexis diagrams showing the selection mechanism.

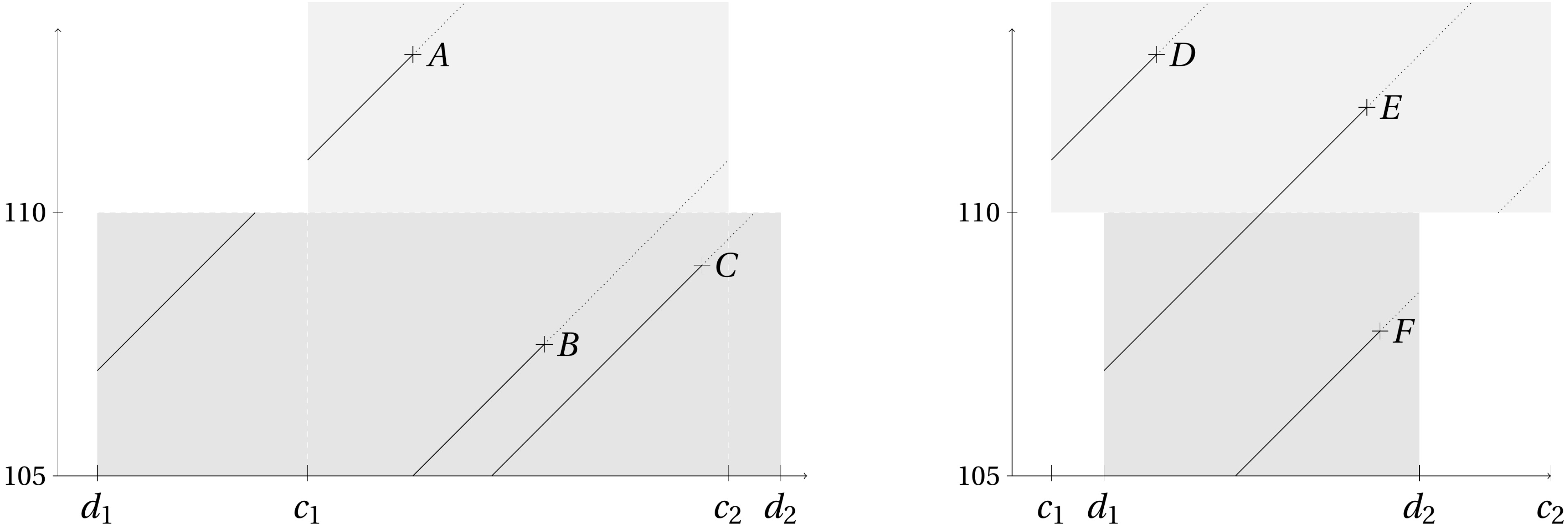
Lexis diagram for Italian data



Lexis diagrams for Istat data with semisupercentenarian and supercentenarians

More complex truncation schemes!

Semisupercentenarians (105-109) who died in window $(d_1, d_2) \neq (c_1, c_2)$.



Lexis diagrams for IDL data with semisupercentenarian and supercentenarians

Truncation can be hidden

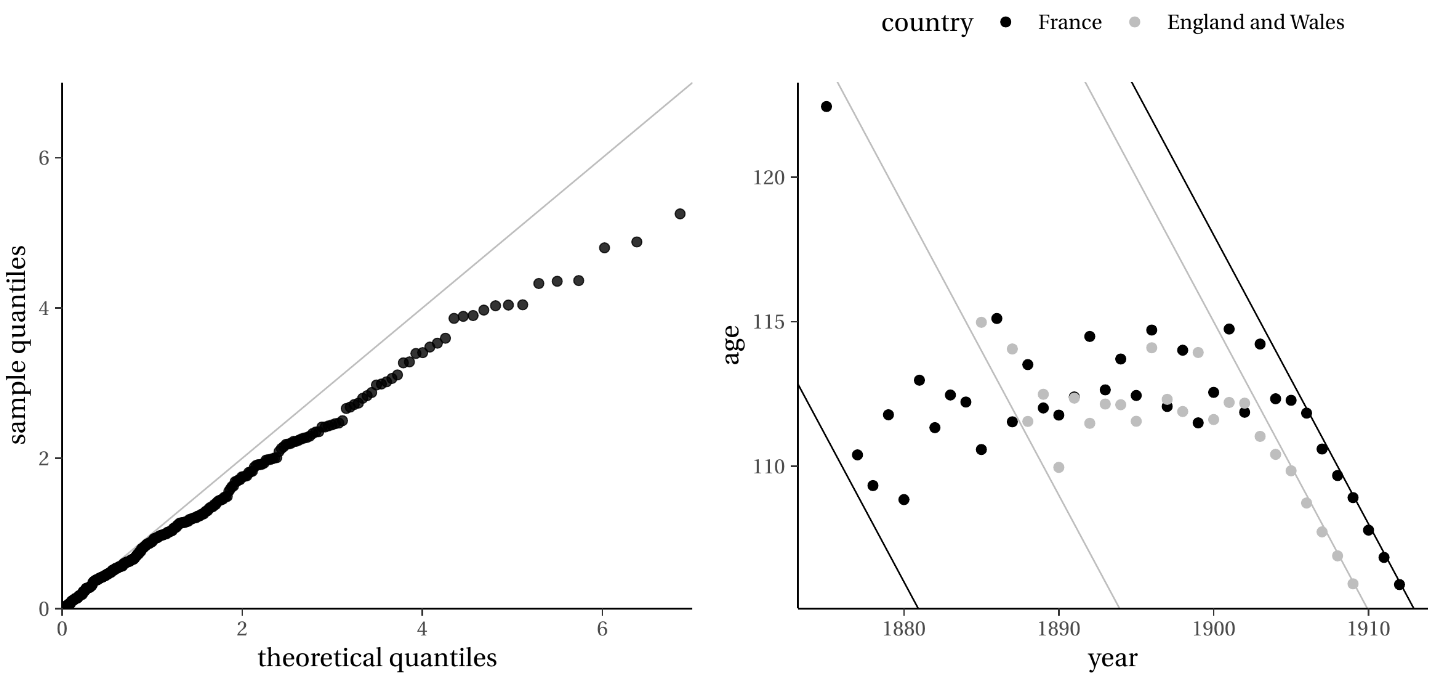
- **Extinct cohort method**: Birth cohorts for which no death has been reported for X consecutive years.
- counts cross-tabulated by years of birth, age and gender.

