Proceedings Paper:

Bullement, A. orcid.org/0000-0001-7091-0972 and Hatswell, A.J. (2018) MO2 - How errors in the implementation of background mortality leads to bias in models. In: Value in Health. ISPOR 8th Asia-Pacific Conference, 08-11 Sep 2018, Tokyo, Japan. Elsevier , S8.

https://doi.org/10.1016/j.jval.2018.07.055

How Errors in the Implementation of Background Mortality Leads to Bias in Models

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Background and Objectives

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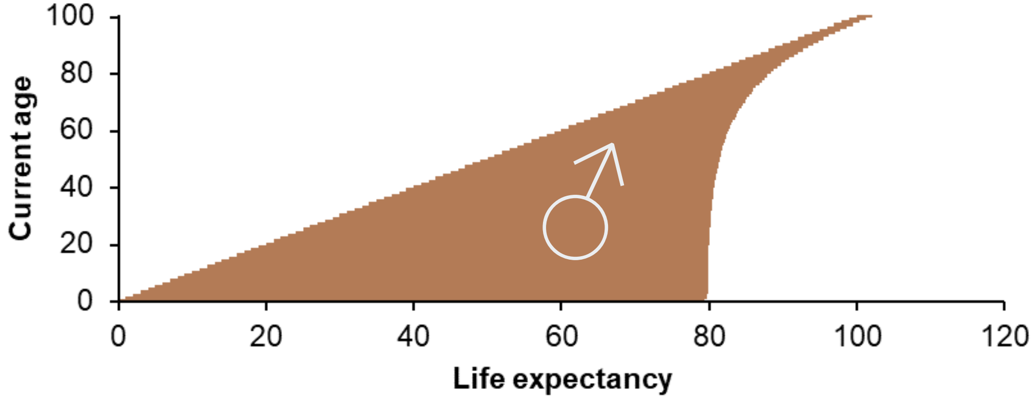
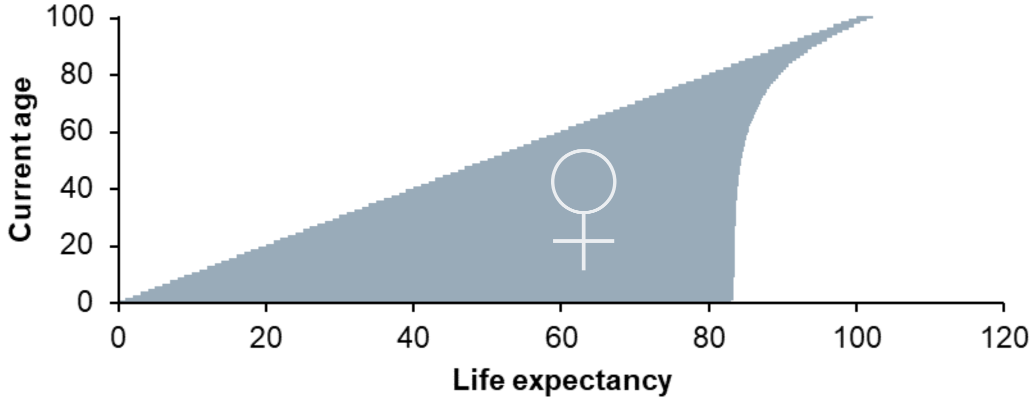
- Patients considered in economic models are typically exposed to ‘competing risks’ of death
  - An example of these ‘competing risks’ is disease-specific and other-cause mortality
- The implementation of other-cause mortality (or ‘background mortality’) is often inappropriately defined and based on a population mean, when the risk is not linearly related to age
- This research looks at the impact of a simplified application of background risk on model results





Figures: Life expectancy by age and sex for the United Kingdom, 2016

Raw data from the UK Office for National Statistics (https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandreferencetables)

