APPENDIX

Notation and Definitions

Consider a longitudinal study of n subjects, with outcome observation times indexed by j, for $j = 0, 1, 2, 3, \cdots, K+1$. Y is defined as an indicator for failure (here death, or cause specific death), L a vector for time varying covariates, and A is an exposure indicator (1:yes, 0:no). $A(k)$ represents exposure at time indexed by k where $k = 0, 1, 2, 3, \cdots, K$. Likewise $L(k)$ is the value of covariate L at time k. The assumed chronological order is $Y(0), L(0), A(0), Y(1), L(1), A(1), Y(2)$ etc. with $Y(0) = 0$ for every individual in order for them to have at least one person year of observations. Note that $Y(k) = 1$ is defined as an individual failing by time k (just before k), provided that $Y(k-1) = 0$. Overbars are used to denote exposure and covariate history, i.e $\overline{A}(k-1)$ denotes the exposure history up to time point $k-1$ ($A(0), A(1), A(2), A(k-1)$). We further denote $g = \overline{\alpha}$, where $\overline{\alpha}$ is any exposure regime $\overline{\alpha} = \overline{\alpha}(K) = (\alpha(0), \alpha(1), \alpha(2), \cdots, \alpha(K))$ under a hypothetical intervention and T_g and $E[Y_g(j)]$ are the counterfactual survival time and risk of failure respectively, under the specified exposure regime g.

A counterfactual outcome is an outcome that a participant would have experienced under a hypothetical exposure history, which may differ from the observed exposure history. In our notation counterfactual exposure histories are represented with lower case letters while observed exposures are represented with upper case notation (e.g. $\alpha(k)$ as opposed to $A(k)$), while counterfactual outcomes are expressed with subscripts of the regime they correspond to (e.g. $T_{\overline{0}}$ is the counterfactual survival time under a never exposed exposure regime).

Standard vs Causal Methods

Standard regression models relying on observational data, in the presence of time-varying confounders that are in turn affected by previous exposure, yield biased results. (The structure of this association and resulting bias can be graphically represented using causal diagrams as described by Hernán et al[39].) Therefore, the inclusion of these types of time varying confounders in standard models will not result in model parameters with a causal interpretation.

Causal methods utilizing structural models, i.e models of the distributions of counterfactual outcomes, can be used to estimate causal parameters of exposure effects from observational data under specific assumptions. In observational studies where exposure is not randomized we usually rely on three identifiability assumptions. The first is conditional exchangeability: the assumption that among those still at risk at time k, given covariates and prior exposure, the counterfactual outcome at time $k+1$ is conditionally independent of the observed exposure, or $Y_g(k+1)$ II $A(k)|\overline{L}(k) = \overline{l}(k), \overline{A}(k-1) = \overline{\alpha}(k-1), Y(k) = 0$, for all $\overline{\alpha}(k-1)$ and $\overline{l}(k)$. Under this assumption there is no unmeasured confounding given measured covariates $L(k)$. It is important to note that this is an unverifiable assumption since we lack data on counterfactual outcomes.

The other two assumptions are consistency and positivity. Consistency is the assumption that if a subject with an observed history $\overline{A}(k) = \overline{\alpha}(k)$ through k, their observed outcome at j will equal their counterfactual outcome under regime $g = \overline{\alpha}(k)$, i.e $Y(j) = Y_{g=\overline{\alpha}(k)}(j)$. Positivity requires that the probability of receiving exposure is nonzero for all non-empty combinations of covariates, or if

$f_{\overline{L}(k),\overline{A}(k-1)}(\overline{l}(k), \overline{\alpha}(k-1)|Y(k) = 0)Pr[Y(k) = 0] \neq 0,$

then $Pr[A(k) = \alpha(k)|\overline{L}(k) = \overline{l}(k), \overline{A}(k-1) = \overline{\alpha}(k-1), Y(k) = 0] > 0$, for all $\alpha(k)$,

where $f_{\overline{L}(k),\overline{A}(k-1)}(\overline{l}(k), \overline{\alpha}(k-1)|Y(k) = 0)$ is the density of exposure and covariate history up to k. In occupational studies, people who are not actively employed are by definition unexposed; therefore the positivity assumption is violated. However, because we are imposing a model and assuming that the model extrapolates to cover missing information in the exposure-covariate combinations that are not possible, we can identify effect estimates despite the positivity violation.