		Year of Birth												
		1875	1876	1877	1878	1879	1880	1881	1882	1883	1884	1885	1886	1887
Male	100	55	69	75	96	120	93	141	146	170	208	185	227	288
	101	32	36	42	57	67	55	83	85	102	135	115	146	185
	102	18	18	26	39	44	33	53	54	63	67	71	90	105
	103	10	7	15	23	28	21	37	30	37	39	38	58	64
	104	4	1	8	13	18	12	20	14	23	19	18	33	33
	105	2	0	5	10	9	7	9	9	15	13	6	17	15
	106	2	0	2	2	7	4	3	6	9	4	5	9	10
	107	2	0	1	0	2	3	2	5	3	1	3	7	7
	108	1	0	1	0	2	1	2	2	1	1	1	5	2
	109	1	0	0	0	1	1	1	0	0	1	0	3	2
	110	1	0	0	0	1	0	0	0	0	1	0	1	1
	111	1	0	0	0	0	0	0	0	0	1	0	1	0
	112	0	0	0	0	0	0	0	0	0	1	0	1	0
	113	0	0	0	0	0	0	0	0	0	0	0	0	0

Annual Vital Statistics Report of Japan (Hanamaya & Sibuya, 2014).

Why does it matter?

Ignoring truncation leads to **underestimation** of the survival probability: population increase and reduction in mortality at lower age translates into larger impact for later birth cohorts.



Impact of truncation on quantile-quantile plots (left) and maximum age by birth year (right).

Accounting for interval truncation

We also need to modify usual inferential tools.

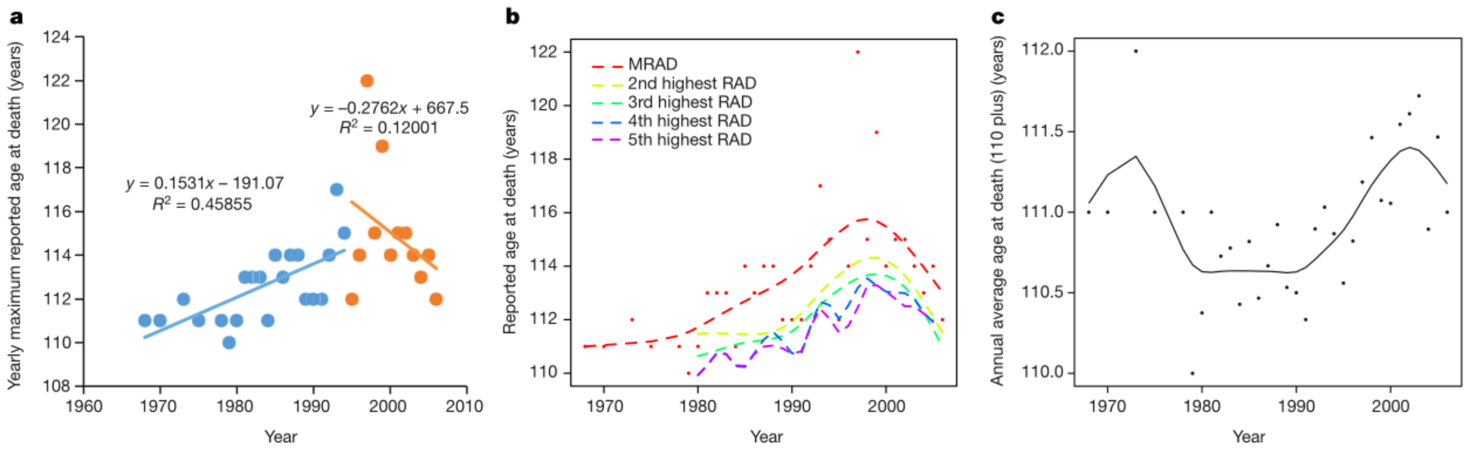
The plotting position for x-axis of Q-Q plot for observation y_i is

$$F_0^{-1}\left[F_0(a_i) + \{F_0(b_i) - F_0(a_i)\}\frac{F_n(y_i) - F_n(a_i)}{F_n(b_i) - F_n(a_i)}\right]$$