Methods

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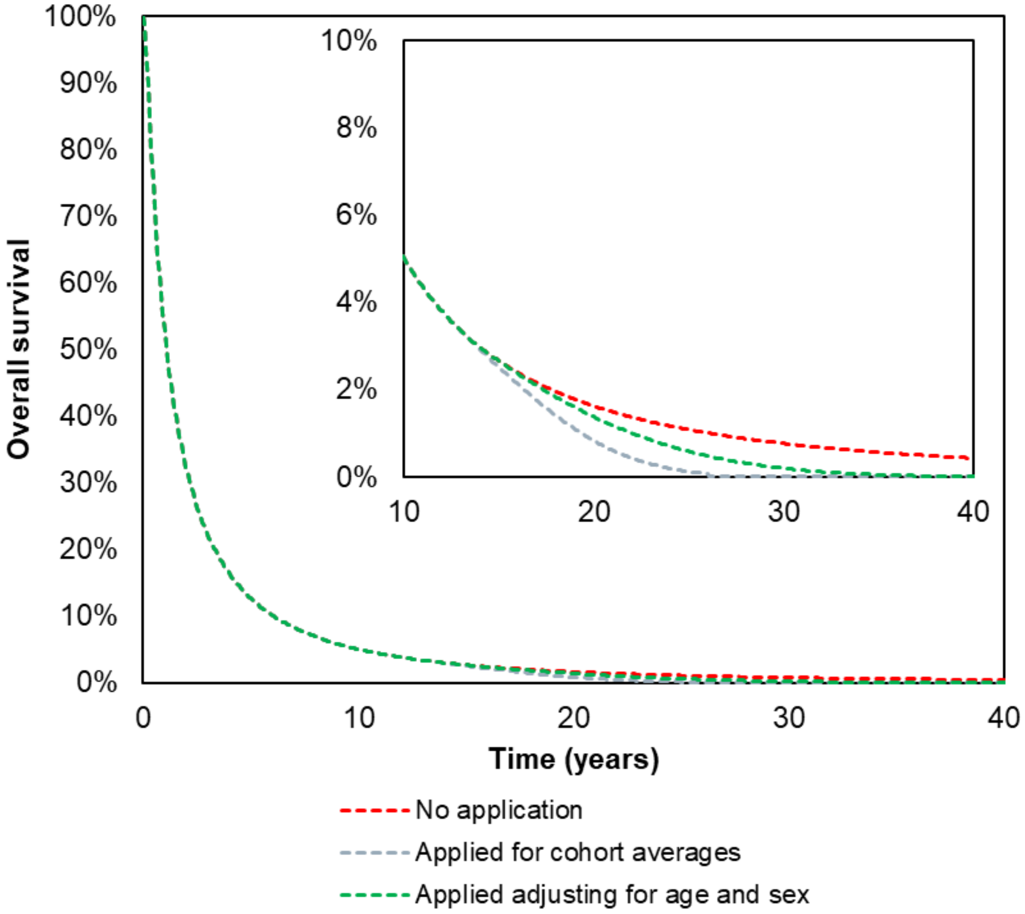
- Three economic models were constructed using simulated disease data:
  1. Example 1: partitioned survival model (PSM) for a cancer treatment
  2. Example 2: state-transition model (STM) for multiple sclerosis
  3. Example 3: individual-level model (ILM) for cyanide poisoning

- The models incorporated mortality according to the following data and assumptions:
  - Disease-specific mortality: parametric survival curves or survival probabilities
  - Background mortality: UK Life Tables

