# Reference adjusted and standardized all-cause and crude probabilities as an alternative to net survival in population-based cancer studies

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  1. differences in cancer mortality rates.
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  3. differences in the age distribution (and other demographic factors).
- We try to 'isolate' the mortality associated with the cancer and (age) standardize to ensure comparisons are 'fair'.

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So we estimate $h_c(t|Z_i)$ without using cause of death information.

# Excess mortality/Relative survival

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$$S(t|Z_i) = S^*(t|Z_i)R(t|Z_i)$$

$$R(t|Z_i) = \frac{S(t|Z_i)}{S^*(t|Z_i)} \quad \text{hence 'relative survival'}$$

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- Estimand of interest is marginal relative survival.

$$R_m(t|Z) = E_Z\left[R(t|Z)\right]$$

- Expectation is over distribution of $Z$.
- Estimated in a model setting by,

$$\bar{R}_m(t|Z) = \frac{1}{N}\sum_{i=1}^{N}\widehat{R}(t|Z_i)$$

- Predict a survival curve for each of the $N$ individuals and then average (see Syriopoulou et al. 2020 [1]).

# Interpretation of relative/net survival

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2. the age distribution was not as it is observed, but as that in a reference population.

- Many examples of the media, politicians, clinicians, patients and scientists interpreting incorrectly.
- See Lambert *et al* 2015 [2], Pavlic and Pohar Perme 2018 [3].

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2. Differences in other cause mortality rates.

- This is the reason we estimate net survival

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## Options

1. Use combined distribution of $X = 1$ and $X = 0$.
2. Use covariate distribution when $X = 1$
3. Use covariate distribution when $X = 0$
4. Use external covariate distribution.

- (4) is the most common (for age), but I will come back to alternatives.

# External weights

- Define a reference population with covariate distribution $Z^{REF}$
- We weight individuals relative to this reference population.
- If we do this in both groups (studies) then differences will not be due to differential $Z$

$$\bar{R}_m(t|Z^{REF}) = \frac{1}{N}\sum_{i=1}^{N} w_i \widehat{R}(t|Z_i)$$

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- A common example of this is age-standardization.

# Age Standardization

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| Age | ICSS 1[a] | ICSS 2[b] | ICSS 3[c] |
|---|---|---|---|
| 15-44 years | 0.07 | 0.28 | 0.60 |
| 45-54 years | 0.12 | 0.17 | 0.10 |
| 55-64 years | 0.23 | 0.21 | 0.10 |
| 65-74 years | 0.29 | 0.20 | 0.10 |
| 75+ years | 0.29 | 0.14 | 0.10 |

[a] Lip, tongue, salivary glands, oral cavity, oropharynx, hypopharynx, head and neck, oesophagus, stomach, small intestine, colon, rectum, liver, biliary tract, pancreas, nasal cavities, larynx, lung, pleura, breast, corpus uteri, ovary, vagina and vulva, penis, bladder, kidney, choroid melanoma, non-Hodgkin lymphoma, multiple myeloma, chronic lymphatic leukaemia, acute myeloid leukaemia, chronic myeloid leukaemia, leukaemia, prostate
[b] Nasopharynx, soft tissues, melanoma, cervix uteri, brain, thyroid gland, bone

[c] Testis, Hodgkin lymphoma, acute lymphatic leukaemia

# Obtaining weights

$w_i^s$ proportion in age group in reference population to which the $i^{th}$ individual belongs.

$w_i^a$ proportion in the age group in the study population to which the $i^{th}$ individual belongs.

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| ageICSS | ICSSwt | w_a | wt |
|---|---|---|---|
| <45 | 0.280 | 0.274 | 1.020 |
| 45-54 | 0.170 | 0.164 | 1.039 |
| 55-64 | 0.210 | 0.222 | 0.944 |
| 65-74 | 0.200 | 0.216 | 0.926 |
| 75+ | 0.140 | 0.223 | 0.627 |