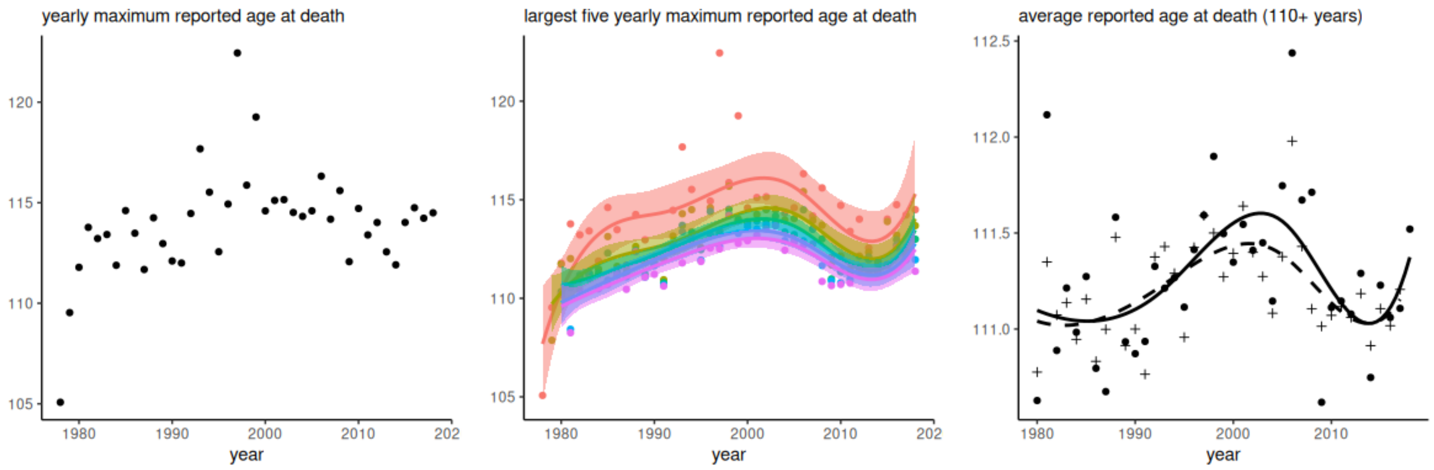
where

- F_0 is the postulated (i.e., fitted) parametric distribution,
- F_0^{-1} is the corresponding quantile function,
- F_n is the NPMLE of the distribution function (Turnbull, 1976).

Artefacts of data collection



Revisiting Dong et al. (2016)



Models

Survival analysis

Denote the lifetime T, a continuous random variable with distribution F, density f, lifespan $t_F = \sup\{t : F(t) < 1\}$ and survivor and hazard functions

$$S(t) = \Pr(T > t) = 1 - F(t),$$
$$h(t) = \frac{f(t)}{S(t)}, \quad t > 0.$$

Poisson process

- Suppose individuals independently reach age u_0 at calendar time x at rate $\nu(x)$, and subsequently die at age $t + u_0$ with density f.
- Events in $\mathcal{C} = [c_1, c_2] \times [u_0, \infty)$ follow a Poisson process of rate

$$\lambda(c, t) = \nu(c - t) f(t), \qquad c \in \mathbb{R}, t > 0$$

  at calendar time c and excess lifetime t.

Poisson process

- The lifetime density for dying in $\mathcal{C}$ is

$$f_{\mathcal{C}}(t) \propto f(t) w_{\mathcal{C}}(t), \quad w_{\mathcal{C}}(t) = \int_{c_1 - t}^{c_2 - t} \nu(x) \mathrm{d}x, \quad t > 0$$

where $w_{\mathcal{C}}$ is decreasing, so $f_{\mathcal{C}}$ is **stochastically smaller** than f.

Likelihood contributions

The likelihood depends on ν, hence consider the conditional likelihood

$$\frac{f(t)}{F(b) - F(a)}, \quad a < t < b$$

for interval truncated data and, for left-truncated and right-censored data,

$$\frac{h(t)^{\delta} S(t)}{1 - F(a)}, \quad t > a,$$

where $[a, b] = [\max\{0, c_1 - x\}, c_2 - x]$.

