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Estimating restricted mean survival time and expected life-years lost in the presence of competing risks within flexible parametric survival models

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Abstract

We present various measures, specifically the expected life-years list due to a cause of death, that can be predicted for a specific covariate pattern to facilitate interpretation in observational studies. These can also be summarised at the population-level using standardisation to obtain marginal measures. The restricted mean survival time (RMST) measure can be obtained in the presence of competing risks using Royston-Parmar flexible parametric survival models (FPMs). Royston-Parmar FPMs can be fitted on either the cause-specific hazards or cumulative incidence scale in the presence of competing risks. An advantage of modelling within this framework for competing risks data is the ease at which other alternative predictions to the (cause-specific or subdistribution) hazard ratio can be obtained. The RMST estimate is one such measure. This has an attractive interpretation, especially when the proportionality assumption is violated. In addition to this, compared to similar measures, fewer assumptions are required and it does not require extrapolation. Furthermore, one can easily obtain the expected number of life-years lost, or gained, due to a particular cause of death, which is a further useful prognostic measure. We describe estimation of RMST after fitting a FPM on either the log-cumulative subdistribution, or cause-specific hazards scale. As an illustration of reporting such measures to facilitate interpretation of a competing risks analysis, models are fitted to English colorectal data.

Keywords: competing risks; restricted mean survival time; restricted mean life time; flexible parametric model; life-years lost; survival analysis

1 Background

In observation studies with a time-to-event outcome, proportional hazards are often assumed; typically analysed using the Cox proportional hazards model. However, the proportional hazards assumption is often not valid, for example, in cancer studies, where the effect of tumor size on cancer mortality will vary over time [1, 2, 3]. When time-dependent effects are considered in order to model the change in the

effect of covariates on the mortality rate over time, only the hazard ratio (HR) or time-dependent HR plot is typically presented. Although the HR is useful for understanding changes in the *rate* of dying in a population, it does not provide an understanding of absolute indiviudal *risk* of dying. This can in fact be very different to the size of effect suggested by the HR [4]. Furthermore, in the presence of time-dependent effects, the time-dependent HR is often presented as a single summary statistic and interpreted as an average over follow-up time. However, this can be misleading as it does not provide the whole picture of how the rate, and thus, treatment effect changes over time. Royston and Parmar [5] proposes estimation of the restricted mean survival time (RMST), also known as the restricted mean lifetime (RMLT), as a useful alternative to the HR as a summary measure, particularly when the proportional hazards assumption does not hold [6, 7]. Merits on the use of the RMST measure are also highlighted by others [8, 9, 6, 5, 10]. RMST is essentially the mean survival before a pre-specified time-point. In the presence of competing risks, Andersen [11] introduces the analogue to the RMST measure for the cumulative incidence function (CIF) which gives the (total) number of years lost before a pre-specified time and demonstrates how this can be decomposed into the number of years lost due to each cause of death [12].

In this paper, we show how the RMST estimate can be obtained within a flexible parametric survival model (FPM) on either the cause-specific hazards or cumulative incidence scale [13, 14]. We also show how other useful measures can be obtained and presented which include marginal/standardised estimates and comparative measures. We begin with a brief description of competing risks in Section 2.1 and highlight particular interest in the cause-specific CIF. This is followed by an introduction of the RMST measure in Section 2.2, including a description to show how these are estimated. In Section 2.2.2, we show how absolute differences between RMST estimates are calculated to assess the impact of a covariate. This

is extended for marginal estimates and associated contrasts using standardisation in Section 2.2.3 which is useful when particular interest is in, for example, the difference between specific covariate groups with multiple confounders. In Section 2.3, we show how these measures can be obtained after fitting a FPM on either the log-cumulative cause-specific hazards or subdistribution hazards scale. Modelling within this framework is advantageous as smooth estimates for the hazard and survival functions are obtained using restricted cubic splines (RCS). As a result, the prediction of other useful estimates, such as RMST, is relatively simple. For illustration of these various measures, English colorectal cancer data obtained from NCRAS is analysed in Section 3 where comparisons between the most and least deprived colorectal cancer patients are made. Finally, the paper is concluded with a discussion on the use and estimation of RMST and further potential extensions. Stata code for obtaining all measures presented in this paper is provided in Appendix A.3. Throughout the paper, we consider specifically application to cancer studies, where the event of interest is death from cancer. However, these methods are generalisable to other time-to-event data.

2 Methods

2.1 Competing risks

In the presence of competing risks, an individual is at risk of failing from more than one event where the occurrence of one event means that others cannot occur. In the context of a cancer survival study, this is when a patient can die from a multitude of other causes as well as the cancer itself. However, if the patient dies from one of these other causes, it means that the time at which the patient would have died from cancer is never observed. One of the key quantities of interest within this framework is the cause-specific CIF [15].

2.1.1 Cause-specific CIF

Let T be a non-negative random variable for the time to death from any cause. Furthermore, let D denote the cause of death in the presence of $k = 1, \ldots, K$ competing risks, where $D = 1, \ldots, K$. It follows that the cause-specific CIF, $F_k(t)$, is defined as,

$$F_k(t) = P(T \leq t, D = k) \tag{1}$$

This is interpreted as the probability of dying from cause k by time t whilst also being at risk of dying from other competing causes of death. Note here that the cause-specific CIF is an improper distribution function since the integral of $F_k(t)$ at infinity is always less than 1 [11].

2.1.2 Cause-specific hazards

A typical competing risks scenario is illustrated in Figure 1(a) in the form of a special-case multi-state model. This has an initial "alive" state and $k = 2$ absorbing states which correspond to each cause of death.

In general, let there be $k = 1, \ldots, K$ competing causes of death where $k = 1$ is the outcome of interest, e.g. death from cancer. This leads to K transition rates from an initial "alive" state to the kth absorbing state which corresponds to dying from a particular cause, $D = k$. These transition rates are referred to as cause-specific hazards, $h_k^{cs}(t)$, which are defined as,

$$h_k^{cs}(t) = \lim_{\Delta t \to 0} \frac{P[t \leq T < t + \Delta t, D = k | T \geq t)}{\Delta t} \tag{2}$$

79   This gives the instantaneous mortality rate from a particular cause k given that

80   the patient is still alive at time t in the presence of all the other causes of death.

81   The probability of occupying one of k death states, i.e. the transition probability

82   for cause k, is defined by the cause-specific CIF such that,

$$F_k(t) = \int_0^t S(u)h_k^{cs}(u)\mathrm{d}u \tag{3}$$

83   where the cause-specific CIF, $F_k(t)$, is a function of all k cause-specific hazard

84   functions since $S(t) = \exp\left(-\sum_{k=1}^K \int_0^t h_k^{cs}(u)\mathrm{d}u\right)$.

85   *2.1.3 Subdistribution hazards*

86   Gray [16] introduces the subdistribution hazard function for cause k, $h_k^{sd}(t)$, which

87   offers a direct relationship with the cause-specific CIF. This has the following math-

88   ematical formulation,

$$h_k^{sd}(t) = \lim_{\Delta t \to 0} \frac{P[t \leq T < t + \Delta t, D = k | T \geq t \cup (T \leq t \cap D \neq k)}{\Delta t} \tag{4}$$

89   which is interpreted as the instantaneous "sub"-rate of failure at time t from

90   cause k amongst those who are still alive, or have died from any of the other $K - 1$

91   competing causes excluding cause k [17].

92   Figure 1(b) provides a conceptual illustration of the competing risks scenario

93   where the "sub-transition" from each state is defined by the subdistribution hazard

94   rate. This is not defined as a typical transition rate as in a usual multi-state model

95   since, in contrast to Figure 1(a), patients who die from a competing cause of death

96   will still remain in the initial state. In other words, the risk-set includes those that

97   are either still alive *or* have died from a competing cause of death. However, if

98 individuals do not experience the competing event, then the transition estimated

99 by the subdistribution hazard rate and the cause-specific hazard rate (estimated

100 from a classical survival model) are both equivalent [18]. It should be noted that,

101 due to the nature of the risk-set in the definition of a subdistribution hazard as

102 shown in Figure 1(b) and Equation 4, it is very difficult to interpret [17].

103   The cause-specific CIF can be directly obtained from the subdistribution hazard

104 for cause k using the standard survival transformation of the cumulative subdistri-

105 bution hazard function for cause k, $H_k^{sd}(t)$, such that,

$$F_k(t) = 1 - \exp\left[-H_k^{sd}(t)\right] \tag{5}$$

106   This shows that a one-to-one correspondence is maintained between the subdis-

107 tribution hazard function for a specific cause of death and the cause-specific CIF.