# Example

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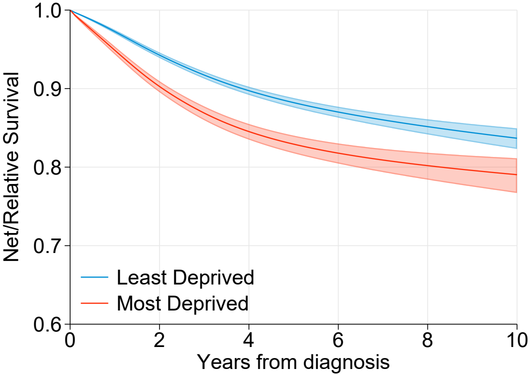
## Model

- Flexible parametric relative survival model [5].
- Restricted cubic splines (rcs) with 6 knots for baseline.
- Age modelled continuously using rcs (4 knots).
- Deprivation binary covariate.
- interactions between age and deprivation.
- Effects of age and deprivation time-dependent (4 knots per covariate).

# Marginal Net Probability of Survival



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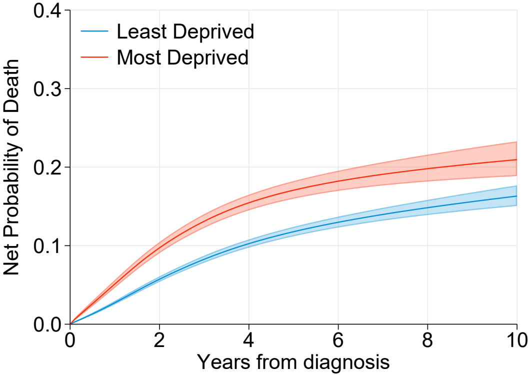

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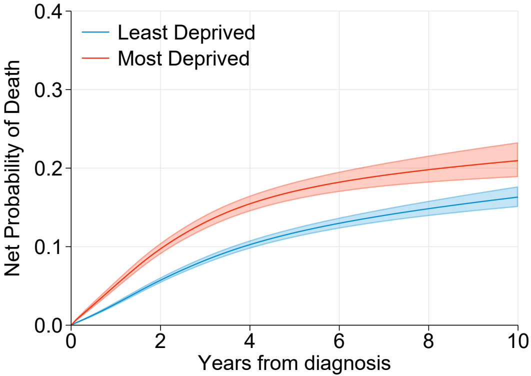


Age Standardization: Internal (within each group)
Fair Comparison: ✗

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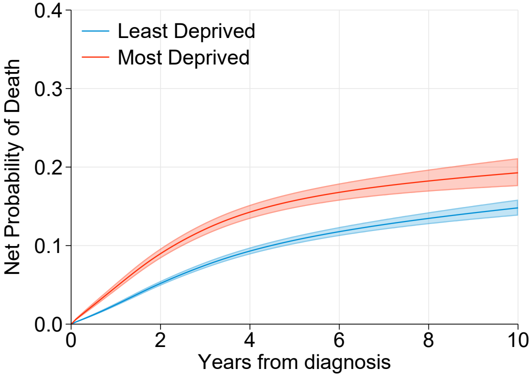


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**However, (2) and (3) depend on other cause mortality.**

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- Partition all-cause probability of death into death to to cancer and death due to other causes

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$$\begin{array}{rcccc} \text{All-cause} & = & \text{prob cancer} & + & \text{prob other cause} \\ \text{prob of death} & & \text{death} & & \text{death} \\ F(t|Z_i) & = & F_c(t|Z_i) & + & F_o(t|Z_i) \end{array}$$

## Crude Probability of Death[6]

$$F_c(t|Z) = \int_0^t S^*(u|Z_i)\widehat{R}(u|Z_i)\widehat{\lambda}(u|Z_i)du$$

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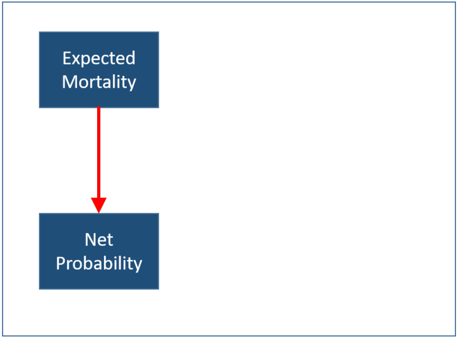