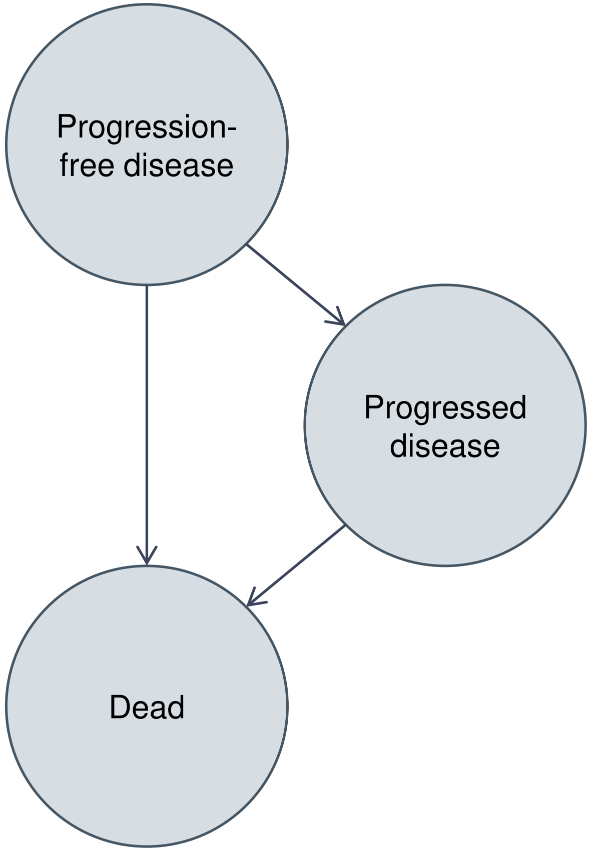
- Model outcomes (undiscounted and discounted life years [LYs]) were compared between background mortality applied using the following methods (where applicable):
  1. Based on mean age and gender split at baseline (“cohort mean”)
  2. Accounting for the dynamic gender split of patients over time (“gender split”)
  3. Considering the distribution of patient age at baseline (“age distribution”)
  4. On a per-patient basis (“individual level”)

Results
Illustration

- Cohort with mean age of 75 years (SD 7.5), 60% female
- Red line shows unadjusted overall survival (OS)
- Grey line shows naïve application of background mortality based on cohort averages at baseline
- Green line shows OS adjusted for age distribution at baseline and gender split variation over time



Results
Example 1 (PSM, cancer)



6.1% lower versus fully-adjusted

15.9% lower versus fully-adjusted

0.2% lower versus fully-adjusted

0.7% lower versus fully-adjusted

	Intervention	Comparator	Δ
"Cohort mean" results			
Undisc. LYs	3.18	2.48	0.70
Disc. LYs	2.69	2.19	0.50
"Gender split" results			
Undisc. LYs	3.19	2.49	0.71
Disc. LYs	2.69	2.19	0.50
"Age distribution" results			
Undisc. LYs	3.38	2.55	0.83
Disc. LYs	2.78	2.23	0.56
"Gender split" + "age distribution" results			
Undisc. LYs	3.39	2.56	0.84
Disc. LYs	2.79	2.23	0.56

Cohort with mean age of 75 years (SD 7.5), 60.0% female

Results
Example 2 (STM, multiple sclerosis)