108 2.2 Restricted mean survival time

109 The RMST measure quantifies the average survival, or time lived, of a patient from

110 time 0 up to a pre-defined time-point, t^*. In the absence of competing risks, the

111 RMST before $t = t^*$, $\mu(t^*)$, of a random variable T is equal to the expectation of

112 $\min(T, t^*)$. RMST, in the absence of covariates, can be expressed as,

$$\mu(t^*) = E(\min(T, t^*)) = \int_0^{t^*} S(u)\mathrm{d}u \tag{6}$$

113   where $S(t)$ is the all-cause survival function. If time is measured in years, this is

114 the average life-years lived before time t^*. The choice of t^* should be pre-determined

115 and clinically motivated, and will vary by, for example, cancer types [5, 6]. This is

116 also often chosen at maximum follow-up time [9, 19].

117   In addition to this, Andersen [11] proposes calculation of the expected number of

118 years lost before time t^* such that,

$$L(0, t^*) = t^* - \int_0^{t^*} S(u)\mathrm{d}u \tag{7}$$

119 *2.2.1 Expected loss in life due to a cause of death*

120 In the presence of competing risks, Andersen [11] shows that the (total) number of

121 years lost, $L(0, t^*)$, can be decomposed into the number of years lost due to each

122 cause k [12]. It follows that since,

$$S(t) = 1 - \sum_{k=1}^{K} F_k(t) \tag{8}$$

123   then the RMST in Equation 6 can be expressed as a function of each cause-specific

124 CIF through the following integral,

$$\mu(t^*) = E(\min(T, t^*)) = \int_0^{t^*} S(u)\mathrm{d}u = \int_0^{t^*} 1 - \sum_{k=1}^{K} F_k(u)\mathrm{d}u$$
$$= t^* - \int_0^{t^*} \sum_{k=1}^{K} F_k(u)\mathrm{d}u \tag{9}$$

125   Equation 7 can also be written as a sum of the integral of each cause-specific CIF

126 such that,

$$L(0, t^*) = t^* - \int_0^{t^*} S(u)\mathrm{d}u = \sum_{k=1}^{K} \int_0^{t^*} F_k(u)\mathrm{d}u \tag{10}$$

¹²⁷ which may also be referred to as restricted mean failure time (RMFT). It follows

¹²⁸ that RMFT can be partitioned where,

$$L_k(0, t^*) = \int_0^{t^*} F_k(u)\mathrm{d}u \tag{11}$$

¹²⁹ which gives the expected number of years lost due to cause k before time t^*.

2.2.2 Comparative predictions

¹³¹ In population-based studies, i.e. non-randomised studies, it may be of interest to

¹³² make absolute or relative comparisons between different covariate groups. As an

¹³³ alternative summary measure to the HR, we can calculate the difference in RMST

¹³⁴ between two covariate groups, or the difference in expected loss in life due to differ-

¹³⁵ ent causes [20]. Let X be a binary covariate that denote the group of interest and Z

¹³⁶ be the set of measured covariates with a specific covariate pattern $\mathbf{z}_j$. To estimate

¹³⁷ the average number of life years gained in group $X = 0$ compared to group $X = 1$,

¹³⁸ we have that,

$$\hat{\mu}(t^* \mid X = 1, Z = \mathbf{z}_j) - \hat{\mu}(t^* \mid X = 0, Z = \mathbf{z}_j) \tag{12}$$

¹³⁹ Alternatively, we can also estimate the expected reduction in the loss (or gain) in

¹⁴⁰ life due to cause k by,

$$\hat{L}_k(0, t^* \mid X = 1, Z = \mathbf{z}_j) - \hat{L}_k(0, t^* \mid X = 0, Z = \mathbf{z}_j) \tag{13}$$

Partitioning in this way is particularly useful if covariates act differently on differ-ent causes of death. For example, those from a particular covariate group may lose (or gain) some life-years due to a specific cause of death in comparison to another covariate group.

Absolute measures of gains or losses in years of life are presented above. To obtain relative measures, the ratio between the RMST estimates, or expected loss in life due to cause k for the two covariate groups are calculated. Extension can also be made for comparisons on a unit increase in a continuous covariate Z, and for time-dependent effects.

2.2.3 Standardisation

Regression standardisation can be used to obtain marginal estimates to make pre-dictions for different covariate groups at each observation given a set of measured confounders [21, 22]. Here, we apply standardisation to RMST and cause-specific CIFs estimates obtained from a flexible parametric competing risks survival model. In this case, it is of interest to compare the average life-years lived before time t^* between two different groups [23, 10]. This is done by obtaining marginal estimates which are calculated as an average over every individual in the observed dataset. This enables comparisons that solely focus on the differences between the two groups of interest by forcing the same covariate distribution over multiple confounders. If all exposures and confounders are measured at baseline, this is essentially equivalent to the G-formula [24]. For example, to compare males and females, estimates must be standardised by age in order to force the same age distribution for both males and females. Extension can be made for multiple covariates and other potential con-founders. This is calculated using an average of RMST estimates for each patient to summarise the risk for a certain covariate group. For instance, let X be an indicator variable that denotes the group of interest and Z be the set of measured covariates. Then the predicted RMST estimate for the ith individual, where $i = 1, \ldots, N$, is,

$$\widehat{\mu}_i = t^* - \int_0^{t^*} \sum_{k=1}^{K} \left[\widehat{F}_k(u \mid X = x, Z = z_i) \right] \mathrm{d}u \tag{14}$$

168   where X is fixed to a specific value, x, and Z is the observed covariate pattern, z_i,

169   for the ith individual. We can then average over the marginal distribution of Z for

170   all the predicted restricted mean life estimates obtained for each individual i such

171   that,

$$E(\widehat{\mu}^{stand} \mid X = x, Z) = \frac{1}{N} \sum_{i=1}^{N} \widehat{\mu}_i \tag{15}$$

172   This allows us to calculate marginal differences between covariate groups. For

173   example, between group $X = 0$ and group $X = 1$, the marginal difference in RMST

174   is,

$$E(\widehat{\mu}^{stand} \mid X = 1, Z) - E(\widehat{\mu}^{stand} \mid X = 0, Z) \tag{16}$$

175   In recent literature, some have advocated the use of RMST as a causal measure

176   [25, 26]. For a causal interpretation, the consideration of additional assumptions

177   are required and by adjusting for all appropriate confounders, these measures can

178   be extended and interpreted as causal effects. This is because, as shown above,

179   they provide marginal comparisons saveraged over the same covariate distribution

180   by using standardisation. Standardisation, otherwise referred to as G-computation,

181   has also been highlighted by Gran et al. [27] as an approach for obtaining use-

182   ful summary causal-effect measures in more complicated multi-state models. How-

183   ever, this is beyond the scope of the paper and estimation of causal effects are not

184 explicitly discussed here. Note also that we only consider time-fixed confounders
185 and that there are additional complexities when considering time-dependent con-
186 founders/exposures [28].

187 2.3 Flexible parametric survival models

188 For competing risks data, many adopt the cause-specific Cox proportional hazards
189 model, or the Fine & Gray approach. However, FPMs are increasing in popularity
190 since the baseline subdistribution or cause-specific hazard function is estimated as
191 part of a fully specified likelihood function [13, 14]. These models were introduced
192 for standard survival data (in the absence of competing risks) on various scales
193 by Royston and Parmar [1] using a general link function, $g(\cdot)$, to better capture
194 and represent the behaviour of real world data. To increase flexibility and more
195 accurately capture complex shapes of the cumulative hazard function, Royston and
196 Parmar [1] proposed the use of RCS (see Appendix A.1). Given a vector of M knots,
197 $\mathbf{m}$, and a vector of $M - 1$ parameters, $\boldsymbol{\gamma}$, with a RCS function, $s(\ln(t); \boldsymbol{\gamma}, \mathbf{m})$ we
198 have that,

$$g(G_k(t \mid \mathbf{x})) = s(\ln(t); \boldsymbol{\gamma}, \mathbf{m}) + \mathbf{x}\boldsymbol{\beta}^T \tag{17}$$

199 where, β, is a vector of co-efficient parameters and, $\mathbf{x}$, is a vector of covariates. This
200 can be fitted on either cause-specific hazards scale [14], where $G_k(t \mid \mathbf{x}) = S_k(t \mid \mathbf{x})$,
201 or cumulative incidence scale [13, 29], where $G_k(t \mid \mathbf{x}) = 1 - F_k(t \mid \mathbf{x})$, based on
202 different link functions, $g(\cdot)$. The relationship of these with the cause-specific CIF
203 are defined in Sections 2.1.2 and 2.1.3.

204 Equation 17 can be easily extended for time-dependent effects to model non-
205 proportionality by fitting interactions between the associated covariates and the
206 spline functions. Using this interaction, a new set of knots, $\mathbf{m}_e$, are introduced,

which represent the eth time-dependent effect with associated parameters $\boldsymbol{\alpha}_e$. If there are $e = 1, \cdots, E$ time-dependent effects, Equation 17 can be extended such that,

$$\eta = g(G_k(t \mid \mathbf{x})) = s(\ln(t); \boldsymbol{\gamma}, \mathbf{m}_0) + \mathbf{x}\boldsymbol{\beta}^T + \sum_{l=1}^{E} s(\ln(t); \boldsymbol{\alpha}_l, \mathbf{m}_l)x_l \tag{18}$$

Further technical details on flexible parametric models for standard survival data in the absence of competing risks can be found elsewhere [1, 30, 31]. Furthermore, a flexible parametric modelling approach on the (log-cumulative) subdistribution hazards scale is detailed by Mozumder et. al. [13] and Lambert et. al. [29], and a (log-cumulative) cause-specific hazards approach is outlined by Hinchliffe et. al. [14].