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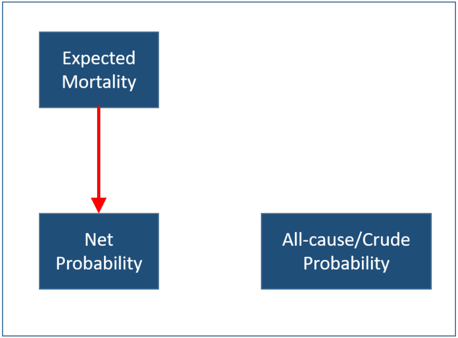

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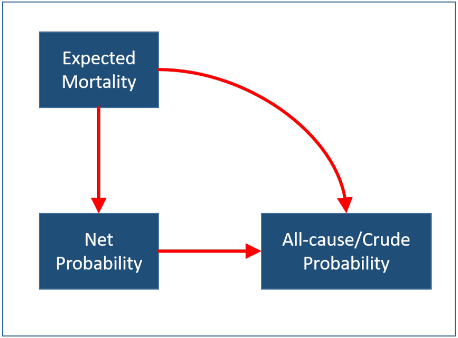

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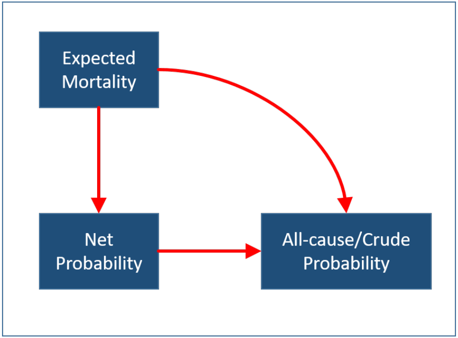


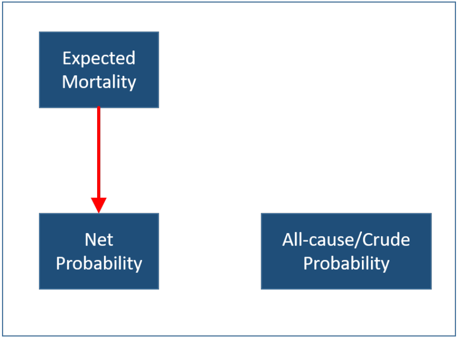

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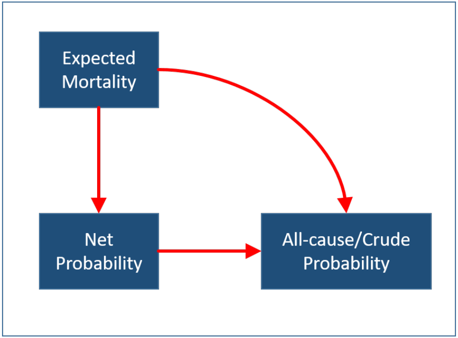


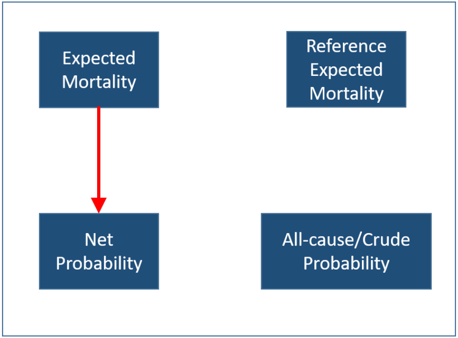

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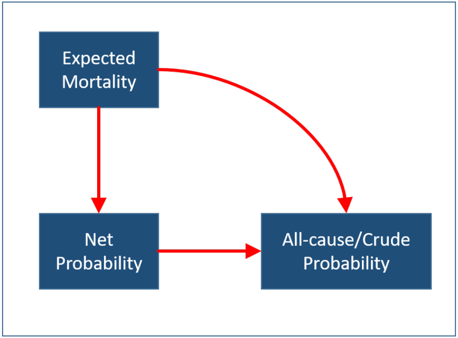