Popular parametric models

Hazard of models frequently used in demography:

- exponential: $h(t) = \sigma^{-1}$ for $\sigma > 0$.
- Gompertz–Makeham (1825, 1860):

$$h(t) = \lambda + \sigma^{-1} \exp(\beta t/\sigma), \qquad \beta, \sigma > 0, \lambda \geq 0.$$

- Logistic–Makeham (Perks, 1932):

$$h(t) = \lambda + \frac{\alpha \exp(\beta t/\sigma)}{1 + \alpha\gamma \exp(\beta t/\sigma)}, \qquad \alpha > 0, \beta\gamma \geq 0.$$

Comparing models

Authors frequently fail to account for non-standard asymptotics for tests.

- The Gompertz model includes the exponential when $\beta \to 0$ (boundary parameter) so likelihood ratio test has $\frac{1}{2}\chi^2_0 + \frac{1}{2}\chi^2_1$ null distribution.
- The Gompertz-Makeham distribution include the exponential distribution as special case, but the parameters are not numerically identifiable when $\beta \to 0$.

Extreme value theory

Most records include only lifetime above u_0 (**threshold exceedances**)

The **unique nondegenerate** limiting distribution for exceedances of a threshold u is **generalized Pareto**.

*Some conditions apply

Generalized Pareto distribution

If a scaling function a_u exists such that $(X - u)/a_u$ has a non-degenerate distribution conditional on $X > u$, then (Pickands, 1975)

$$\lim_{u \to t_F} \frac{\Pr\{(X - u)/a_u > t\}}{\Pr(X > u)} \to \begin{cases} (1 + \xi t/\sigma)_+^{-1/\xi}, & \xi \neq 0 \\ \exp(-t/\sigma), & \xi = 0. \end{cases}$$

where $c_+ = \max\{c, 0\}$.

Penultimate approximation

At lower levels, the behaviour of the fitted model depends on the reciprocal hazard, $r(t) = 1/h(t)$; under mild regularity conditions,

$$\xi = \lim_{t \to t_F} r'(t)$$

and a pre-asymptotic shape is $\xi_u = r'(u)$.

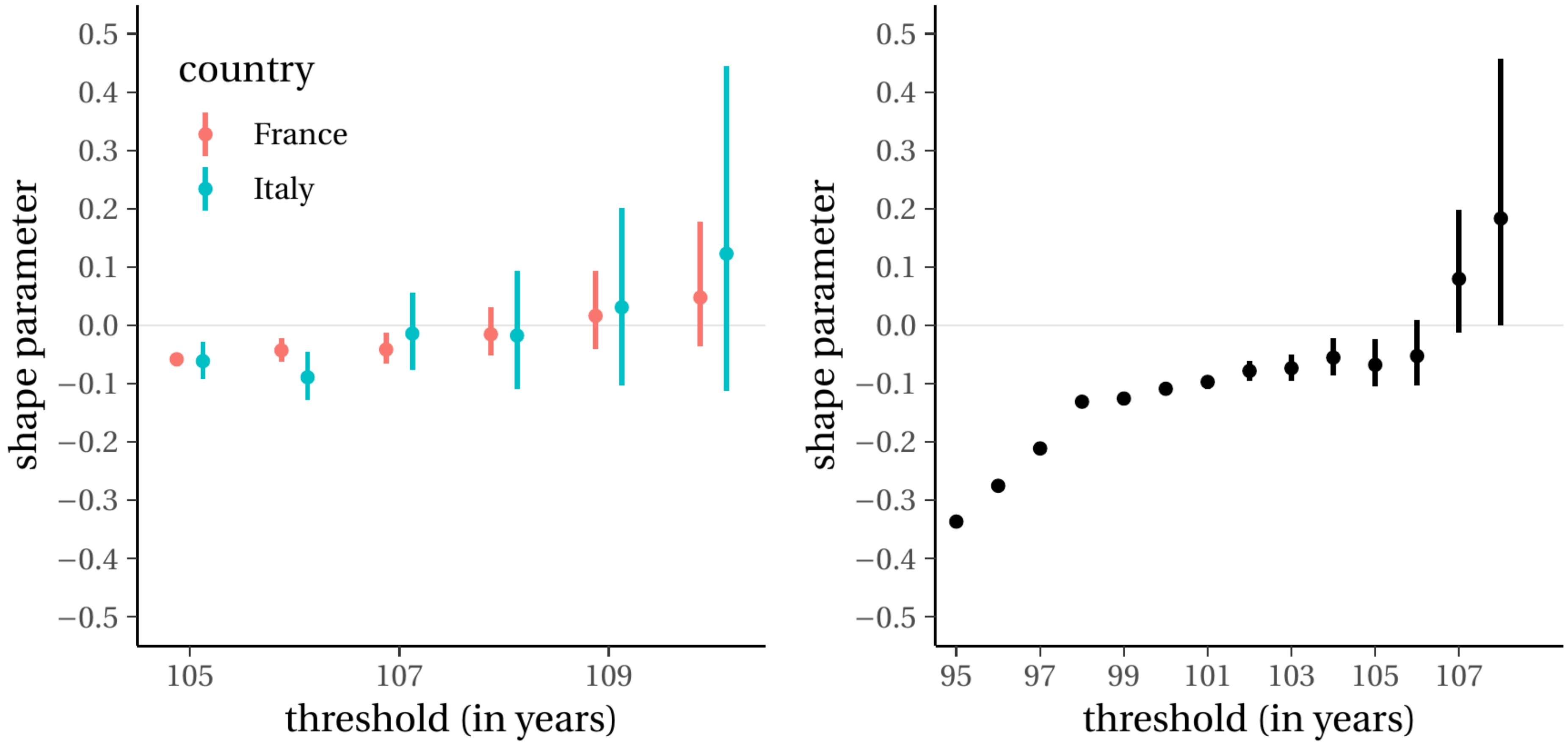
- the Gompertz model has $\xi_u \nearrow 0$: estimates of ξ tend to be negative.