Structural Nested Cumulative Failure Time model (SNCFTM) (adapted from Picciotto et al.[17])

The failure time model considered in the main analysis of this study is a structural nested cumulative failure time model. A cumulative failure time model operates under a rare failure assumption and can be expressed as

$$\frac{E[Y_{g=(\overline{A}(k),\underline{0})}(j)|\overline{L}(k)\overline{A}(k-1),A(k),Y(k)=0]}{E[Y_{g=(\overline{A}(k-1),\underline{0})}(j)|\overline{L}(k)\overline{A}(k-1),A(k),Y(k)=0]} = exp[\gamma(j, \overline{L}(k), \overline{A}(k-1), A(k); \psi^{\star})] \quad (1)$$

where $E[Y_{g=(\overline{A}(k),\underline{0})}(j)|\overline{L}(k)\overline{A}(k-1), A(k), Y(k)=0]$ is the counterfactual risk of failure at or before time j among those alive at time $k < j$, given their observed exposure and covariate history up to time k, counterfactual exposure history $g = (\overline{A}(k), \underline{0})$ denotes an exposure history where subjects actually have their observed exposure history up to time point k and are unexposed thereafter and likewise exposure history $g = (\overline{A}(k-1), \underline{0})$ denotes an exposure history where subjects only have their observed exposure history up to time point $k-1$ and are unexposed thereafter. $\gamma(j, \overline{L}(k), \overline{A}(k-1), A(k); \psi)$ is a function of exposure and covariate history including an unknown parameter ψ with a true value of $\psi = \psi^{\star}$.

The model in (1) compares the conditional risk of failure at time j under two exposure histories that can only differ at time k. Function $\gamma(j, \overline{L}(k), \overline{A}(k-1), A(k); \psi)$ is also referred to as a blip function because the CFT model described models the effect for only a final blip of exposure at time k. One possible function is $exp[\gamma(j, \overline{L}(k), \overline{A}(k-1), A(k); \psi)] = exp[\psi A(k)]$. A possibly more realistic function is

$$exp[\gamma(j, \overline{L}(k), \overline{A}(k-1), A(k); \psi)] = 1 + \tfrac{exp[\psi A(k)]-1}{j-k} \tag{2}$$

where the effect of $A(k)$ is the same as the one above for $j = k+1$, but declines as j increases with respect to k. The function defined in (2) is actually equivalent to an AFT model similar to the one described later in the appendix under specific assumptions[38]. Function (2) will be the one used for g-estimation of the SNCFTM in this study.

G-estimation For the G-estimation process of the SNCFTM consider the function:

$$\begin{aligned} H(k, j, \psi) &= Y(j) exp\{-\sum_{m=k}^{j-1} \gamma(m, j(\overline{L}(m), \overline{A}(m-1), A(m); \psi))\} \qquad \text{if } Y(k) = 0 \\ &= 1 \qquad \text{if } Y(k) = 1 \end{aligned}$$

where the mean of this quantity is the same as $E[Y_{g=(\overline{A}(k-1),\underline{0})}(j)]$, conditional on covariate history when $\psi = \psi^{\star}$, based on the assumptions of consistency and conditional exchangeability from above.

We estimate $E[A(k)|\overline{L}(k), \overline{A}(k-1), Y(k)=0]$ using a pooled logistic model for the exposure:

$$\text{logit}Pr[A(k) = 1|\overline{L}(k), \overline{A}(k-1), Y(k)=0] = \beta_0(k) + \beta_1 \overline{A}(k-1) + \beta_2 \overline{L}(k) \tag{3}$$

The estimator $\hat{\psi}$ solving the estimating equation $U(\psi) = 0$ is the g-estimate for this method and a consistent estimate of $\psi^\star$, where:

$$U(\psi) = \frac{1}{n}\sum_{i=1}^{n}\sum_{k=0}^{K}(1 - Y_i(k)) \times \{A_i(k) - E[A(k)|\overline{L}(k), \overline{A}(k-1), Y(k) = 0]\} \times \sum_{K+1}^{j=k+1} H(k, j, \psi) \quad (4)$$

In order to obtain this estimate we use the Newton-Raphson optimization method on a quadratic form of $U(\psi)$, after an initial grid-search of ψ values to determine the initial value for the optimization procedure. The procedure was repeated in 200 bootstrap samples to obtain a 95% confidence interval for the g-estimate $\hat{\psi}$.