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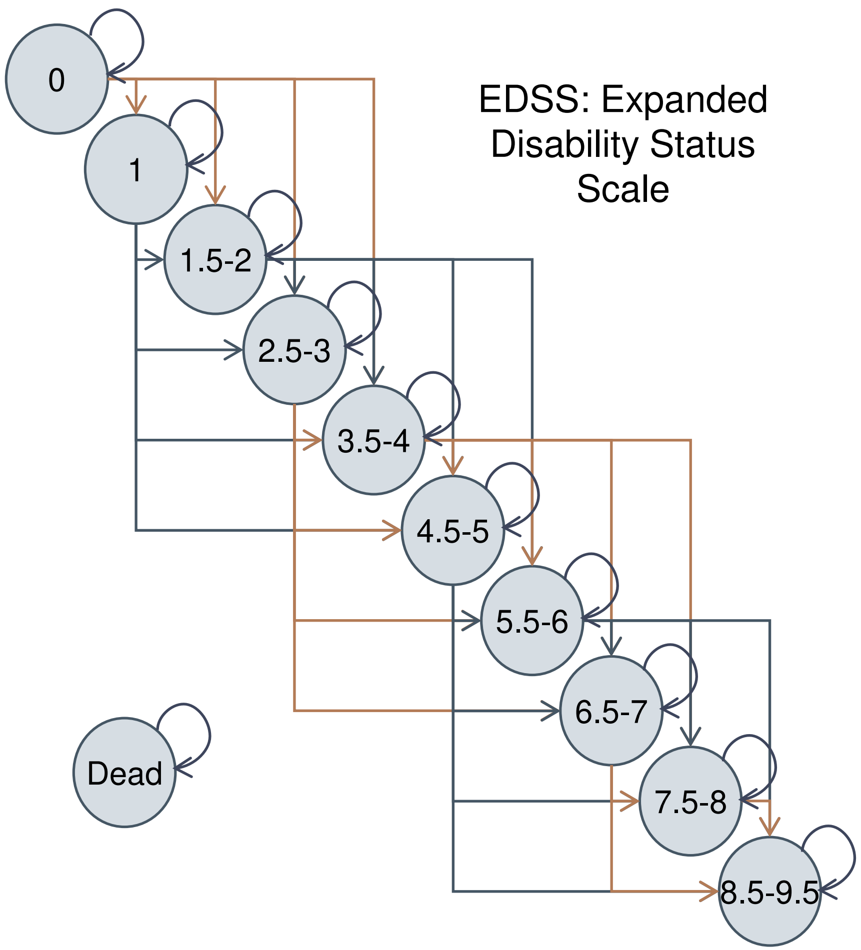