3 Results: Colorectal cancer survival in England

3.1 Data

Data was obtained from the National Cancer Registration and Analysis Service (NCRAS) to illustrate the estimation of various measures introduced in Section 2.2. The data consist of English colorectal (ICD10: C18, C19 and C20) male and female cancer patients aged between 45 and 90 years old. Patients are diagnosed from 1998 with follow-up restricted to either 10 years or 31 Dec 2013. Analysis is further restricted to patients from the most or least deprived groups as defined by the upper and lower quintiles of the English index of multiple deprivation 2010 (IMD 2010). The final data consisted a total of 159,022 individuals of which 48,845 die from cancer, 7,987 from cardiovascular disease (CVD) and 32,133 from other causes. In Appendix A.2, summary statistics on the age distribution, and number of patients in each deprivation and sex groups are provided.

3.2 Model

For demonstration purposes, predictions are obtained after fitting a log-cumulative subdistribution hazards FPM simultaneously for all k causes of death and standard errors for confidence intervals (CIs) are obtained using the delta method. However, predictions are also available after fitting log-cumulative cause-specific hazard FPMs. This paper focusses on the various measures we can obtain from such models, namely, the RMST measure and expected life-years lost. The choice of which scale to model on depends entirely on the research question to be answered which would relate to other quantities specific to the modelling approach that may be of interest. For instance, if primary interest is in aetiological outcome, then interest would be in the cause-specific hazard rates. For interest in prognostic outcome, one may wish to quantify effects on the risk of dying from a specific cause of death which requires modelling on the subdistribution hazards scale. Further discussion on this topic is provided elsewhere [4, 32].

Models are fitted simultaneously for all k causes of death using the approach of Lambert et al. [29] and Geskus [33]. This fits the model after restructuring the data and applying time-dependent weights that are obtained parametrically to the censoring distribution of the competing causes of death. Alternatively, using the approach described by Jeong and Fine [34], models can be fitted on individual-level data using the full likelihood function [35]. Models for each of the causes of death include sex, IMD 2010 deprivation group (upper and lower quintile only) and a non-linear effect of continuous age using RCS with 3 DF centred at 45 years old at diagnosis. Time-dependent effects to relax the proportionality assumptions are included for sex, non-linear age and deprivation group with 2 DF and 3 DF are used for the baseline RCS function. In order to evaluate whether assuming non-proportional (subdistribution) hazards was more sensible, and is more consistent with the data, a likelihood ratio test was performed. This compared the log-cumulative subdistri-

bution flexible parametric model with time-dependent effects to relax the proportionality assumption to the one without that assumed proportional subdistribution hazards. The likelihood ratio test statistic was 752.94 and the associated p-value was less than 0.0001. This shows that relaxing the proportionality assumption leads to a statistically significant improvement in model fit. Note that this is an illustrative model and we therefore omit formal evalutation of the model performance. When evaluating the model in practice, we recommend conducting a sensitivity analysis, particularly in the selection of the number of knots. This can be done by comparing the Akaike information criterion and the Bayesian information criterion as an informal guide to selecting the appropriate number of knots and covariates [29]. The estimated subdistribution HRs are difficult to communicate and clinical interpretation is limited [36, 17, 37]. For example, although SHRs give the *direction* in association between covariates and the risk of dying from either cancer, other causes or CVD, the exact magnitude of effect in the SHRs cannot be quantified due to the unusual definition of the risk-set for subdistribution hazards [38]. Alternatively, cause-specific CIFs conditional on covariates can be easily obtained using the usual survival transformation as shown in Equation 5. These are presented in Figure 2 for male colorectal cancer patients. The probability of dying from cancer at 10 years from diagnosis for the most deprived male patients is approximately 36.5% (95% CI: 35.5%, 37.5%) for those aged 50 years old at diagnosis. This slightly increases to approximately 40.5% (95% CI: 39.8%, 41.1%) for those aged 80 years old at diagnosis. However, the largest change is in the probability of dying from other causes and CVD which have an increasing contribution to the probability of dying from any cause for older male patients from the most (and least) deprived groups. For instance, the probability of dying from any cause by 10 years from diagnosis for the most deprived 50 year old male patients at diagnosis is 53.6% of which 17.1% is due to other causes and CVD. In contrast, the all-cause probability of death for the

most deprived male patients aged 80 years old diagnosis is much higher at 92.5%.

However, although the probability of dying due to cancer has only increased from

36.5% to 42.5%, much of the overall probability of dying is due to other causes

(38.4%) and CVD (13.6%).

Absolute CIF differences between the most and least deprived male patients aged

50, 65 and 80 years old at diagnosis are presented on the third row of Figure 2.

This shows that, for 50 year olds, the difference between CIFs for the most and

least deprived groups are similar for deaths due to cancer and other causes. There

is very little difference between the two deprivation groups for deaths due to CVD,

however, this is due to a generally very low probability of death due to CVD.

On the other hand, for older male patients, the difference in the probability of

dying from other causes and CVD between the most and least deprived is larger

and increases over time. This leads to a greater disparity in the probability of

dying from other causes and CVD between the most and least deprived patients

compared to the difference in the probability of dying due to cancer. Furthermore,

after approximately 1 year from diagnosis for 65 year olds, and 2 years for 80 year

olds, the difference in the probability of dying due to cancer for the most deprived

compared to the least deprived patients reduces. This change in difference between

the most and least deprived is greatest for the 80 year old male patients with cancer-

specific CIF difference reducing from approximately 4.6% (95% CI: 4.2%, 5.0%) at

1 year from diagnosis to 3.2% (95% CI: 2.6%, 3.7%) by 10 years from diagnosis.

3.2.1 Restricted mean survival time and expected number of life-years lost due to a

       particular cause of death

As discussed in Section 6, as a useful summary measure, the RMST estimate can be

obtained. This is equivalent to the white area of the associated stacked plot in Figure

2 up to t^* for a particular covariate pattern. Conversely, the area of the stacked areas

give an estimate of the RMFT. The area of each of the partitioned stacks for each

of the respective causes of death yield the expected life years lost due to cancer, CVD and other causes. These are presented for the most and least deprived 50, 65 and 80 year old male patients in Figure 3. Each of the stacks represent the average life-years lived in total and life-years lost due to a specific cause. The plots here present life-years lost and lived before different points in time up to 10 years from diagnosis. However, particular interest here is in the life-years lived, or lost, *before* 10 years from diagnosis. For example, total average life-years lived before 10 years from diagnosis for the most deprived 50 year old male patients is 3.99 years (95% CI: 3.84 years, 4.14 years). Of the 6.01 years of the total life-years lost, 2.72 years (95% CI: 2.60 years, 2.85 years) are due to cancer, 0.07 years (95% CI: 0.06 years, 0.09 years) are due to CVD and 1.19 (95% CI: 1.11 years, 1.28 years) due to other causes.

Table 1 presents differences in life-years lost due to each cause of death before 10 years from diagnosis between the most and least deprived groups for 50, 65 and 80 year olds, along with their associated 95% CIs. The absolute estimates of expected life-years lost for the most and least deprived patients at the individual ages are also presented. This provides us with an understanding of how many additional life-years most deprived patients are expected to lose due to a specific cause of death in comparison to the least deprived patients. For instance, at 10 years from diagnosis, 50 year old male patients from the most deprived group lose an additional 0.32 (95% CI: 0.28, 0.36) life-years due to cancer, 0.01 (95% CI: 0.01, 0.02) life-years due to CVD and 0.33 (95% CI: 0.30, 0.36) life-years due to CVD compared to the least deprived group. For older male patients aged 80 years old, there is a greater disparity in life-years lost due to CVD (0.16 life-years) and other causes (0.76 life-years) between the most and least deprived.

3.2.2 Standardisation

When interest is in the covariate effects of particular groups, for example, between deprivation groups, it is useful to obtain standardised estimates as described in Section 2.2.3. By marginalising over the same covariate distribution, fairer comparisons can be made between particular covariate groups of interest. In this example, we standardise by age and sex in order to summarise the differences in survival between patients from the most and least deprived groups. Figure 4 illustrates standardised CIFs stacked for each cause of death and Figure 5 presents absolute risk differences for each cause between the least and most deprived patients.