We then go on to calculate marginal (unconditional) risks under certain exposure regimes. The function used in (2) satisfies the assumption of no exposure-time varying confounder interaction on the multiplicative failure scale required for this step[17]. We chose to estimate risks for 'never exposed': $g = \overline{0}$ and 'always exposed': $g = \overline{1}$ and compare these to the risks under the natural course of exposure in the observed data.

To obtain marginal risks under different interventions we use the $\hat{\psi}$ estimate from above to generate the different counterfactual risks as described in detail by Picciotto et al[17].

Hazard Ratio approximation: The counterfactual conditional risk ratio in equation (1) can approximate the conditional $HR(t|\overline{L}(k), \overline{A}(k)) = \frac{\lambda_{T_{(\overline{A}(k),\underline{0})}}(t|\overline{L}(k),\overline{A}(k))}{\lambda_{T_{(\overline{A}(k),\underline{0})}}(t|\overline{L}(k),\overline{A}(k))}$ at the time $t \in (k, k+1]$, under the assumptions that the probability of failure is small and that the HR is constant in the interval $(k, k+1]$[17,38].

Structural Nested Accelerated Failure Time model (SNAFTM) (adapted from Chevrier et al.[16] and Hernán et al.[39])

AFT model: Unlike the Cox proportional hazards model, which measures effect on the hazard ratio scale, the accelerated failure time (AFT) model measures effect on the survival time ratio scale. The structural AFT used in our analysis is $T_\alpha = T_0 exp[-\psi^\star \alpha]$ where the causal parameter $-\psi^\star$ can be expressed as $exp[-\psi^\star] = \frac{T_{\alpha=1}}{T_{\alpha=0}}$, where $\frac{T_{\alpha=1}}{T_{\alpha=0}}$ is the ratio of median survival times measuring

the effect of exposure A on mortality.

We rearrange the above model in the form :

$$T_0 = T_\alpha exp[\psi^\star \alpha]$$

which assumes that each subject's counterfactual unexposed survival time $T_0 = T_{\alpha=0}$ is a simple function of $T_{\alpha=1}$ and $\psi^\star$. In order to account for time varying exposures, the above model can be extended to:

$$T_{\overline{0}} = \int_0^{T_{\overline{\alpha}}} exp[\psi^\star \alpha(t)]dt$$

where now $[exp(-\psi^\star)]$ is the expansion or contraction in survival time comparing continuous exposure to no exposure, or $[exp(-\psi^\star)] = \frac{T_{\overline{1}}}{T_{\overline{0}}}$. Under the assumption of consistency we substitute counterfactual (and unobserved) variables for observed variables and the expression becomes:

$$T_{\overline{0}} = \int_0^{T} exp[\psi^\star A(t)]dt$$

with observed exposure $A(t)$ at time t replacing counterfactual exposure $\alpha(t)$ and the observed survival time T replacing the counterfactual survival time $T_{\overline{\alpha}}$ under counterfactual exposure history $\overline{\alpha}$. The values of $T_{\overline{0}}$ and $\psi^\star$ remain unknown.

The model is rewritten as:

$$H(\psi) = \int_0^{T} exp[\psi^\star A(t)]dt \tag{5}$$

where ψ can take any value and $H(\psi) = T_{\overline{0}}$ only when $\psi = \psi^\star$. We apply g-estimation to equation (5) to estimate the true value $\psi^\star$.