Threshold stability

A key property of the generalized Pareto distribution is **threshold stability**.

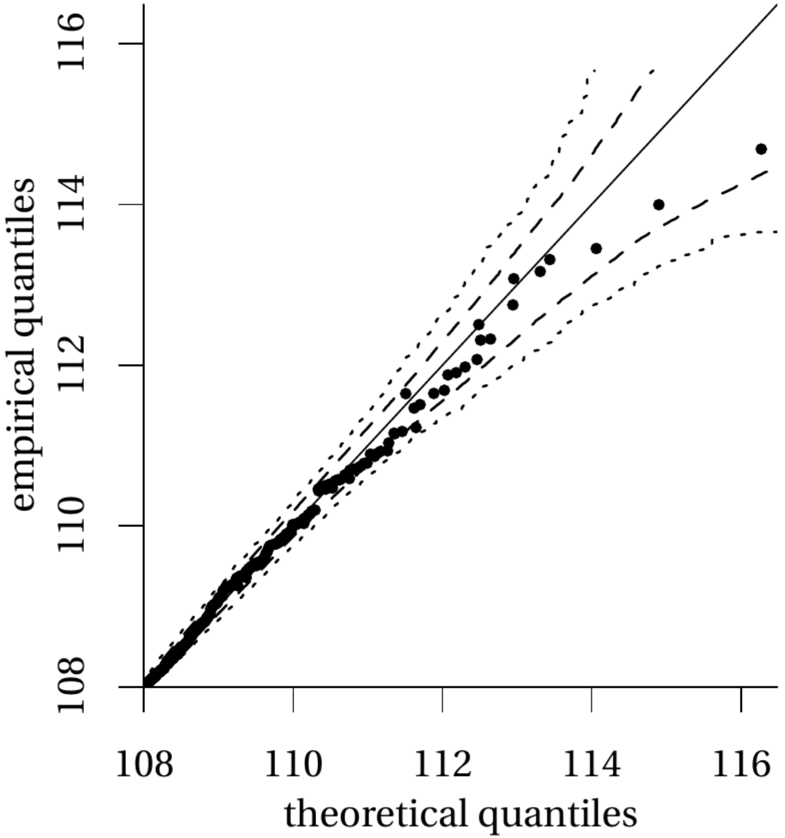
- can extrapolate behaviour of F at higher levels
- useful for choosing u in applications
  - fit model at multiple threshold $u_1 < \cdots < u_k$.
  - check whether shape ξ agrees over range.

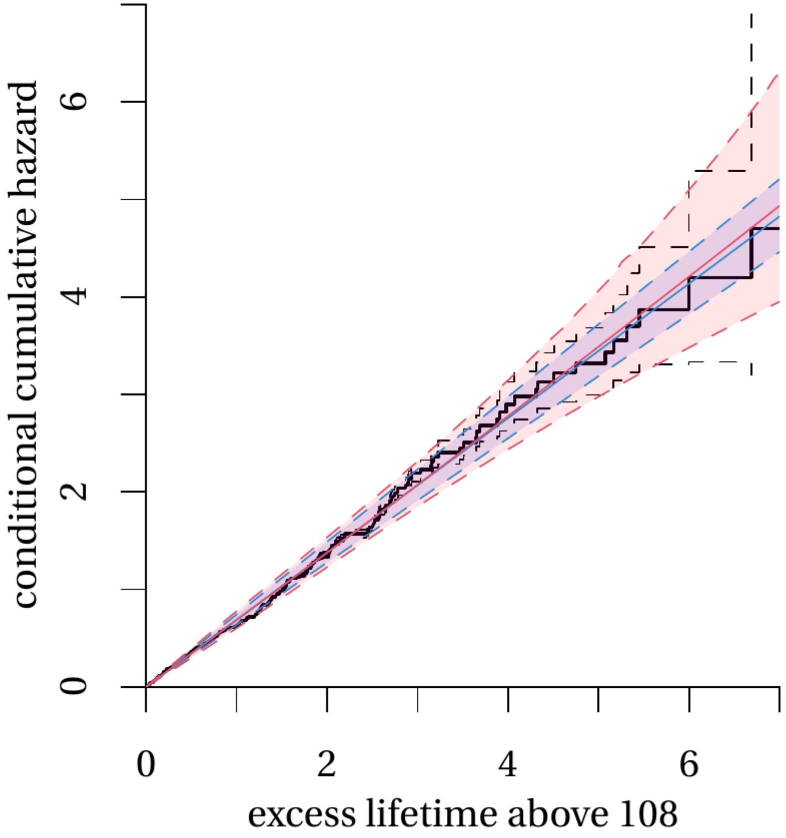
Lack of (threshold) stability



Threshold stability plots for France and Italy (left), and Netherlands (right).