As illustrated in Figure 4, patients from the most deprived group have a higher probability of dying from any cause (73.8%) compared to those from the least deprived group (63.3%). However, when partitioned into the different causes of death, the difference in total mortality between the most and least deprived groups is mostly due to other causes and CVD as indicated by the area proportions. The cause-specific marginal risk difference between the most and least deprived are presented in Figure 5 along with their respective 95% CIs. As can be seen here, the largest difference in risk is due to other causes and the largest difference in risk between the least and most deprived groups is due to other causes at 10 years from diagnosis (6.3%; 95% CI: 5.8%, 6.9%). Generally, the disparity in the probability of dying from other causes or CVD between the most and least deprived patients continues to increase over follow-up time. However, the cancer-specific risk difference between the most and least deprived increases only for the first 2 years. After this point, the disparity in the probability of dying due to cancer between the most and least deprived begins to decrease.

3.2.3 Expected life-years lost for the most deprived compared to the least deprived

In Figure 3, the expected life-years lost and total average life-years lived were presented for each cause of death before various time-points, t^*. By obtaining marginal

estimates through standardisation over age and sex, we can focus on specific comparisons between the least and most deprived patients. The marginal expected life-years lived for each cause of death and total average life-years lived before each time, t^*, are similarly illustrated in Figure 6. If $t^* = 10$, then we have that the total average life-years lived before 10 years from diagnosis for the most deprived patients is 4.39 (95% CI: 3.78, 5.00). Of the 5.61 total expected life-years lost, 3.03 (95% CI: 2.66, 3.46) years are lost due to cancer, 0.46 (95% CI: 0.27, 0.81) years due to CVD and 2.11 (95% CI: 1.76, 2.53) years due to other causes. By obtaining marginal estimates of expected life-years lost, we are able to directly compare both deprivation groups and determine the additional life-years lost for patients that are the most deprived standardised by age and sex. Thus, where $t^* = 10$, we have that the additional life-years lost due to cancer, CVD and other causes before 10 years from diagnosis for the most deprived patients is 0.31 (95% CI: 0.25, 0.37), 0.05 (95% CI: 0.02, 0.08) and 0.44 (95% CI: 0.33, 0.54) life-years respectively.

4 Discussion

This paper presents estimation of RMLT and expected life-years lost from within the flexible parametric survival modelling framework. This can be done either on the cause-specific hazards or cumulative incidence scale and allows easy incorporation of time-dependent effects to relax the proportionality assumption [13, 14]. We illustrate how one can easily obtain comparative predictions based on the expected number of life-years lost due to a specific cause of death in addition to other useful measures, such as absolute differences in the cumulative incidence functions. Marginal estimates using standardisation are also presented which allow for fairer comparisons when marginal differences between two particular covariate groups are of interest. These can all be obtained from a single model, including predictions to illustrate changes over time.

Cause-specific Cox, or Fine & Gray regression models are commonly adopted for the analysis of competing risks data. These provide estimates of the cause-specific HR or subdistribution HR which provide a relative comparison between covariate groups. The (cause-specific) HR is also commonly reported as a single summary measure. However, others have highlighted that the (cause-specific) HR can be misleading, especially when one is interested in how a covariate differs in terms of its effect on the risk of dying, which is usually of interest from the patient's perspective [5, 10, 20]. For example, although one may observe a high relative change in the rate of dying, when translated to changes in risk, the effect may in fact be much smaller. In addition, if modelling on the subdistribution hazards scale, the subdistribution HR offers little in terms of real-world interpretation due to the unusual nature in its definition [36]. Therefore, alternative measures that offer a more attractive interpretation are proposed, one of which is RMST. This measure allows the researcher to evaluate the overall impact of different covariates on prognosis and can be used to facilitate risk communication. Here, we have demonstrated estimation in the presence of competing risks within the flexible parametric modelling framework. It follows that the RMFT measure can be further partitioned to give the expected life-years lost due to a particular cause of death. Difference in RMST between two groups has also been identified as a clinically useful measure alternative to the HR [23, 9, 20]. One way in which this can be estimated is by obtaining marginal estimates using standardisation as described in Section 2.2.3. Other approaches exist for the estimation of RMST in this context, most notably, through regression models using pseudo-observations which is the approach outlined by Andersen (2013) [11, 39]. However, these models only allow estimates for specific predictions at a single time-point. For example, separate models must be fitted to estimate either the cause-specific CIF or RMLT when it may be of interest to obtain both. Furthermore, multiple models are required in order to obtain measures at different

time-points, which is important when estimating cause-specific CIFs. On the other

hand, we only require fitting a single FPM from which the researcher can obtain various measures of interest over any appropriate time interval. Alternatively, one can use inverse probablity weighted estimating equations to predict RMLT. However, different estimators will need to be calculated subject to whether it is of interest to obtain marginal or non-marginal estimates [40, 41].

There is, however, a limitation to the interpretation of the RMLT measure. Although communication in terms of changes in life-years lost to clinicians and patients rather than probabilities is attractive, applying an upper bound, t^*, to the time interval may add some difficulty in understanding of the measure. This is because the RMLT estimate for an arbitrary choice of t^* can only be used to estimate the average risk within a restricted time period for a group of patients. Furthermore, it should be highlighted that the expected life-years lost makes comparison with an immortal cohort where patients are alive for the whole interval from 0 to time t^*. A similar "unrestricted" measure can be estimated within the relative survival framework which is based on extrapolation on the excess hazard rate. This is usually referred to as the number of life years lost, or the loss in expectation of life and is calculated based on a comparison of the life-expectancy of cancer patients to a comparable population group who are assumed to be cancer-free [42, 43, 44]. However, this relies on the assumption that this extrapolation is appropriate which is not made for the RMLT estimate. In addition to the above, due to the dependence of the interpretation of RMST on follow-up time, comparison between different studies, for example, between countries, becomes difficult. It has also been further shown that the difference in RMST between two covariate groups depends on the outcome rates within each group. Therefore, it is recommended that differences in RMST are reported alongside their respective survival, or cumulative incidence functions,

in order to allow comparability and to obtain the entire picture of the impact of different groups on outcome [45].

5 Conclusions

The RMLT measure is presented as a useful summary measure with an attractive interpretation which can aid in the analysis of competing risks data. As discussed by others, it is also useful to present estimated cause-specific CIFs alongside cause-specific hazards [4, 29]. FPMs allow easy estimation of all measures from a single model which can be further extended to obtain marginal estimates. Note that, although not discussed here, if appropriate confounders are adjusted for, one can also infer causal effects between two groups using standardisation. However, one must also consider the additional complexities and issues in interpretation with the inclusion of time-dependent confounders [28]. Furthermore, the RMLT measure can be easily extended for obtaining conditional estimates, for example, the average life-years lived before t^* years given survival to time t_0 from diagnosis. Example Stata code for the model and prediction of measures provided in this paper is outlined in Appendix A.3.

6 List of Abbreviations

CIF	Cumulative incidence function
CI	Confidence interval
CVD	Cardiovascular disease
DF	Degrees of freedom
FPM	Flexible parametric survival model
HR	Hazard ratio
LYL	Life-years lost
RCS	Restricted cubic splines
RMFT	Restricted mean failure time
RMLT	Restricted mean lifetime
RMST	Restricted mean survival time

Declarations

Ethics approval and consent to participate

The study received ethical approval from North West - Greater Manchester East Research Ethics Committee
(14/NW/1449).

Consent for publication

Not applicable.

Availability of data and material

The data that support the findings of this study are available from Public Health England
(https://www.gov.uk/government/publications/accessing-public-health-england-data/about-the-phe-odr-and-
accessing-data), but restrictions apply to the availability of these data, which were used under license for the current
study, and so are not publicly available.

Competing interests

SIM works at Roche 0.5 WTE (working-time-equivalent). All other authors declare that they have no competing
interests.

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Author's contributions

Contributions of each author to the work detailed in the manuscript are as follows. All authors, SIM, MJR and PCL,
equally contributed towards the conception and design, acquisition of data, and interpretation of data. Specifically,

478 SIM carried out the analysis of the data and prepared the manuscript. PCL and MJR supervised the project and

479 contributed comments and suggestions throughout. All authors were involved in the drafting and submission of this

480 research article.

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Table 1: Expected LYL for each cause for males aged 50, 65 and 80 years old at diagnosis.

	Most Deprived			Least Deprived			Difference		
	LYL	95% LCI	95% UCI	LYL	95% LCI	95% UCI	LYL	95% LCI	95% UCI
50 Yrs Old									
Cancer	2.724	[2.604,	2.848]	2.407	[2.299,	2.519]	0.317	[0.277,	0.357]
CVD	0.069	[0.055,	0.088]	0.056	[0.044,	0.071]	0.014	[0.009,	0.018]
Other causes	1.195	[1.113,	1.282]	0.864	[0.804,	0.929]	0.330	[0.300,	0.361]
65 Yrs Old									
Cancer	2.654	[2.179,	3.232]	2.340	[1.913,	2.864]	0.313	[0.250,	0.377]
CVD	0.271	[0.149,	0.495]	0.219	[0.120,	0.400]	0.052	[0.019,	0.085]
Other causes	1.662	[1.285,	2.149]	1.212	[0.930,	1.580]	0.449	[0.339,	0.559]
80 Yrs Old									
Cancer	3.415	[3.055,	3.818]	3.018	[2.690,	3.386]	0.397	[0.340,	0.454]
CVD	0.840	[0.468,	1.508]	0.681	[0.378,	1.228]	0.159	[0.063,	0.255]
Other causes	2.845	[2.426,	3.337]	2.120	[1.792,	2.508]	0.725	[0.618,	0.833]

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607   **Figures**

608   **Tables**

(a) Transitions described by the cause-specific hazard rate. The typical competing risks scenario.