EDSS: Expanded Disability Status Scale

2.1% lower versus fully-adjusted

4.7% lower versus fully-adjusted

4.8% lower versus fully-adjusted

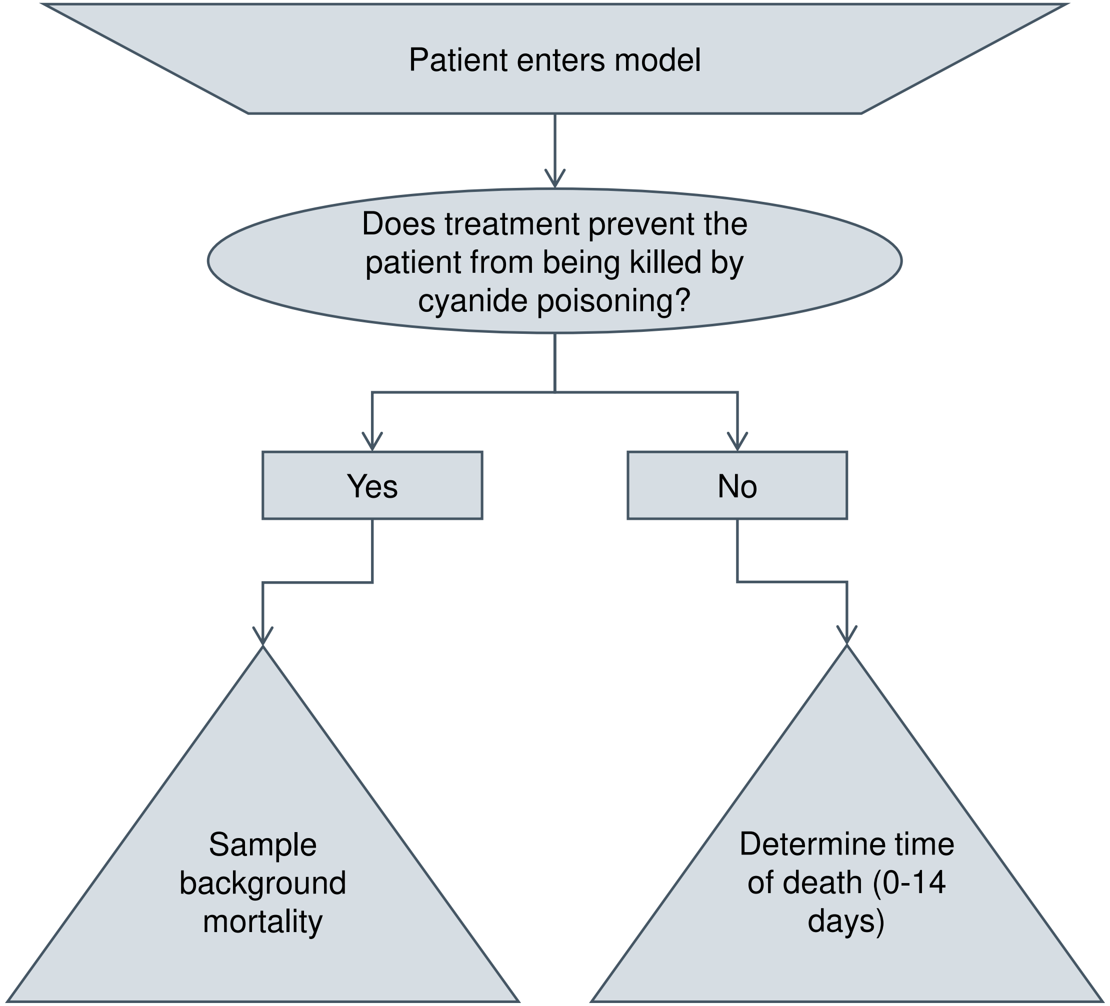
0.1% lower versus fully-adjusted

0.1% lower versus fully-adjusted

	Intervention	Comparator	Δ
"Cohort mean" results			
Undisc. LYs	32.04	30.86	1.18
Disc. LYs	19.23	18.78	0.45
"Gender split" results			
Undisc. LYs	32.06	30.88	1.18
Disc. LYs	19.24	18.79	0.44
"Age distribution" results			
Undisc. LYs	31.34	30.10	1.24
Disc. LYs	18.98	18.50	0.47
"Gender split" + "age distribution" results			
Undisc. LYs	31.36	30.13	1.24
Disc. LYs	18.98	18.51	0.47

Cohort with mean age of 35 years (SD 4.0), 66.7% female

Results
Example 3 (ILM, cyanide poisoning)



	Intervention	Comparator	Δ
“Cohort mean” results			
Undisc. LYs	38.68	21.50	17.18
Disc. LYs	20.13	11.23	8.96
“Individual level” results			
Undisc. LYs	39.07	21.73	17.34
Disc. LYs	18.53	10.31	8.23

Cohort with mean age of 40 years (SD 23.6), 50.5% female

Large number of total incremental LYs

9.0% lower versus fully-adjusted

0.9% lower versus fully-adjusted

Results
Summary

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- Predicted LYs using alternative applications of background mortality can vary dramatically, particularly where patients have a wide spread in age, and low disease-specific mortality

- Examples 1 and 2 demonstrate the error in undiscounted LYs for a given treatment could be substantial – up to 6.1% in our stylised examples
    - This magnitude of error has the potential to influence decision making

- Even in a simplistic individual level model (Example 3), simplification of background mortality implementation could lead to a percentage error in undiscounted LYs of 0.9%
    - The impact of discounted LYs however was ten times as large (9.0%). If discounted incremental LYs were translated into discounted incremental quality-adjusted life years (QALYs), a substantial impact may be observed in the cost per QALY gained in a cost-utility analysis (not presented here)

Conclusions

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- The implementation of background mortality in economic models is often flawed, which has the potential to meaningfully alter results
- The level of bias introduced varies, being relatively small when patients are close in age and disease-specific mortality constitutes the majority of risk
  - Conversely this can be large when there is a large age range, and capacity to demonstrate benefit in the longer term (for example, cancer immunotherapies, chimeric antigen receptor t-cell [CAR-T] therapy, stem cell transplantation [SCT])
  - Accounting for the change in gender split over time is good practice, though it does not have a large impact in our results
- While the impact of simplifying background mortality is highly context dependent, modellers should be mindful of the risks over-simplification could pose
  - This is particularly where background mortality is a major cause of death

Thank you

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