How good is the approximation?





Quantile-quantile plots with 95% pointwise and simultaneous bands (left) and conditional cumulative hazard (right) for Istat.

Flexibility is key

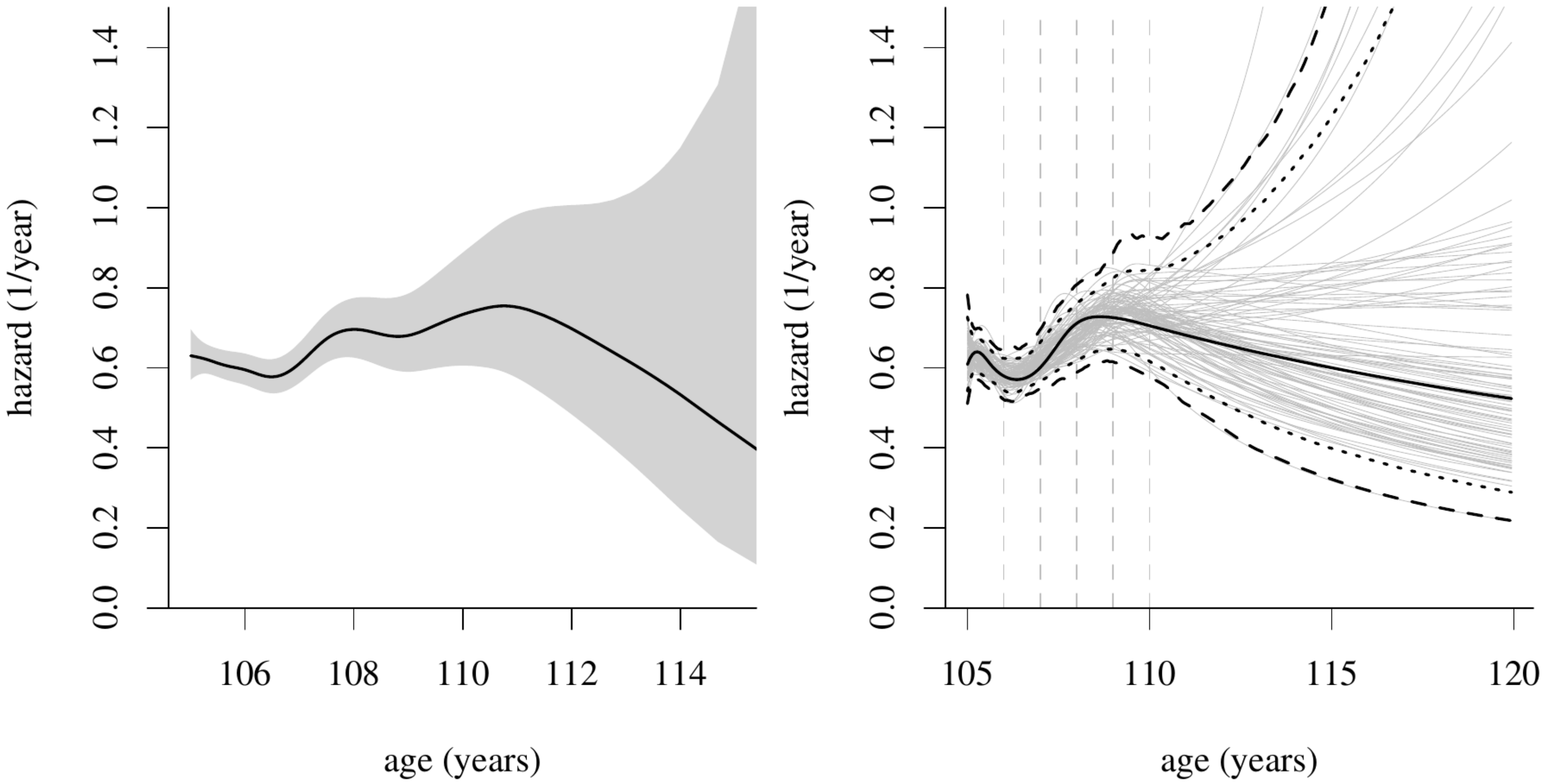
We fit a semiparametric hazard function

$$h(t) = \{\sigma + \xi t + g(t)\}_+^{-1}$$

with $g(t) \to 0$ as $t \to t_F$ with $g(t)$ a cubic regression spline

- generalizes generalized Pareto model
- reduces to parametric model in upper tail
- equispaced knots

Let the tail speak for itself!