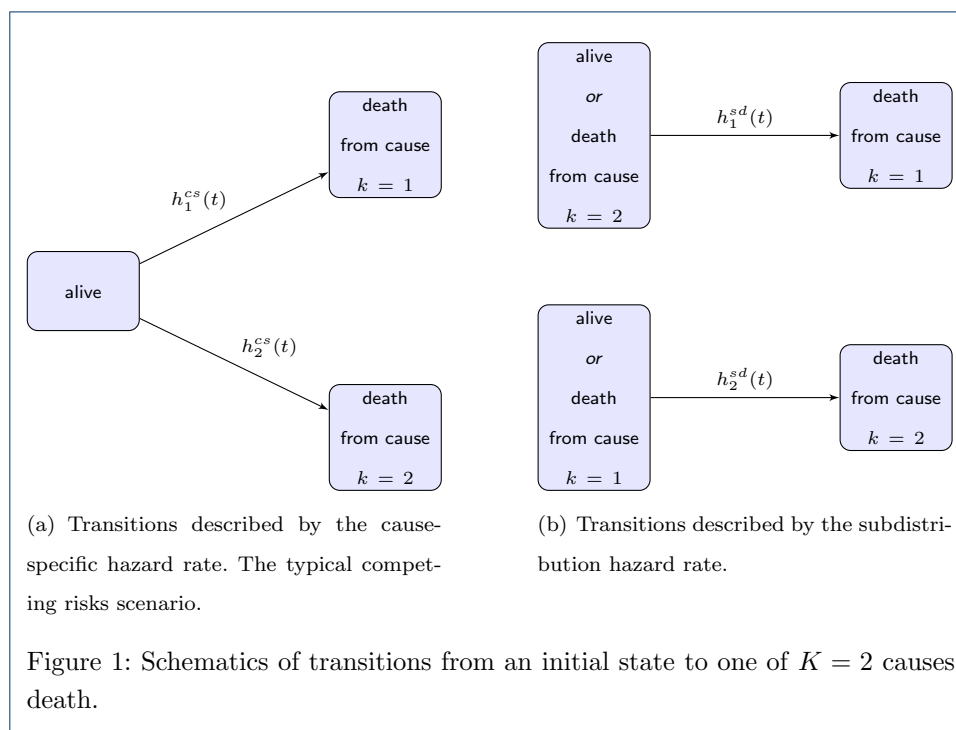(b) Transitions described by the subdistribution hazard rate.

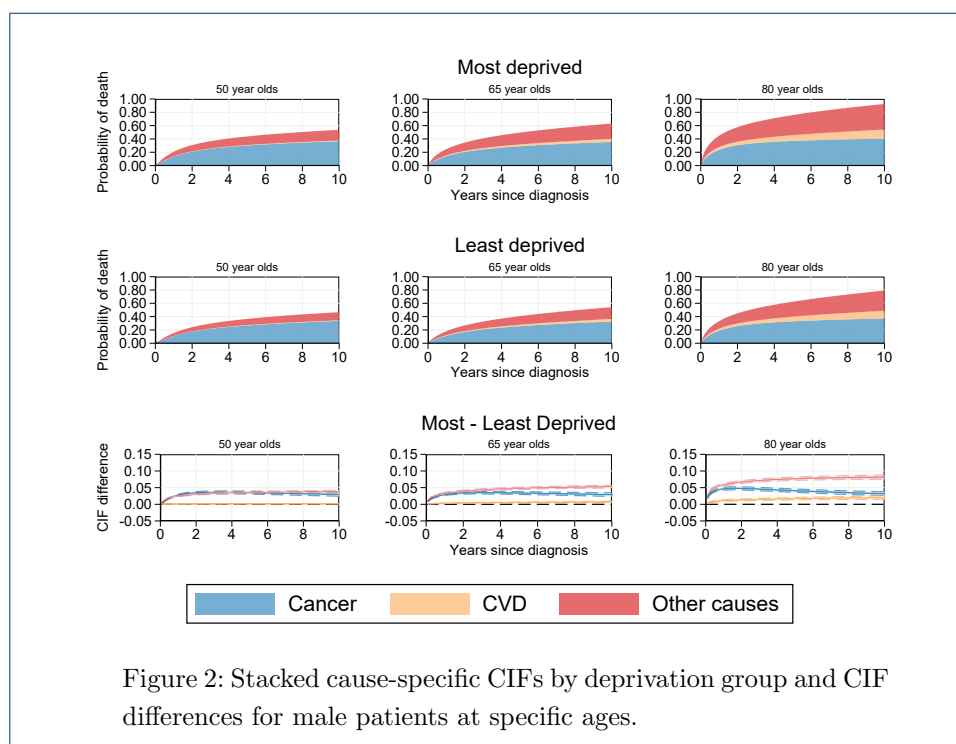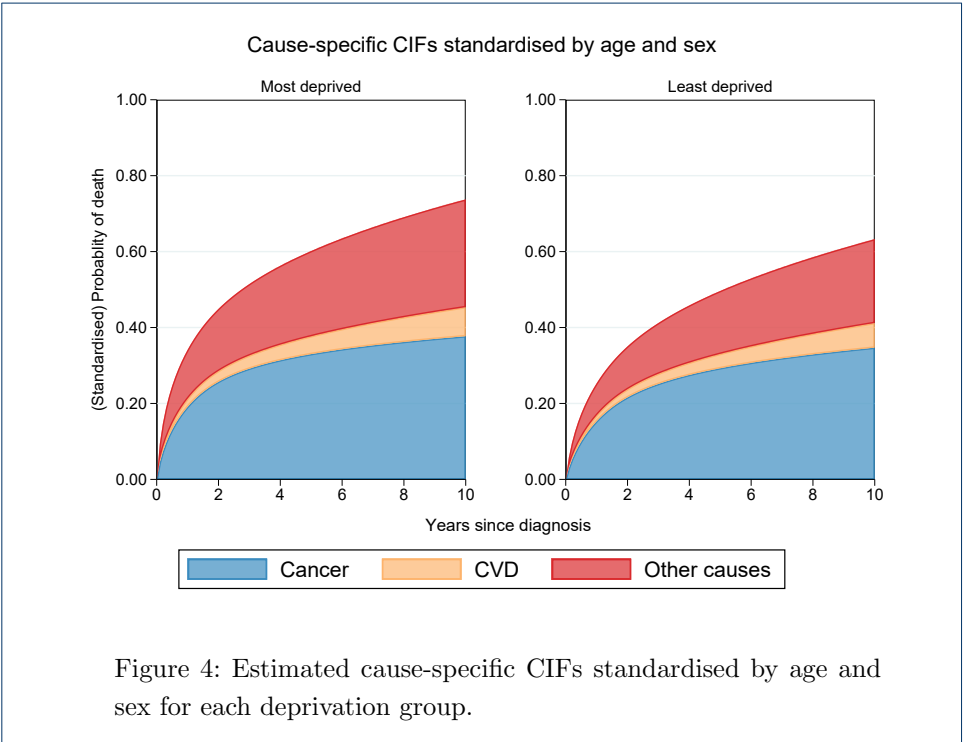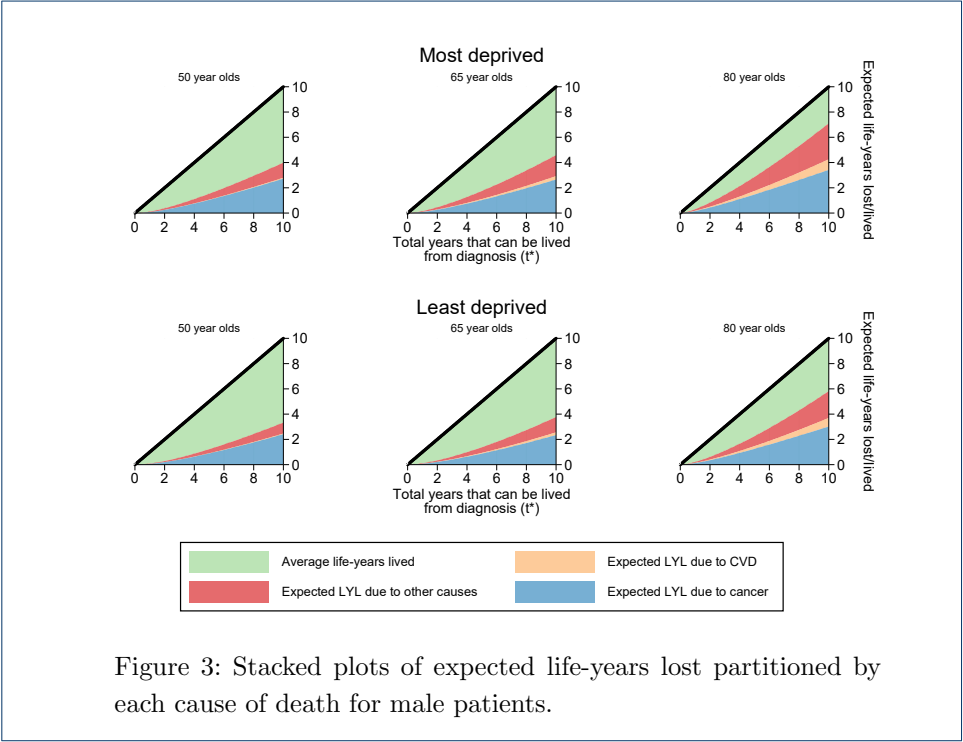Figure 1: Schematics of transitions from an initial state to one of $K = 2$ causes of death.