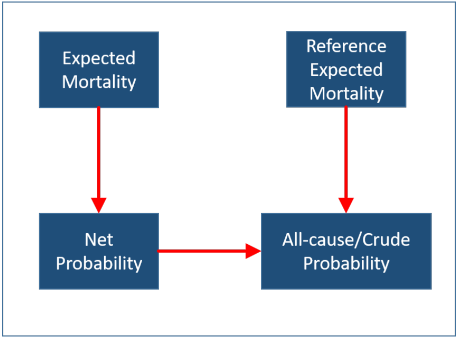

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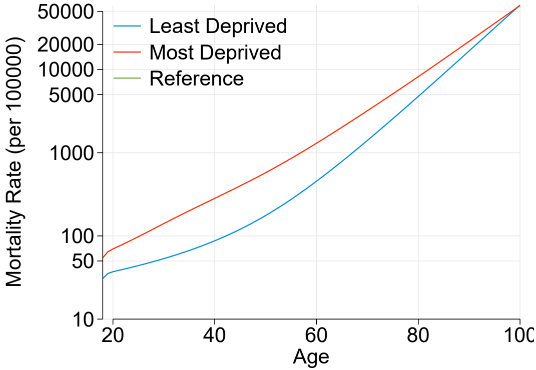


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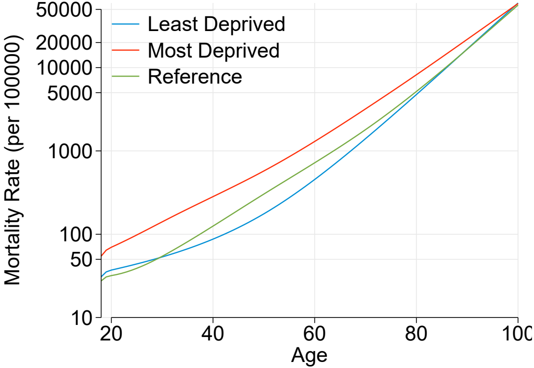


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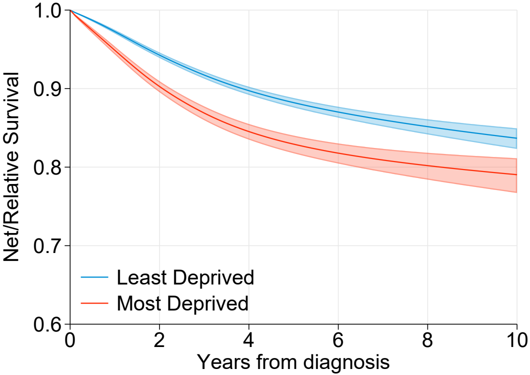
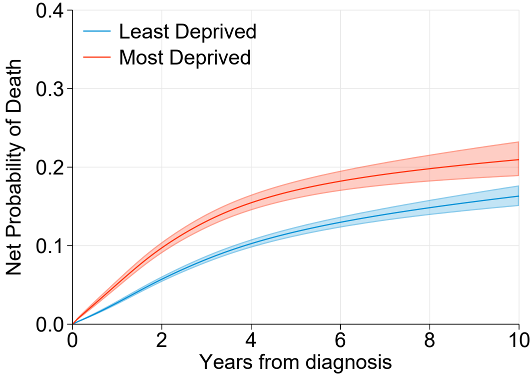
Note if $S^{**}(t|Z_i) = 1$ for all $Z_i$, this reduces to $1 - \bar{R}_m(t|Z)$.