Nonparametric hazard (left) and semiparametric generalized Pareto (right).

Semiparametric estimator suggest a wide range of plausible behaviour, including constant risk.

Extrapolation

Is there a finite lifespan?

Mathematically speaking, is $t_F = \sup\{t : F(t) < 1\} = \infty$?

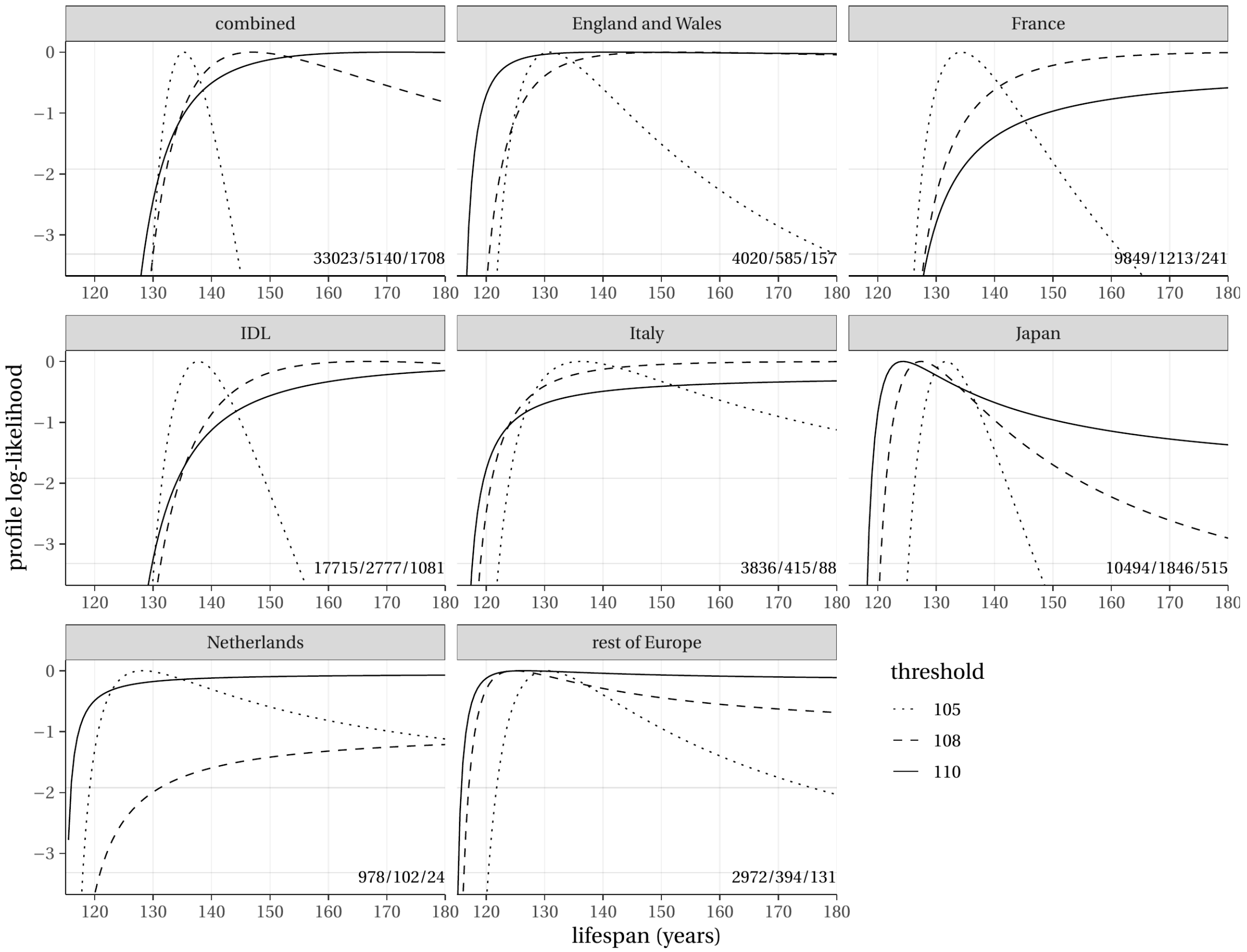
Hard to convey to the average reader:

- $t_F = \infty$ does not imply immortality.
- $\Pr(T > u) < \varepsilon$ does not imply finite lifespan $t_F < u$.

the answer may be in the model.

- Gompertz–Makeham has no right endpoint and $t_F = \infty$.
- exponential model has a constant hazard (**plateau of mortality**).
- the generalized Pareto implies a lifespan of $u - \sigma/\xi$ if $\xi < 0$.

Is the lifetime distribution bounded?



Profile likelihood for endpoint for various countries and three thresholds.

Human lifespan

No discernible differences between

- earlier and later birth cohorts,
- countries,
- men and women, except that after age 108 French men have lower survival.

Not to be confused with gender inbalance due to lower survival of men.