Figure 2: Stacked cause-specific CIFs by deprivation group and CIF differences for male patients at specific ages.

Figure 3: Stacked plots of expected life-years lost partitioned by each cause of death for male patients.

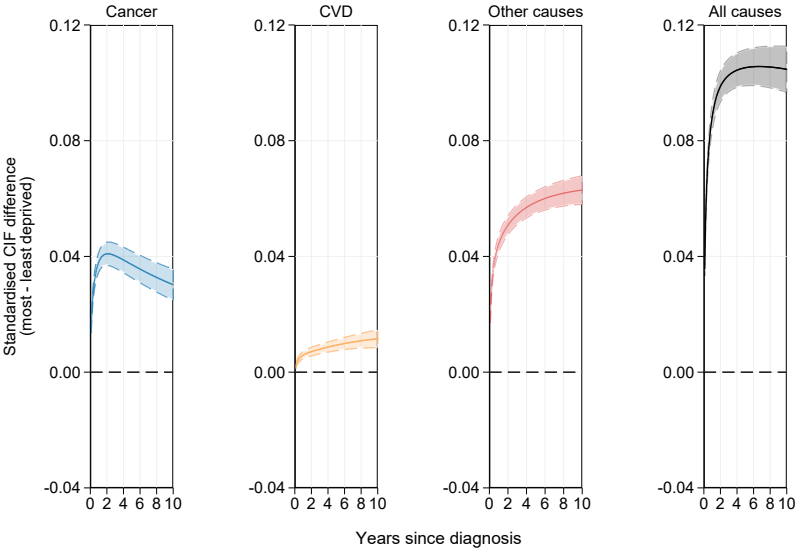Figure 4: Estimated cause-specific CIFs standardised by age and sex for each deprivation group.

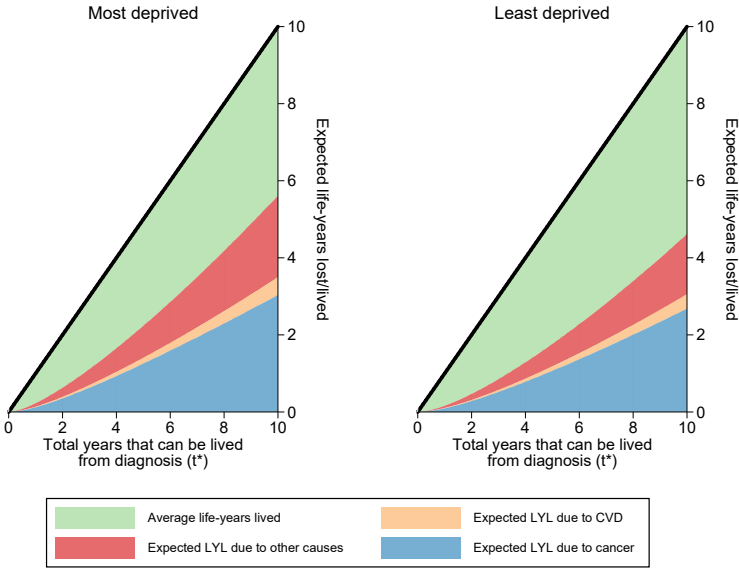Figure 5: Estimated CIF differences for each cause of death standardised by age and sex with 95% CIs.

Figure 6: Stacked plots of expected life-years lost for each cause of death standardised by age and sex.

609 Appendix A: Appendix

610 A.1 Restricted cubic spline variables

Given a vector of M knots, $\mathbf{m}$ and a vector of $M-1$ parameters, $\boldsymbol{\gamma}$, with $M-1$ degrees of freedom (df), the restricted cubic spline function, $s(\ln(t); \boldsymbol{\gamma}, \mathbf{m})$, is defined as,

$$s(\ln(t); \boldsymbol{\gamma}, \mathbf{m}) = \gamma_0 + \gamma_1 z_1 + \cdots + \gamma_{(M-1)} z_{(M-1)} \tag{19}$$

Where $z_1, \cdots, z_{(M-1)}$ are the basis functions of the restricted cubic splines and are defined as,

$$z_1 = \ln(t) \tag{20}$$

$$z_j = (\ln(t) - m_j)_+^3 - \phi_j(\ln(t) - m_1)_+^3 - (1 - \phi_j)(\ln(t) - m_M)_+^3, \quad j = 2, \cdots, M-1$$

where,

$$\phi_j = \frac{m_M - m_j}{m_M - m_1} \tag{21}$$

and

$$(u)_+ = \begin{cases} u, & \text{if } u > 0 \\ 0, & \text{otherwise} \end{cases} \tag{22}$$

611 Usually, M knots are placed at equally spaced centiles of the distribution of the

612 uncensored log-survival times including two boundary knots at the 0th and 100th

613 centiles.

Table 2: Distribution of data on key covariates included in the analysis for n = 159,022 patients

	Females, n(%)	Least deprived, n(%)	Age, mean(sd)
Cancer	21 137 (43.27)	25 084 (51.35)	72.25 (10.57)
CVD	3 158 (39.54)	3 853 (48.24)	76.78 (7.96)
Other Causes	13 716 (42.71)	14 955 (46.57)	74.04 (9.64)
All Causes	38 011 (42.74)	43 892 (49.35)	73.30 (10.13)
Alive/Censored within 10 yrs	30 663 (43.76)	43 079 (61.47)	68.05 (9.97)
Total	68 974 (43.19)	86 971 (54.59)	70.99 (10.39)

A.2 Additional summary statistics

Table 2 provide summary statistics on the distribution of key covariates of interest for inclusion in analysis i.e. sex, deprivation group (least/most deprived) and age, by cause of death, and in total.

Figure 7 represents the cause-specific cumulative incidence functions estimates obtained by the non-parametric Aalen-Johansen estimator. This summarises the probability of dying from each cause of death by sex and deprivation groups.
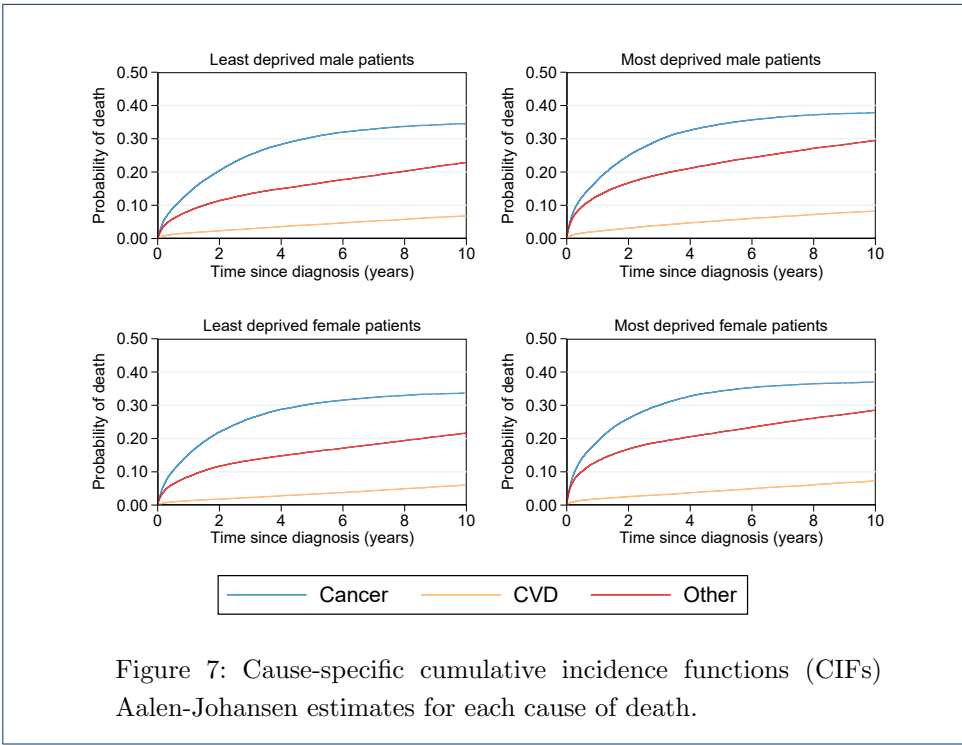

Figure 7: Cause-specific cumulative incidence functions (CIFs) Aalen-Johansen estimates for each cause of death.