G-estimation: The g-estimation process models the probability of exposure at each time point k, conditional on previous exposure and covariate history where $H(\psi)$ for different values of ψ from equation (5) is also entered in the model. The fitted model is as follows:

$$\begin{aligned} &\text{logit}Pr[A(k) = 1|\overline{A}(k-1), \overline{L}(k), T > u(k), H(\psi)] = \\ &\beta_0(k) + \beta_1 \overline{A}(k-1) + \beta_2 \overline{L}(k) + \beta_3 H(\psi) \end{aligned} \tag{6}$$

Given the assumption of conditional exchangeability discussed earlier, the probability of receiving treatment is independent of any counterfactual survival times once we control for exposure and

covariate history. Therefore under the true value of $\psi = \psi^\star$, the parameter β_3 will be 0 as $H(\psi^\star)$ is not a predictor of the probability of exposure. Equation (6) is fitted for a grid of ψ and $H(\psi)$ values. Using the Wald test for the parameter β_3 the true value $\psi = \psi^\star$ is estimated as the one with β_3 closest to 0 (and consequently a p-value for the Wald test closest to 1). 95% confidence intervals for $\psi^\star$ can also be estimated from this process, using the values of ψ on either side of $\psi^\star$ for which the Wald test p-value is closest to 0.05 as the bounds for the 95% confidence interval.

Administrative Censoring: Equation (6) applies when all individuals are followed until failure. However, administrative censoring is present because not all participants are actually followed until failure. There is a right-censoring of those people who have not yet failed, and they are censored at the end of follow up with their true survival time T having never been observed. If we simply include all individuals with observed survival times we induce a form of selection bias. This is because if exchangeability holds at the beginning of follow up, certain individuals who are exchangeable at baseline but have different exposure histories will be differentially included in the analysis based on administrative censoring.

In order to avoid this, we must somehow account in the analysis if an individual's survival times would have been observed under all possible interventions. We thus alter the variable $H(\psi)$ in equation (6) to a variable $\Delta(\psi)$ where $\Delta(\psi)$ is a function of $H(\psi)$ and the maximum length of follow up K for each individual given the administrative end of follow-up.

While any function of $H(\psi), K$ can be used in equation (6,) we use the function $\Delta(\psi) = min(H(\psi), K)$ for $\psi \geq 0$ and $\Delta(\psi) = min(H(\psi), exp(\psi K))$ for $\psi < 0$[12]. The pooled logistic model of the exposure used in g-estimation thus becomes:

$$\begin{aligned} &\text{logit}Pr[A(k) = 1|\overline{A}(k-1), \overline{L}(k), T > u(k), \Delta(\psi)] = \\ &\beta_0(k)+\beta_1\overline{A}(k-1)+\beta_2\overline{L}(k)+\beta_3\Delta(\psi)+\beta_4 K \end{aligned} \tag{7}$$

with $\Delta(\psi)$ replacing $H(\psi)$ and K entered into the model as it is part of the revised conditional exchangeability assumption

$\Delta(\psi^\star)$ II $A(k)|\overline{L}(k) = \overline{l}(k), \overline{A}(k-1) = \overline{\alpha}(k-1), T > u(k), K$ for all $\overline{\alpha}(k-1)$ and $\overline{l}(k)$.

In our analysis we rearrange equation (8) to

$$\text{logit}Pr[A(k) = 1|\overline{A}(k-1), \overline{L}(k), T > u(k), Emp = 1, \Delta(\psi)] =$$
$$\beta_0(k)+\beta_1\overline{A}(k-1)+\beta_2\overline{L}(k)+\beta_3\Delta(\psi)+\beta_4 K \tag{8}$$

thus restricting to those who are actively employed (Emp=1), as the probability of exposure among those not actively employed is by definition equal to zero. We fit equation (8) for various ψ and $\Delta(\psi)$ values to obtain an estimate $\hat{\psi}$ and and 95% confidence intervals for the true value $\psi^\star$ using a Wald test for parameter β_3 as described above. As in the CFT model described above, an estimate $\hat{\psi}$ for $\psi^\star$ can be obtained using an estimating equation but because such an equation is not differentiable on ψ, a grid search or non-gradient based optimizers have to be used as opposed to standard optimization methods[38]. We did not use such an estimating function for the AFT model in our analysis.

Hazard Ratio approximation: Under the assumption that survival time follows a Weibull distribution, we can adjust the AFT model parameter estimate $\hat{\psi}$ to the equivalent of the parameter from a marginal structural Cox model $\hat{\theta}$, where $exp(\hat{\theta})$ is the hazard had all subjects been continuously exposed divided by the hazard had all subjects been never exposed. Under the Weibull distribution assumption, $\theta = \phi\psi^\star$ where ϕ is the is the shape parameter of the Weibull distribution of survival time $T_{\overline{0}}$ obtained by the AFT model[39].