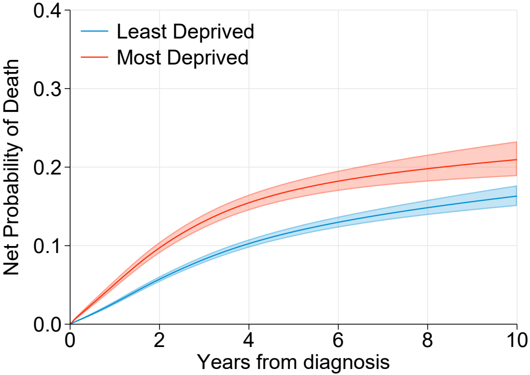
# Net Probability of Survival



# Net Probability of Death

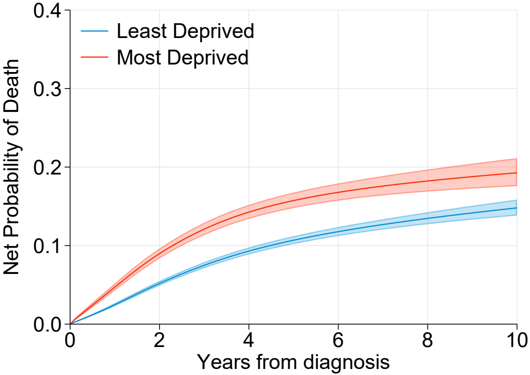


# Net Probability of Death



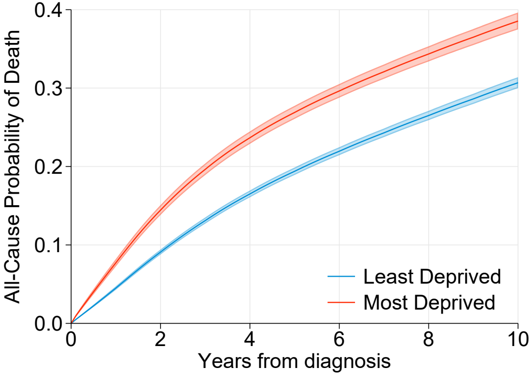

Age Standardization: Internal (within each group)
Fair Comparison: ✗

# Net Probability of Death



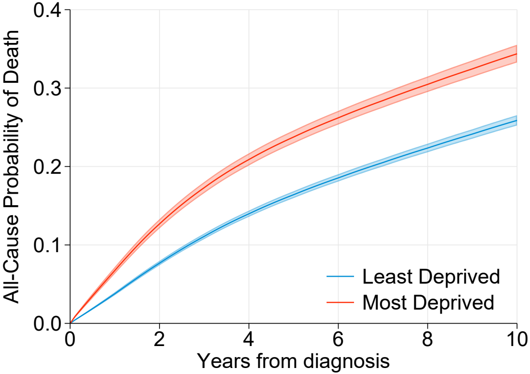

Age Standardization: ICSS
Fair Comparison: ✓

# All-cause Probability of Death



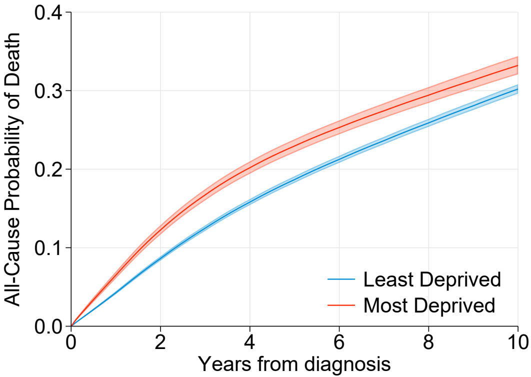

Age Standardization: Internal (within each group)
Expected Rates: Separate
Fair Comparison: ✗

# All-cause Probability of Death



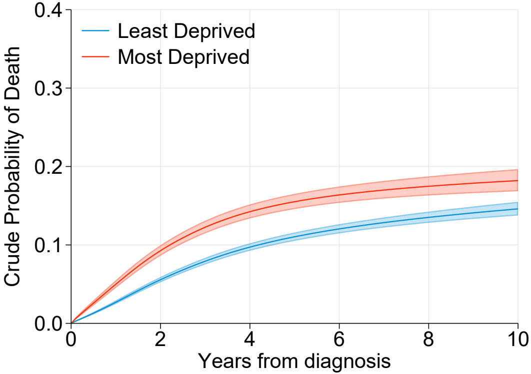

Age Standardization: ICSS
Expected Rates: Separate
Fair Comparison: ✗

# All-cause Probability of Death



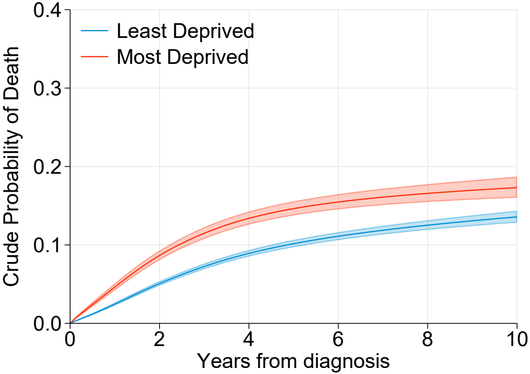

| | |
|---|---|
| Age Standardization: | ICSS |
| Expected Rates: | Reference |
| Fair Comparison: | ✓ |