₆₂₁   Figure 8 illustrates the all-cause survival probabilities obtained by the non-

₆₂₂ parametric Kaplan-Meier estimator. This summarises the all-cause probability of

₆₂₃ survival by sex and deprivation groups.
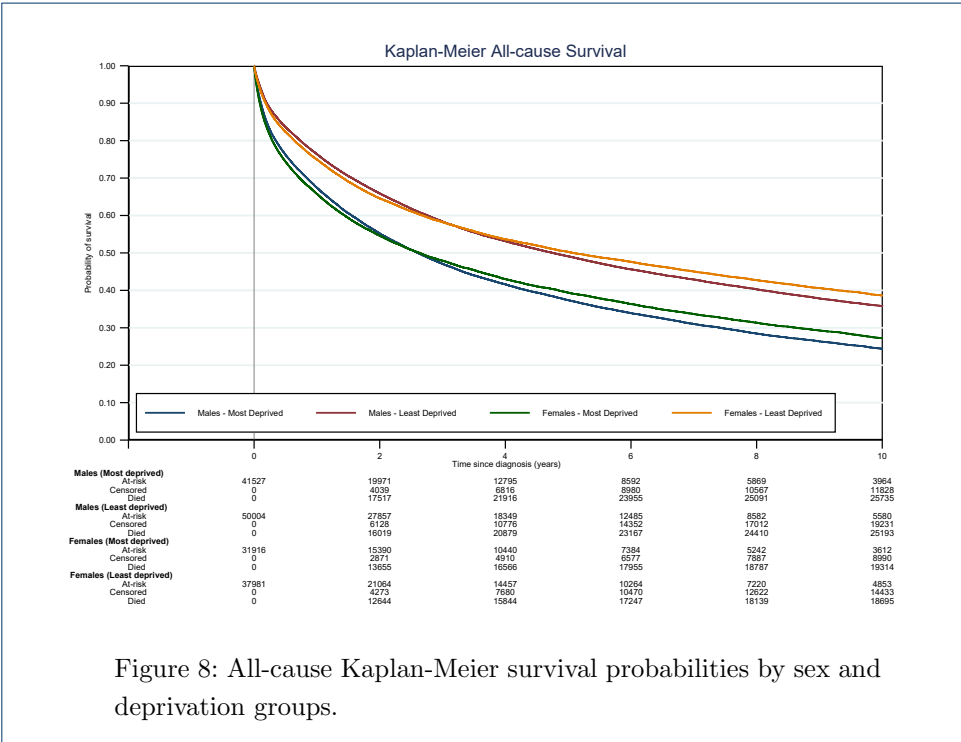

Figure 8: All-cause Kaplan-Meier survival probabilities by sex and deprivation groups.

₆₂₄ A.3 Stata code for obtaining predictions

₆₂₅ This appendix outlines Stata code used to obtain predictions presented in the paper.

₆₂₆ Some user-defined Stata commands are required which can be installed from the

₆₂₇ Boston College Statistical Software Components (SSC) archive by calling,

₆₂₈ `ssc install [command]`

₆₂₉   The following must be installed before running the code:

₆₃₀   • `stpm2`: To fit the flexible parametric models described in Section 2.3.

₆₃₁   • `rcsgen`: To generate the restricted cubic spline functions.

₆₃₂   • `stcrprep`: To restructure data and calculate time-dependent censoring

₆₃₃   weights in order to fit models on the subdistribution hazards scale using

₆₃₄   standard Stata commands.

635   To obtain marginal (and non-marginal) estimates using standardisation, the

636 `standsurv` command must be installed. This will be released on SSC soon, however,

637 in the meantime, it can be installed by running,

638 `net from https://www.pclambert.net/downloads/standsurv`

A.3.1 Preparing the data for analysis

640 To prepare the data for a survival analysis in Stata, we must first run the `stset`

641 command. We identify the variable that records survival time (in days), `exit2`, the

642 indicator variable for cause of death, `cod`, where death from `cancer = 1`, `CVD = 2`

643 and `other causes = 3` and finally the variable for date of diagnosis, `dx`. The `scale`

644 option is used to transform the survival time into years from days and we use the

645 `exit` option to restrict follow-up time to 10 years from diagnosis and censor those

646 still alive at 2014. In order to ensure that the death indicator, `_d`, generated after

647 `stset` matches the death indicator for cause of death, we create a new cause of

648 death indicator, `cod2`, so that those who die either after 10 years from diagnosis

649 or 2014 are administratively censored. Finally, to generate restricted cubic spline

650 variables for the non-linear effect of age centred at 45 years old at diagnosis, we use

651 `rcsgen`. For 3 degrees of freedom, 3 new age spline variables are created, `rcsage1`

652 − `rcsage3`, and we store knot positions and matrix for orthogonalization which

653 are required for post-estimation predictions at specific ages.

```
stset exit2, failure(cod=1,2,3) id(id) scale(365.25) origin(dx) ///
>    exit(time min(dx + 365.25*10.01,mdy(12,31,2013)))

//must ensure that those that die after follow-up time
//   are administratively censored
gen cod2 = cond(_d==0,0,cod)

//center non-linear age (rcsage) at 45 years old
rcsgen age, gen(rcsage) df(3) orthog center(45)
//store knot positions in global macro
global knots `r(knots)´
//save matrix for orthogonalization
```

666   `matrix Rage = r(R)`

667   To restructure the data and calculate the time-dependent censoring weights so

668 that we may fit a model on the subdistribution hazards scale, we use `stcrprep`[46].

669 Here, we specify `wtstpm2` to estimate the censoring distribution using a Royston-

670 Parmar flexible parametric model with covariates included in the `censcov` option.

671 The data is restructured based on the variable `failcode`, which splits the data

672 according to the cause of interest. This is used to fit identify for which cause the

673 model is to be fitted for. For clarity, we create dummy variables for each of the causes

674 of death from `failcode` and generate `_cancer`, `_cvd` and `_other`. Another indicator

675 variable, `event`, is also created to identify at which split time interval, or row, death

676 (from any cause) is observed for that patient. To incorporate the calculated weights

677 from `stcrprep`, we must `stset` the data again with `tstart` and `tstop`. These are

678 also provided by `stcrprep` and give the times at which an individual starts and

679 stops being at risk.

```
680     stcrprep, events(cod2) keep(age mostdep sex rcsage?) trans(1 2 3) ///
681     >    wtstpm2 censcov(mostdep sex rcsage?) every(1)
682
683     gen event = cod2 == failcode
684
685     stset tstop [iw=weight_c], failure(event) enter(tstart) noshow
686
687     tab failcode, gen(cause)
688     rename cause1 _cancer
689     rename cause2 _cvd
690     rename cause3 _other
```

691 *A.3.2 Model*

692 The model described in Section 2.3 can be fitted in two ways after preparing the

693 data. We can either fit separate models for each of the causes of death, or fit a single

694 model to cancer, CVD and other causes simultaneously. Here, we demonstrate for

695 the latter to make illustration of the code for obtaining predictions post-estimation

696 easier. However, in order to fit the equivalent single model with coefficients com-

697 parable to the models fitted individually to each of the causes of death, the knot

698 locations on the cause-specific survival time distributions must be stored. These are

699 stored in global macros for each of the causes of death.

```
700      global knotstvc_opt
701      global bknotstvc_opt
702
703      foreach cause in cancer other cvd {
704       2.    global lnbhknots_`cause´
705       3. }
706
707      foreach cause in cancer other cvd {
708       2.    stpm2 mostdep sex rcsage? if _`cause´==1, df(3) ///
709       >        tvc(mostdep sex rcsage?) dftvc(2) scale(h) eform
710       3.    global bhknots_`cause´ `e(bhknots)´
711       4.    global boundknots_`cause´ `e(boundary_knots)´
712       5.    foreach cov in mostdep sex rcsage1 rcsage2 rcsage3 {
713       6.      global knotstvc_opt ${knotstvc_opt} ///
714       >          `cov´_`cause´ `e(tvcknots_`cov´)´
715       7.    }
716       8.    global knotstvc_opt ${knotstvc_opt} _`cause´ ${bhknots_`cause´}
717       9.    global bknotstvc_opt ${bknotstvc_opt} _`cause´ ${boundknots_`cause´}
718      10. }
```

719 Here we define a global macro of the list of covariates to be included in the single

720 model. As the data is stacked, interactions need to be created between the covari-

721 ates and the indicator variable for each cause of death. See Lunn and McNeil[47]

722 for further details. The baseline coefficient, i.e. the constant in the cause-specific

723 model, is calculated in _cancer, _cvd and _other. We therefore fit a model for

724 each of the causes of death simultaneously without a constant using nocons and