You have no power in here!

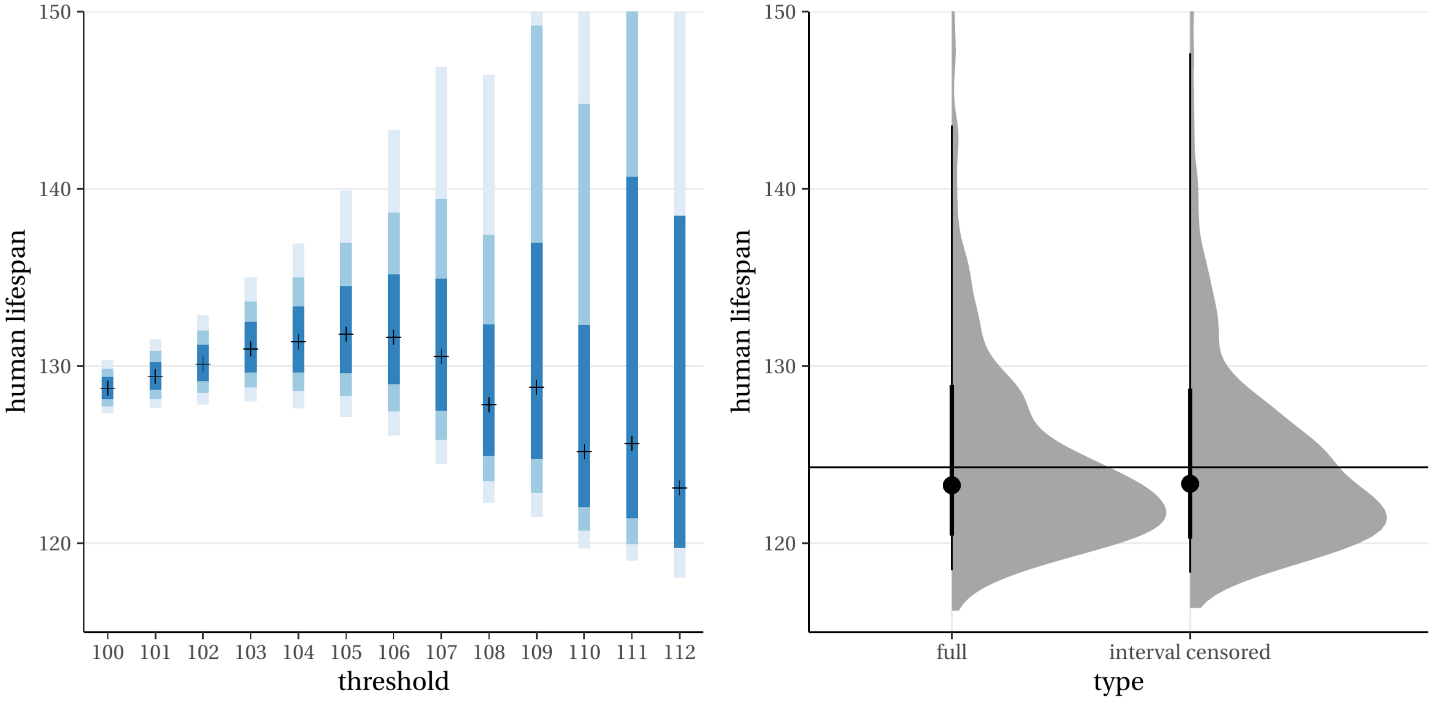
The power of a likelihood ratio test for detecting a finite endpoint (obtained by simulating records with a generalized Pareto distribution with lifespan t_F) is high: based on France/Italy/IDL data (2016 version),

- 125 years: combined power of 97%;
- 130 years: combined power of 83%;
- 135 years: combined power of 66%.

Suggests that the human lifespan lies well beyond any lifetime yet observed.

Huge uncertainty

Japanese (unvalidated) data are interval-censored and right-truncated



Posterior credible intervals by threshold (left) and sampling distribution with(out) rounding (right).

Supercentenarians [don't] live forever...

Estimated exponential distribution above 110 years for IDL has mean 0.5 (0.46, 0.53): a coin toss.

Surviving until 130 years conditional on surviving until 110 years

- is equivalent to obtaining 20 heads in a row,
- a less than one-in-a-million chance...

Anticipated increase in number of supercentenarians make it possible to observe 130, but higher record is highly unlikely (Pearce & Raftery 2021).

Take home messages

cannot use low thresholds
for extrapolation.

goodness-of-fit diagnostics suggest
generalized Pareto model fits well.

hazard doesn't stabilize
until about 108 years.

shape estimates suggest
a **decrease** of the risk above 108.

References

- Léo R. Belzile, Anthony C. Davison, Holger Rootzén and Dmitrii Zholud (2021). Human mortality at extreme age., Royal Society Open Science, 8, `doi:10.1098/rsos.202097`.
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- Léo R. Belzile (2022) Heads or tails: What statistical models tell us about the probability of living beyond 110, The Conversation
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