# Crude Probability of Death



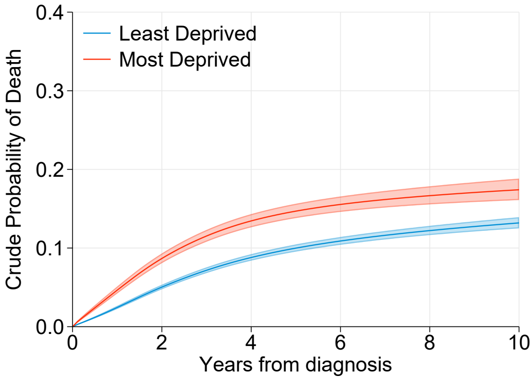

| | |
|---|---|
| Age Standardization: | Internal (within each group) |
| Expected Rates: | Separate |
| Fair Comparison: | ✗ |

# Crude Probability of Death




| | |
|---|---|
| Age Standardization: | ICSS |
| Expected Rates: | Separate |
| Fair Comparison: | ✗ |

# Crude Probability of Death




Age Standardization: ICSS
Expected Rates: Reference
Fair Comparison: ✓

# Choice of Hypotheticals

## Net Probability of Death

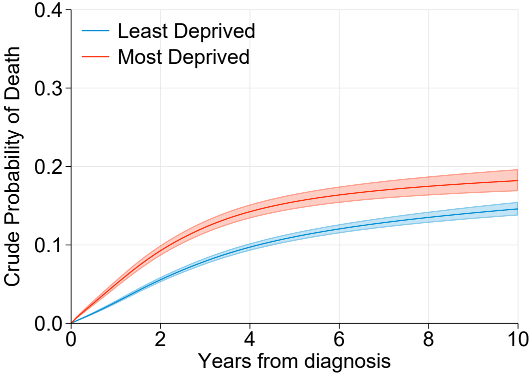
1. Age distribution is that of reference.
2. Mortality rate due to other causes is zero

## All-cause/Crude Probability of Death

1. Age distribution is that of reference.
2. Mortality rate due to other causes is that of reference.

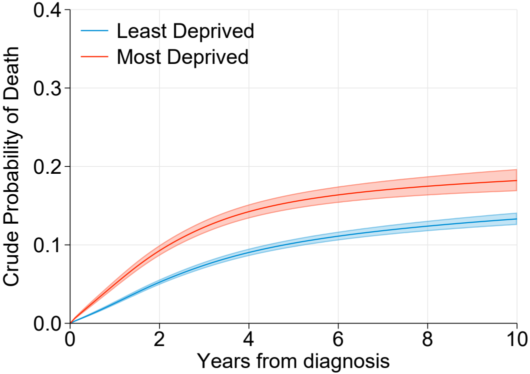
- In some situations it is useful to select one group to be non-hypothetical.
  - Standardize to age distribution of selected group.
  - Use expected mortality rates of selected group.

# Crude Probability of Death



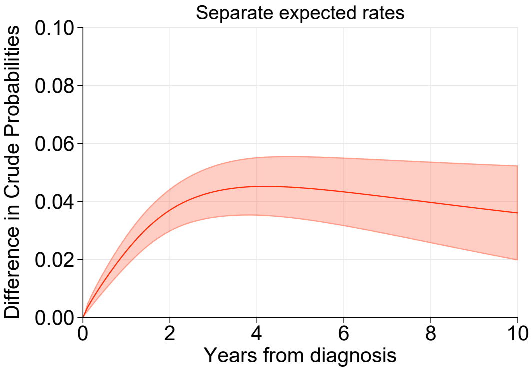

Age Standardization: Internal (within each group)
Expected Rates: Separate
Fair Comparison: ✗