725 the baseline splines using rcsbaseoff. Instead, the baseline splines are specified as

726 time-dependent splines for the coefficient that corresponds to the constant in its

727 respective model for that particular cause of death. These were stored in the global

728 macro bknotstvc_opt. Since knots are specified according to the time scale, rather

729 than the log-time scale, the knscale(time) option is used.

```
730      global covlist
```

```
731        global covlist_tvc
732
733        foreach cause in cancer cvd other {
734     2.    global covlist $covlist _`cause´
735     3.    global covlist_tvc $covlist_tvc _`cause´
736     4.    foreach cov in mostdep sex rcsage1 rcsage2 rcsage3 {
737     5.       gen `cov´_`cause´ = `cov´*_`cause´
738     6.       global covlist $covlist `cov´_`cause´
739     7.       global covlist_tvc $covlist_tvc `cov´_`cause´
740     8.    }
741     9. }
742
743     di "$covlist"
744     _cancer mostdep_cancer sex_cancer rcsage1_cancer rcsage2_cancer rcsage3_cancer
745     _cvd mostdep_cvd sex_cvd rcsage1_cvd rcsage2_cvd rcsage3_cvd
746     _other mostdep_other sex_other rcsage1_other rcsage2_other rcsage3_other
747
748      stpm2 $covlist ///
749   >     , scale(h) tvc($covlist_tvc) knotstvc(${knotstvc_opt}) ///
750   >      bknotstvc(${bknotstvc_opt}) knscale(time) rcsbaseoff eform nocons
```

A.3.3 Predictions

Although `standsurv` was written for obtaining marginalised predictions, it can also

be used to obtain non-marginalised estimates. This is done by simply specifying the

entire covariate pattern so that the predictions are not averaged over any covariate

distribution. To obtain predictions at a specific age, we need to calculate the spline

variables at that particular age centred at 45 years old with the same knot locations

and projection matrix as before. The spline variables are stored in the local macros

`c1`, `c2` and `c3`. An example is given below when the cause of interest is cancer and

we want to make comparisons between the most and least deprived male patients

aged either 50, 65, or 80 years old at diagnosis.

```
761        foreach age in 50 65 80 {
762     2.    rcsgen, scalar(`age´) knots($knots) rmatrix(Rage) gen(c) center(45)
763
764     3.    global cancer_mostdep_`age´_male sex_cancer 0 sex_cvd 0 sex_other 0 ///
765   >           mostdep_cancer 1  mostdep_cvd 0  mostdep_other 0   ///
766   >           rcsage1_cancer `=c1´ rcsage2_cancer `=c2´ rcsage3_cancer `=c3´ ///
767   >           rcsage1_other 0 rcsage2_other 0 rcsage3_other 0 ///
768   >           rcsage1_cvd 0 rcsage2_cvd 0 rcsage3_cvd 0 _cancer 1 _cvd 0 _other 0
769
```

```
770        4.    global cancer_leastdep_`age´_male sex_cancer 0 sex_cvd 0 sex_other 0 ///
771    >              mostdep_cancer 0 mostdep_cvd 0 mostdep_other 0 ///
772    >              rcsage1_cancer `=c1´ rcsage2_cancer `=c2´ rcsage3_cancer `=c3´ ///
773    >              rcsage1_other 0 rcsage2_other 0 rcsage3_other 0 ///
774    >              rcsage1_cvd 0 rcsage2_cvd 0 rcsage3_cvd 0 _cancer 1 _cvd 0 _other 0
775        5.    }
```

As we do not average over each observation, we must tell `standsurv` to only take

the first observation in the stacked data to calculate non-marginalised predictions.

This is done using `if _n == 1`. The `failure` option is used to obtain the cumulative

incidence functions that is specified in each `at` option. To calculate the difference

between `at1` and `at2`, we use `contrast(difference)`.

```
781        range tempt 0 10 101
782
783        foreach age in 50 65 80 {
784        2.    foreach cause in cancer other cvd {
785        3.        standsurv if _n==1, at1(${`cause´_leastdep_`age´_male}) ///
786    >              at2(${`cause´_mostdep_`age´_male}) ///
787    >              atvars(Fage`age´_`cause´_male_least CIF_`age´_`cause´_male_most) ///
788    >              contrastvar(CIF_`age´_`cause´_male_diff) ///
789    >              contrast(difference) failure timevar(tempt) ci
790        4.    }
791        5.    }
```

Since we are making predictions at particular covariate patterns for each of the

causes separately, specifying `rmft` gives us estimates of the expected life-years lost

due to a particular cause of death. To calculate RMLT, we need to take the sum

of all of the `at` options, where the expected life-years lost due to cancer, CVD and

other causes is specified in each. We do this by creating our own contrast in a user-

defined mata function which can be called in the option `userfunction`. An example

of this is also given below.

```
799        foreach age in 50 65 80 {
800        2.    foreach cause in cancer cvd other {
801        3.        standsurv if _n==1, at1(${`cause´_leastdep_`age´_male}) ///
802    >                  at2(${`cause´_mostdep_`age´_male}) ///
803    >                  atvars(LYL_`age´_`cause´_leastdep LYL_`age´_`cause´_mostdep) ///
804    >                  contrast(difference) contrastvar(LYL_`cause´`age´_diff) ///
```

```
805   >              rmft timevar(tempt) ci
806     4.    }
807     5. }
808
809    mata mata clear
810    mata
811    function RMFT(at) {
812   2.    return((at[1]:+at[2]:+at[3]))
813   3. }
814
815     end
816
817
```

In order to obtain marginalised estimates, in each `at` option, only the covariate

pattern for the group of interest need to be given. For the covariate distribution

that we want to average over, as we have created interactions between the covariates

and the causes of death, these must be mapped to each covariate e.g. `sex_cancer`

`= sex`. The others are excluded from the `at` option for the other causes of death. In

this case, because we want to average over covariates that we wish to standardise

by, we need to identify the row for each patient in the stacked data that corresponds

to the failure time of that individual. This is done by creating the indicator variable

`first` and using it as an `if` condition in `standsurv`. As before, we give an example

for specifying macros for use in the `at` options for deaths due to cancer.

```
828   global cancer_mostdep_stand sex_cvd 0 sex_other 0 sex_cancer = sex ///
829   >   mostdep_cancer 1  mostdep_cvd 0 mostdep_other 0 ///
830   >   rcsage1_cancer = rcsage1 rcsage2_cancer = rcsage2 rcsage3_cancer = rcsage3 ///
831   >   rcsage1_other 0 rcsage2_other 0 rcsage3_other 0 ///
832   >   rcsage1_cvd 0 rcsage2_cvd 0 rcsage3_cvd 0 ///
833   >   _cancer 1 _cvd 0 _other 1
834
835    global cancer_leastdep_stand sex_cvd 0 sex_other 0 sex_cancer = sex ///
836   >   mostdep_cancer 0  mostdep_cvd 0 mostdep_other 0 ///
837   >   rcsage1_cancer = rcsage1 rcsage2_cancer = rcsage2 rcsage3_cancer = rcsage3 ///
838   >   rcsage1_other 0 rcsage2_other 0 rcsage3_other 0 ///
839   >   rcsage1_cvd 0 rcsage2_cvd 0 rcsage3_cvd 0 ///
840   >   _cancer 1 _cvd 0 _other 1
841
842    bysort failcode id (_t): gen first = _n==1
```

843   The cause-specific CIF differences are thus calculated as follows,

```
844     foreach cause in cancer other cvd {
845      2.   standsurv if first, at1(${`cause´_leastdep_stand}) ///
846    >          at2(${`cause´_mostdep_stand}) ///
847    >          atvars(Fstand_`cause´_least Fstand_`cause´_most) ///
848    >          contrast(difference) contrastvars(Fdiff_`cause´) ///
849    >          failure timevar(tempt) ci
850      3. }
```

851   As highlighted above, we can write user-functions to define our own contrasts.

852   Below is an example for when interest is in calculating the difference in RMLT

853   between the most and least deprived patients.

```
854     mata mata clear
855     mata
856    : function RMFTdiff(at) {
857    2.   return((at[1]:+at[2]:+at[3]) :- (at[4]:+at[5]:+at[6]))
858    3. }
859
860    : end
861
862     standsurv if first, at1(${cancer_mostdep_stand}) ///
863    >    at2(${cvd_mostdep_stand}) ///
864    >    at3(${other_mostdep_stand}) ///
865    >    at4(${cancer_leastdep_stand}) ///
866    >    at5(${cvd_leastdep_stand}) ///
867    >    at6(${other_leastdep_stand}) ///
868    >    atvars(LYLcancer_stand_mostdep LYLcvd_stand_mostdep ///
869    >    LYLother_stand_mostdep LYLcancer_stand_leastdep ///
870    >    LYLcvd_stand_leastdep LYLother_stand_leastdep) ///
871    >    userfunction(RMFTdiff) userfunctionvar(RMFT_diff) ///
872    >    failure timevar(tempt) ci
```