# Crude Probability of Death



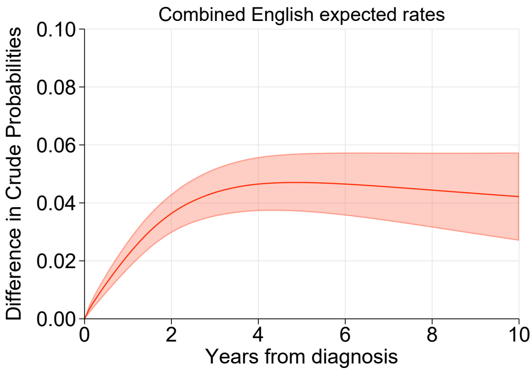

Age Standardization: Most Deprived
Expected Rates: Most Deprived
Fair Comparison: ✓

# Contrasts



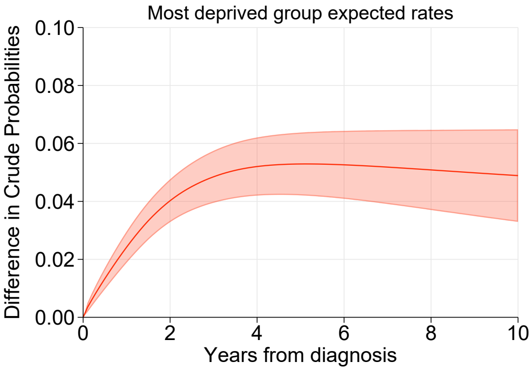

| | |
|---|---|
| Age Standardization: | Internal (within each group) |
| Expected Rates: | Separate |
| Fair Comparison: | ✗ |

# Contrasts




Age Standardization: ICSS
Expected Rates: English combined
Fair Comparison: ✓

# Contrasts




| | |
|---|---|
| Age Standardization: | Most Deprived |
| Expected Rates: | Most Deprived |
| Fair Comparison: | ✓ |

# We have a choice when making comparisons

- We want to compare probabilities of survival/death
- Need to 'remove' differences due to other causes.
- We can do this by

1. Assume rate of death due to other causes is the same in both groups and is equal to zero for all ages (net probability).
2. Assume rate of death due to other causes is the same in both groups and is equal to a reference population (reference adjusted all-cause or crude probability).

# We have a choice when making comparisons

- We want to compare probabilities of survival/death
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1. Assume rate of death due to other causes is the same in both groups and is equal to zero for all ages (net probability).
2. Assume rate of death due to other causes is the same in both groups and is equal to a reference population (reference adjusted all-cause or crude probability).
    1. Using a common external reference population
    2. Using one of the groups as the reference.

# Summary

- Possible to make fair comparisons using all-cause or crude probabilities.
  - Need to (age) standardize
  - Need to use reference expected mortality rates.
- Useful alternative/complement to marginal net survival.
- I have explained from a modelling perspective - non-parametric possible. Builds on work by Sasieni and Brentnall 20016 ([7])
- Modelling more generalisable.
- Ideas also work for competing risks models ('separable effects').
- Need to think about which covariate distribution to standardize over.
- Need to think which reference expected rates to use.

# Software

- All analysis in Stata.
- `standsurv` works for a many parametric models
  - Exponential, Weibull, Gompertz, LogNormal, LogLogistic
  - Flexible parametric (Splines:log-hazard or log cumulative scales)
- Standard, relative survival and competing risks models
  - Can use different models for different causes.
- Various Standardized related measures.
  - Survival, restricted means, centiles, hazards... and more
- Standard errors calculated using delta-method or M-estimation with all analytical derivatives,so fast

**More information on `standsurv` available at**

https://pclambert.net/software/standsurv/

# More details...[8]

International Epidemiological Association

*International Journal of Epidemiology*, 2020, 1–10
doi: 10.1093/ije/dyaa112
Original Article

Original Article

## Reference-adjusted and standardized all-cause and crude probabilities as an alternative to net survival in population-based cancer studies

**Paul C Lambert,[1,2]* Therese M-L Andersson,[2] Mark J Rutherford ,[1,3] Tor Åge Myklebust[4,5] and Bjørn Møller[4]**

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[8] Lambert PC, Andersson TML, Rutherford MJ, Myklebust TÅ, Møller B. Reference-adjusted and standardized all-cause and crude probabilities as an alternative to net survival in population-based cancer studies. *International Journal of Epidemiology* 2020;.

# References 2